The brain as a symbol-processing machine.

Armando F Rocha
THE BRAIN AS A SYMBOL-PROCESSING MACHINE

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Abstract—The knowledge accumulated about the biochemistry of the synapsis in the last decades completely changes the notion of brain processing founded exclusively over an electrical mechanism, toward that supported by a complex chemical message exchange occurring both locally, at the synaptic site, as well as at other localities, depending on the solubility of the involved chemical substances in the extracellular compartment. These biochemical transactions support a rich symbolic processing of the information both encoded by the genes and provided by actual data collected from the surrounding environment, by means of either special molecular or cellular receptor systems. In this processing, molecules play the role of symbols and chemical affinity shared by them specifies the syntax for symbol manipulation in order to process and to produce chemical messages. In this context, neurons are conceived as message-exchanging agents. Chemical strings are produced and stored at defined places, and ionic currents are used to speed up message delivery. Synaptic transactions can no longer be assumed to correspond to a simple process of propagating numbers powered by a factor measuring the presynaptic capacity to influence the postsynaptic electrical activity, but they must be modeled by more powerful formal tools supporting both numerical and symbolic calculations. It is proposed here that formal language theory is the adequate mathematical tool to handle such symbolic processing. The purpose of the present review is therefore: (a) to discuss the relevant and recent literature about trophic factors, signal transduction mechanisms, neuromodulators and neurotransmitters in order (b) to point out the common features of these correlated processes; and (c) to show how they may be organized into a formal model supported by the theory of fuzzy formal languages (d) to model the brain as a distributed intelligent problem solver. © 1997 Elsevier Science Ltd.

1. Introduction
2. DNA reading
3. Nuclear RNA processing
4. Protein production, editing and destruction
5. Transportation
6. Signal transduction pathways
   6.1. G-protein pathways
   6.2. The PTK pathways
   6.3. Calmodulin signaling
7. Neurotrophic and differentiation factors
8. Chemical talk at the synapsis
   8.1. Excitatory amino acids
   8.2. The thalamic relay neuron
   8.3. The cortical circuits in primary sensory areas
9. Distributed cellular systems
   9.1. Signal processing
   9.2. Genetic network
   9.3. Cellular processing
10. Formal languages
    10.1. Definition
    10.2. Ambiguity
    10.3. Logic capabilities
    10.4. Learning
    10.5. Non-linear fuzzy strings
    10.6. Chemical languages
    10.7. An example genetic network
11. Distributed intelligent processing systems
    11.1. Decision making by DIPS
    11.2. Message organization
    11.3. Organizing knowledge

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### CONTENTS (continued)

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>12. Visual systems</td>
<td>178</td>
</tr>
<tr>
<td>12.1. Central organization of the visual system</td>
<td>178</td>
</tr>
<tr>
<td>12.2. Sensor: an artificial visual system</td>
<td>179</td>
</tr>
<tr>
<td>13. Natural language</td>
<td>183</td>
</tr>
<tr>
<td>13.1. JARGON</td>
<td>185</td>
</tr>
<tr>
<td>13.2. Finding words</td>
<td>185</td>
</tr>
<tr>
<td>13.3. The phrase structure</td>
<td>186</td>
</tr>
<tr>
<td>13.4. The used grammars</td>
<td>188</td>
</tr>
<tr>
<td>13.5. Answering the queries</td>
<td>190</td>
</tr>
<tr>
<td>14. Conclusion</td>
<td>191</td>
</tr>
<tr>
<td>References</td>
<td>193</td>
</tr>
</tbody>
</table>

### ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
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<tr>
<td>Ach</td>
<td>Acetylcholine</td>
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<tr>
<td>ACTH</td>
<td>Adrenocorticotropic hormone</td>
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<tr>
<td>ADP</td>
<td>Adenosine diphosphate</td>
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<tr>
<td>AMPA receptor</td>
<td>z-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) ionic glutamate receptor</td>
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<tr>
<td>ATP</td>
<td>Adenosine triphosphate</td>
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<tr>
<td>BNDF</td>
<td>Brain-derived neurotrophic factor</td>
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<tr>
<td>CamK</td>
<td>Cyclic adenosine monophosphate</td>
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<td>CCK</td>
<td>Cholecystokinin</td>
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<tr>
<td>CDF</td>
<td>Cholinergic differentiation factor</td>
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<td>CGM</td>
<td>Calcium-guided movement</td>
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<td>cGMP</td>
<td>Cyclic guanine monophosphate</td>
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<tr>
<td>CNNTF</td>
<td>Ciliary neurotrophic factor</td>
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<tr>
<td>CPT</td>
<td>Channel protein transport</td>
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<td>CRE</td>
<td>cAMP Responsive element</td>
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<td>CREB</td>
<td>CRE Binding protein</td>
</tr>
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<td>CRE</td>
<td>Corticotropin-releasing factor</td>
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<td>DA neuron</td>
<td>Dopaminergic neuron</td>
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<td>DAG</td>
<td>Diacylglycerol</td>
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<td>DCV</td>
<td>Dense-core vesicle</td>
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<td>DIPS</td>
<td>Distributed intelligent processing system</td>
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<tr>
<td>dsRAD</td>
<td>Double-stranded RNA adenosine deaminase</td>
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<td>eEF</td>
<td>Elongation factor</td>
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<td>Epidermal growth factor</td>
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<tr>
<td>eIF</td>
<td>Initiation factor</td>
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<td>EPSP</td>
<td>Excitatory postsynaptic potential</td>
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<tr>
<td>ER</td>
<td>Endoplasmic reticulum</td>
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<tr>
<td>FRP</td>
<td>Ferritin repressor protein</td>
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<td>FRT</td>
<td>Fast-released transmitter</td>
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<td>GAP</td>
<td>GTP-ase-activating protein</td>
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<td>Guanine diphosphate</td>
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<td>GTP</td>
<td>Guanine triphosphate</td>
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<td>Histaminergic terminal</td>
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<td>Heterogeneous nuclear RNA</td>
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<td>Inositol trisphosphate</td>
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<td>Inhibitory postsynaptic potential</td>
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<td>IRE</td>
<td>Iron-responsive element</td>
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<td>Jak</td>
<td>Janus kinase</td>
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<td>KA receptor</td>
<td>Kainate glutamate receptor</td>
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<td>LC</td>
<td>Locus coeruleus</td>
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<td>LDCV</td>
<td>Large dense-core vesicle</td>
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<tr>
<td>LGN</td>
<td>Lateral geniculate nucleus</td>
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<td>LHHR</td>
<td>Luteinizing hormone-releasing hormone</td>
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<td>LTP</td>
<td>Long-term potentiation</td>
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<td>MAPK</td>
<td>Mitogen-activated protein kinase</td>
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<td>Met-tRNA</td>
<td>Methionyl-tRNA</td>
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<td>MFR</td>
<td>Midbrain reticular formation</td>
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<td>mGlur</td>
<td>Metabotropic glutamate receptor</td>
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<td>mRNA</td>
<td>Messenger RNA</td>
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<td>Noradrenergic terminal</td>
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<td>N-ethylmaleimide-sensitive factor</td>
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<td>Protein kinase A</td>
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<td>PKC</td>
<td>Protein kinase C</td>
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<td>Pol I</td>
<td>Poly(A)polymerase I</td>
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<td>poly(A)</td>
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<td>PTK</td>
<td>Protein-tyrosine kinase</td>
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<tr>
<td>PTKR</td>
<td>Protein-tyrosine kinase receptor</td>
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<td>RAba3</td>
<td>Traffic protein in the synaptic vesicle</td>
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<td>Ras</td>
<td>A protein in the G-protein and PTK signal transduction pathway</td>
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<tr>
<td>RAS</td>
<td>Reticular activating system</td>
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<tr>
<td>REM</td>
<td>Rapid eye movement</td>
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<tr>
<td>RGS</td>
<td>Regulator of G-protein signals</td>
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<td>RNA–protein complex</td>
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<td>rRNA</td>
<td>Ribosomal RNA</td>
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<td>Reticular sensory neuron</td>
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<td>Retinol X receptor</td>
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<td>SDCV</td>
<td>Small dense-core vesicle</td>
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<td>SNAP</td>
<td>Synapsosomal-associated protein</td>
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<td>snRNA</td>
<td>Small nuclear RNA</td>
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<td>Somatostatin</td>
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<td>SR</td>
<td>Substance P</td>
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<td>SRC</td>
<td>A type of homology binding site</td>
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<td>SRE</td>
<td>Steroid receptor element</td>
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<td>SRP</td>
<td>Signal receptor protein</td>
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<td>SRT</td>
<td>Slow-released transmitter</td>
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The discovery that much cerebral processing is supported by electrochemical transactions at the synaptic sites and the axon hill was a milestone achievement of the scientific endeavor which began in the XIX Century, with the purpose of understanding the brain’s physiology. The works of Hodgkin and Huxley (1952) and Fatt and Katz (1951) outlined the classical modeling of neuronal signaling and processing supported by ionic currents at the membrane and the chemical interactions taking place at the synapsis. Briefly, transmitters (1) are released at the presynaptic sites by the augmentation of the intracellular calcium concentration triggered by the incoming axonic electrical activity; (2) in order to bind to postsynaptic receptors; and (3) in order to promote local ionic conductance modifications supporting a correlated postsynaptic electrical activity at both dendrites; cell body and the axon hill. It is assumed that the local electrical responses may have either excitatory or inhibitory effects upon the action potential genesis at the axon hill, and that the activities of all presynaptic inputs are integrated to determine the amount of postsynaptic axonic activation. Hodgkin and Huxley (1952) proposed the mathematical model of their ionic hypothesis, which was and continues to be the main source of inspiration of most, if not all, works on the subject published up to date (see, e.g. Rocha, 1992; Segev, 1995). Katz (1966) proposed the transmitter quantum theory which continues to receive strong support from studies about peripheral and central synapsis (see, e.g. Kennedy, 1994; Kuno, 1995; Stevens, 1993).

By the time electrophysiologists were formulating the above models, McCulloch and Pitts (1943) synthesized current ideas in their proposal of a formal neuron as a binary logical device, mimicking the elementary synaptic integration of the presynaptic activity and the filtering properties of the axonic membrane. Their proposal was responsible for much of the early excitement in the emerging field of computer sciences about building intelligent machines (Rosemblatt, 1958). Because the proposal seemed to warrant the development of electronic machines to simulate human or, at least, animal brain behavior.

The idea is so strong that it supports nowadays by itself an entire area of very active research named the neural nets (NN) theory (Churchland and Sejnowski, 1990, 1993; Hinton, 1989). The main paradigm of this theory says that if aᵢ is the activity at the presynaptic neuron nᵢ; wᵢ is the strength of its presynaptic connections to the postsynaptic neuron nᵢ, and m is the total number of the presynaptic neurons reaching nᵢ, then the postsynaptic output aᵢ is obtained as:

\[ vᵢ = \sum_{i=1}^{m} aᵢ * wᵢ \]

\[ aᵢ = f(vᵢ), \]  

i.e. \( aᵢ \) is a function \( f \) of the weighted \( (wᵢ) \) average of the presynaptic inputs \( aᵢ \). In general, \( f \) is a Boolean function such that:

\[ aᵢ = 1 \text{ if } vᵢ > x \text{ otherwise } aᵢ = 0 \]

but it may be defined as any other filtering function. Learning procedures (backpropagation being the most famous among them) change synaptic weights according to the success (reward) or failure (punishment) of \( nᵢ \) to provide the solution to the problem being studied. In this condition, \( wᵢ \) is a measure of the statistical uncertainty of the contribution of \( nᵢ \) to the problem solution. Neurons usually are organized into layers, to form nets specialized in solving particular complex problems by means of the way the neurons are connected. Knowledge is assumed to be encoded by means of the net connectivity, because each neuron performs the same simple computations defined in Equation (1).

The knowledge accumulated about the biochemistry of the synapsis in the last decade completely changes the notion of brain processing, found exclusively over an electrical mechanism, toward that supported by a complex chemical message exchange occurring both locally at the synaptic site as well as at other localities, depending on the solubility of the involved chemical substances in the extracellular compartment. Synaptic transactions can no longer be assumed to correspond to a simple process of propagating numbers powered by a factor measuring the presynaptic capacity to influence the postsynaptic electrical activity, but they must be modeled by more powerful formal tools supporting both numerical and symbolic calculations (Hasselho, 1995; Pedrycz et al., 1995; Rocha et al., 1992; Rocha, 1992; Serapião et al., 1996; Sutton, 1996). Briefly, the electrical activity arriving at the presynaptic terminal releases specific transmitters (or ligands) into the extracellular space (see Fig. 1) in amounts proportional to the degree of this incoming activity. These transmitters have to bind to specific postsynaptic receptors \( r \) in order to modify the postsynaptic electrical and/or chemical activity. These actions are performed by other special mol-

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1. INTRODUCTION

The discovery that much cerebral processing is supported by electrochemical transactions at the synaptic sites and the axon hill was a milestone achievement of the scientific endeavor which began in the XIX Century, with the purpose of understanding the brain's physiology. The works of Hodgkin and Huxley (1952) and Fatt and Katz (1951) outlined the classical modeling of neuronal signaling and processing supported by ionic currents at the membrane and the chemical interactions taking place at the synapsis. Briefly, transmitters (1) are released at the presynaptic sites by the augmentation of the intracellular calcium concentration triggered by the incoming axonic electrical activity; (2) in order to bind to postsynaptic receptors; and (3) in order to promote local ionic conductance modifications supporting a correlated postsynaptic electrical activity at both dendrites; cell body and the axon hill. It is assumed that the local electrical responses may have either excitatory or inhibitory effects upon the action potential genesis at the axon hill, and that the activities of all presynaptic inputs are integrated to determine the amount of postsynaptic axonic activation. Hodgkin and Huxley (1952) proposed the mathematical model of their ionic hypothesis, which was and continues to be the main source of inspiration of most, if not all, works on the subject published up to date (see, e.g. Rocha, 1992; Segev, 1995). Katz (1966) proposed the transmitter quantum theory which continues to receive strong support from studies about peripheral and central synapsis (see, e.g. Kennedy, 1994; Kuno, 1995; Stevens, 1993).

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\[ aᵢ = f(vᵢ), \]

i.e. \( aᵢ \) is a function \( f \) of the weighted \( (wᵢ) \) average of the presynaptic inputs \( aᵢ \). In general, \( f \) is a Boolean function such that:

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but it may be defined as any other filtering function. Learning procedures (backpropagation being the most famous among them) change synaptic weights according to the success (reward) or failure (punishment) of \( nᵢ \) to provide the solution to the problem being studied. In this condition, \( wᵢ \) is a measure of the statistical uncertainty of the contribution of \( nᵢ \) to the problem solution. Neurons usually are organized into layers, to form nets specialized in solving particular complex problems by means of the way the neurons are connected. Knowledge is assumed to be encoded by means of the net connectivity, because each neuron performs the same simple computations defined in Equation (1).

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Fig. 1. Signal transduction pathways from the cellular membrane to the nucleus. Three different pathways are illustrated, for conveying information from the outside of the cell to the nucleus in order to control the DNA reading: (I) Tyrosine kinase pathway: the ligand induces homo (or hetero) receptor dimerization, which promotes the autophosphorylation on tyrosine residues inside and outside the kinase domain. The role of outside domain phosphorylation is to allow the docking and phosphorylation of downstream signal transduction molecules (e.g., MAPKs) in charge of conveying information from the membrane to the nucleus (Heldin, 1995; Marshal, 1995); (II) G-Protein pathway: the ligand binding to the receptor induces the GTP/GDP exchange by the associated G-Protein. The GTP binding to the α units of the G-Protein, dissociates this unit from the complex formed by the β and γ units. The free GTP-α units may now phosphorylate other downstream signal transduction molecules (e.g. PKA) which way reach the nucleus and control and DNA reading. The βγ complex may also exercise a control over other downstream routes (Neer, 1995); (III) CamK pathways: the ligand association to the receptor opens a calcium channel. Calmodulin binds to the calcium ions moved to the intracellular compartment; and this complex may activate calcium-calmodulin kinases (CamK), that are responsible for controlling both cytosolic and nuclear signal transduction pathways (Ghosh and Greenberg, 1995).

Because of this, it may be said that the synaptic transactions involve both numeric and symbolic calculations.

The role played by controllers may be very complex, as pointed out by research about:

(a) signal transduction mechanisms (Fig. 1): showing how different types of ligand couple to different classes of membrane receptors to activate defined classes of molecules (e.g. G-proteins, tyrokinases, phosphokinases, etc.) in charge of controlling important cellular activities such as mitosis, apoptosis, cellular specialization, etc.

(b) trophic factors: showing that molecules released by effector cells or neurons are imported by the axonic terminal branches and moved to the cell body by means of a retrograde transportation, where they influence DNA reading and are supposed to inhibit apoptosis, and:

\[ a(c) = f(a(t),a(r),\mu(t,r)) \]
(c) neuromodulators and neurotransmitters: showing that the same messenger may act upon a variety of receptors in the same or neighboring cells, both to elicit ionic effects as well as to influence either metabolic processes or DNA reading.

These biochemical transactions support a rich symbolic processing of the information both encoded by the genes and provided by actual data collected from the surrounding environment, by means of either special molecular or cellular receptor systems. In this processing, molecules play the role of symbols, while chemical affinity shared by them specifies the syntax for symbol manipulation in order to process and produce chemical messages (Fig. 1). In this context, neurons are conceived as message-exchanging agents. Chemical strings are produced and stored at defined places, and ionic currents are used to speed up message delivery (Rocha, 1992). Formal language theory (Chomsky, 1957, 1965; Hunter, 1993; Mizumoto et al., 1973; Negoita and Ralescu, 1975; Rocha et al., 1980) is an adequate mathematical tool to handle such symbolic processing (Rocha, 1982a,b; Rocha et al., 1996a; Serapião et al., 1996).

Distributed intelligent problem-solving systems (DIPS) are defined as a collection of agents (intelligent or not) which interact to solve a problem in a defined knowledge domain (Chandrasekaran, 1981; Davis and Smith, 1983; Durfee and Montgomery, 1991; Hewitt, 1977; Hewitt and Inman, 1991; Kornfield and Hewitt, 1981; Lesser, and Corkill, 1981; Lesser, 1991). According to this approach, the solution of the problem may be broken down to a set of solutions of sub-tasks (problems), and each DIPS agent is assigned to solve one of these sub-tasks. The sub-tasks may be of any sort, e.g. database activities (memory), microtheory proving (reasoning), effenter device control (muscle control), data acquisition (sensoric activity), etc. Since sub-tasks are supposed not necessarily to require intelligent solutions, this property arises mainly by means of the way in which agents interact to solve the whole problem. Basically, agents (neurons) ask and furnish information from and to other agents, respectively. Information flow may be specified by means of either mail (axonic) systems, when at least one of the agents (the presynaptic neuron) knows precisely the address of the other (the postsynaptic neuron); or by means of message broadcasting (neuromodulators, hormones, etc.), when agents select messages in which they are interested based on their contents; these messages are distributed among agents by means of more or less non-specific transportation systems (e.g. the bloodstream). Implicit on both strategies is that communication is supported by a set of specific or general relations. In both cases, some sort of connectionism is assumed. Central to the notion of using a set of agents to obtain an intelligent solution for a given problem are the concepts of conflict, consensus and negotiation. Since agents are assumed to be independent in solving the tasks they are specialized for, and different agents may be assigned to handle the same task, conflicting (inconsistent) information may be available. Consensus may be used as a way to solve conflict if opposing pieces of information exhibit clearly different degrees of confidence (truthfulness) and the agents furnishing them enjoy marked degrees of relevance, because in this condition consensus may be calculated depending on message confidence and agent relevance (Rocha, 1992).

Otherwise, negotiation has to be used to change message confidence and/or agent relevance in the attempt to obtain a consensual solution. Hierarchy is another process to be used in conflict solving and negotiation. However, hierarchy must be kept within boundaries, otherwise the system intelligence is reduced to that (if any) of the higher agent in power. Message delivery synchronization is also an useful strategy to maintain conflict to a minimum, because it prevents different agents from processing information about the same variable, collected at different times. The brain is being indicated as an example of one of the most complex natural DIPS (Dennet, 1991; Edelman, 1987; Luck, 1995; Maunsell, 1995; Ornstein, 1991; Rocha, 1992; Singer, 1995; Stoerig and Cowey, 1995; Ungerleider, 1995).

The purpose of the present review is (a) to discuss the relevant and recent literature about trophic factors, signal transduction mechanisms, neuromodulators and neurotransmitters; (b) in order to point out the common features of these correlated processes; (c) to show how they may be organized into a formal model supported by the theory of fuzzy formal languages (Mizumoto et al., 1973; Negoita and Ralescu, 1975; Rocha et al., 1980, 1996b; Rocha, 1992); and (d) to model the brain as a distributed intelligent problem solver (Rocha, 1992; Serapião et al., 1996). The review is intended to be selective rather than extensive in its analysis of the available literature, in order to guide discussion toward a specific strategy in brain modeling and understanding. Also, attention will be given to reviews published within the last 5 years, in virtue of the rapid pace of new discoveries in some of the above areas. To accomplish its purpose, the review is organized as follows. The initial sections summarize the current knowledge about DNA transcription, RNA nuclear processing, and RNA translation at both cytosolic and ribosome sites, because transmitters, neuromodulators and hormones are proposed to control proteic synthesis by means of the control of the DNA reading, and the produced proteins are assumed to influence the physiology of the neuron and of the synapsis. Section 5 discusses molecular transportation across membranes and within the cytoplasm, because compartmentation of chemical (fuzzy) language processing is a key issue to constraint ambiguity and to increase efficiency of the chemical (language) transactions. Section 6 briefly summarizes the actual knowledge about signal transduction pathways, paying attention to the G-protein pathways and the tyrokinase and calmodulin systems. Section 7 discusses the role played by neurotrophic and differentiation factors in the physiology of the neuron. Section 8 is devoted to the analysis of the chemical talk taking place at the synapsis, paying attention to the role of excitatory amino acids and the synaptic transaction at the thalamic relay neurons and the primary sensory cortical
2. DNA READING

Any gene is composed of two different substrings: the coding and control strings. The coding string is constituted from a defined number of codons specifying one or a family of proteins. The control string is formed by a set of nucleotide sequences: the promoter, inducers and repressors, in charge of controlling what type of gene, and when and how it is transcribed.

Eukaryotes contain three distinct RNA polymerase enzymes, each responsible for the transcription of a subclass of nuclear genes: Polymerase I (Pol I) is in charge of the transcription of ribosomal RNA (rRNA), Polymerase II (Pol II) reads protein coding genes and small nuclear RNAs (snRNAs), and Polymerase III (Pol III) does the same job in the cases of 5S RNA, tRNA, and other types of genes. The DNA transcription is a three-step process (Das, 1993): (1) firstly, the initiation complex is assembled; (2) secondly, the transcribed nucleotide chain is elongated; and (3) finally, the transcription is terminated. Initially, a group of proteins (promoters and inducers) is assembled over the control string to position the polymerase so as to begin the transcription of the first codon of the coding string. The transcript elongation involves an inchworm-like translocation of polymerase and the production of the RNA chain. This periodic translocation mechanism involves bipartite sites on the RNA polymerase for binding both DNA and the RNA product (Das, 1993). At least two sites are proposed to bind RNA: the leading product site, filled during each successive cycle of extension of the RNA chain by about 10 nt, and the lagging product site, occupied by the pre-translocation empties the leading site, hence permitting the next cycle of elongation. The RNA chain is not extended at a fixed rate along the DNA (Das, 1993). Two prevalent types of sites are know to impede elongation: (a) the so-called 'pause' sites, which induce a temporary, reversible block to nucleotide addition, maybe with the purpose of error editing in the transcribed RNA chain; and (b) terminators, which cause the release of RNA, either intrinsically, or upon activation by a diffusible factors and protein binding. Transcription termination is the last step of the gene-reading process.

For RNA Pol II to transcribe a gene, an array of over 20 proteins must be assembled at the promoter (Buratowski, 1994; Burley and Roeder, 1996; Comai et al., 1992; Conaway and Conaway, 1993; Goodrich and Tijian, 1994; Kornberg, 1996; Roeder, 1996; Sharp, 1993; Struhl, 1996; Svejstrup et al., 1996; Tijian and Maniatis, 1994; Zawl and Reinberg, 1995). Despite this biochemical complexity, the assembling of the initiation complex to support the DNA reading is accomplished in four main steps. An initial committed complex is formed by TFII D (transcription factor II D) binding to the TATA element of a promoter, by means of one of its components, the TATA binding protein (TBP) [Fig. 2(II)]. The TATA element is a consensus nucleotide sequence composed predominately by thymine and adenine. The TBP shape resembles a saddle made up from two roughly symmetrical halves. The inner surface of the saddle interacts with the minor groove of the TATA element, causing distortions in the DNA. The outer surfaces of the proteins are accessible for interactions with other TFII D transcription factors. In the second step, the TFII complex acts as a binding site for TFII B, which can recruit Pol II and TFII F. Subsequently, TFII F and TFII H associate with the initiation complex. Once the complete complex is assembled, ATP-dependent activation [Fig. 2(II)] is necessary for promoter clearance and transcription to occur (Buratowski, 1994; Goodrich and Tijian, 1994). Once Pol II is released to continue the transcription of the other codons, a new Pol II may be assembled to start a new gene copy [Fig. 2(III)]. A gene may, at any given moment, be transcribed by many polymerases. This number is reported to average 120 in the case of Balbiani Ring 1 Gene (Baurin and Wieslander, 1994).

Besides the formation of the initiation complex, transcriptional activation of eukaryotic genes during development or in response to extracellular signals involves the regulated assembly of other multiprotein complexes on other DNA sites, called enhancers/silencers (Bjöklund and Kim, 1996; Kaiser and Meisterernst, 1996; Kornberg, 1996; Roeder, 1996; Verrijer and Tijian, 1996). Recent studies have shown that (a) the activity of at least some natural enhancers/silencers requires proteins that function as architectural components; (b) interactions between proteins within the enhancer are crucial for the activation of DNA transcription; and (c) changes in the relative position or orientations of protein binding sites within the enhancer lead to inactivation of the enhancer. Thus, activation of at least some enhancers appears to require the assembly of a highly specific three-dimensional nucleoprotein complex. Many molecules released and activated by different signal transduction pathways (Fig. 1) are moved to the nucleus to bind to specific sites of the control string or to the initiation complex in order to modulate the DNA reading (Hill and Treisman, 1995; Taniguchi, 1995).

A large number of neuuropeptides and neurotransmitters stimulate neuronal cells through the second messenger cAMP. These synaptic signals often cause profound changes in neuronal function by altering basic patterns of gene expression, because cAMP may regulate [Fig. 2(III)] a number of these genes through a conserved cAMP response element (CRE). Recently, a nuclear CRE-binding protein (CREB) has been shown to bind to the CRE and stimulate the transcription of cAMP-responsive genes (Alberini et al., 1994; Bartsch et al., 1995;
Fig. 2. DNA reading and RNA processing. The building and activation of the initiation complex (I and II) begins the gene transcription. Elongation proceeds by means of an inchworm-like translocation of polymerase (III). The velocity of gene reading and the number of RNA copies may be controlled by both cAMP responsive elements (III) and inducers (IV). The produced RNA (a) undergoes a complex editing, which involves intron splicing (b and C) and addition of cap and tail base sequences (d), with the purpose of protecting the RNA from enzymatic action and guiding its nuclear exportation (e) by means of active transportation carried out by a nuclear export complex (NEC) formed by a group of nuclear proteins. See text for further details.

Moons and Cooper, 1995; Montminy et al., 1990; Yin et al., 1995). Since known cellular effects of cAMP occur via the catalytic subunit (C subunit) of cAMP-dependent protein kinase (PKA), the regulation of these genes by the same pathway appears likely. Furthermore, microinjection of the C subunit into cells specifically activates transcription of cAMP-responsive genes (Montminy et al., 1990).

The palindromic sequence (or motif) conserved among cAMP genes is 5' ... TGACGTCA ... 3'. The CREB is a protein composed by 341 amino acids and may be subdivided in three identifiable domains: a trans-activation region containing a cluster of phosphorylations sites, a DNA-binding domain (BD) consisting primarily of basic amino acids and a leucine-zipper dimerization domain. The CREB binds to the gene by means of the interactions between BD and the CRE consensus motive. The putative trans-activation domain, extending over amino acids 88–160, contains potential phosphorylation sites for kinase A, C and casein kinase II. Upon phosphorylation, these sites may activate transcription by providing an acidic surface which can interact which target proteins in the RNA polymerase II transcription complex [Fig. 2(III)]. The CREB activation is supposed to increase the initiation complex stability and to increase the number
of polymerases transcribing a gene at a given moment.

The nuclear receptor superfamily is comprised of over 150 different proteins that have evolved to mediate a complex array of extracellular signals into transcriptional responses (Beato et al., 1995; Mangelsdorf and Evans, 1995; Mangelsdorf et al., 1995; Silva and Burbach, 1995; Tsai and O'Malley, 1994). Many, but not all, of these proteins directly bind to signaling molecules which, because of their small lipophilic character, easily can enter the target cell (Fig. 2IV). Thus, unlike membrane-bound receptors, the nuclear receptors are intracellular and function to control the activity of target genes directly (Mangelsdorf and Evans, 1995). Three main classes of nuclear receptors are commonly distinguished: (a) steroid receptor family, binding steroid hormones; (b) heterodimeric receptor family, of which the most studied receptor is the retinal X receptor (RXR); and (c) orphan receptor family, for most of which receptors the ligand is not yet discovered. The ligands for the last two families are chemically diverse, including vitamin D, retinoids, prostanoids and thyroid hormone. Furthermore, not all of these ligands are exclusively endocrine, and they may be activated by metabolic pathways within the target cells (Mangelsdorf and Evans, 1995). Nuclear receptors are characterized by a central DNA-binding domain composed of two highly conserved zinc fingers that set the nuclear receptors apart from other DNA-binding proteins; the C-terminal half which possesses the essential property of ligand recognition, and a variable N-terminal region, which is supposed to exercise some action upon gene transcription (Mangelsdorf et al., 1995; Tsai and O'Malley, 1994).

Nuclear receptors primarily act through direct association with specific DNA sequences known as hormone response elements (HREs; or SRE for steroid receptor elements). For the non-steroid members of the receptor superfamily, the HREs consist of a minimal core hexad consensus sequence, AGGTCA, that can be configured into a variety of structured motifs (Glass, 1994). These HREs directly reflect the mode of receptor binding, which can be as heterodimers, homodimers, or monomers. In contrast, the steroid hormone receptors bind exclusively as homodimers to palindromes separated by three nucleotides (Mangelsdorf et al., 1995). The palindromes are in general imperfect inverted sequences. The half-site of SRE is in general either GGTCAn or TGTTCCT (Tsai and O'Malley, 1994). The binding motifs for metabolic ligand receptors are less well understood.

The complex ligand–nuclear receptor stimulates the formation of a preinitiation complex by increasing its rate of formation and/or by stabilizing a pre-formed pre-initiation complex (Tsai and O'Malley, 1994). In this case, it is assumed the DNA binding occurs after the ligand/receptor complex is assembled. Some nuclear receptors may bind to their HREs in the absence of their ligands. In this condition, the receptor may exercise an inhibitory action upon the gene transcription by means of an association with inhibitory co-factors. It is supposed, in this case, that ligand binding releases this inhibitory co-factor in order to stimulate the DNA reading. This stimulation may require the association of another stimulatory co-factor (Mangelsdorf and Evans, 1995; Marshal, 1995; Schindler and Darnell, 1995; Tsai and O'Malley, 1994).

Whenever the induction of a gene occurs with no intervening protein synthesis, but requires only the modulation of pre-existing transcriptional modulators by ligands, the gene is classified as a primary response gene (G0 in Fig. 3). Many of the same primary response genes are induced in a variety of biological contexts as diverse as mitogenic responses and neuronal responses to neurotransmitters and sensory stimuli (Herschman, 1991). Whenever the induction of a gene occurs after the activation of other genes and requires de novo production of proteins, the gene is classified as secondary response gene (G1 and G2 in Fig. 3). The products of these genes may either function as controllers of the activity of other genes (Gi in Fig. 3), or constitute new controlling messages to cytoplasmic processes or raw material for cell maintenance (Gc, in Fig. 3). Implicit to this assumption is that the transcription factors induced as a primary response to the ligand binding (stimulus) serve as intermediates that regulate expression of secondary response genes, whose products are assumed as the response of the processing triggered by the ligand. In this way, e.g., the glutamate binding to the NMDA receptor in the presence of depolarization induced by bursts of high-frequency bursts postsynaptic stimulation, may activate primary response genes in charge of coordinating the activation of secondary response genes to produce the proteins necessary for supporting long-term potentiation (LTP) of synaptic transmission at many different areas in the brain (Alberini et al., 1994; Bach et al., 1995; Bartsch et al., 1995; Kuno, 1995; Moons and Cooper, 1995; Mayford et al., 1995; Montminy et al., 1990; Yin et al., 1995).

A substantial body of work now suggests that biological diversity in response to alternative inductive signals can be understood, at least in principle, to occur as a consequence of unique combinatorial utilization of a common pool of genes, rather than as the result of the induction of transcripts unique to a particular ligand or cell type. The variability of biological response resulting from the employment of genes whose products are used in many contexts occurs as a consequence (Herschman, 1991) of (a) differential quantitative induction of primary response genes by distinct ligands; (b) differing kinetics of induction of the primary response genes and their products; (c) formation of changing patterns of heterodimeric transcription factors, with alternative transcriptional capacities, during the course of ligand-stimulated responses; (d) cell type-specific restriction of the expression of subsets of primary response genes; (e) ligand- and cell-specific post-translational modification of primary response gene products and consequent alterations in the biological properties of these proteins; and (f) differential production of autocrine and paracrine factors that modulate initial inductive responses.
3. NUCLEAR RNA PROCESSING

Messenger RNA (mRNA) conveying the information required for the synthesis of a given protein is formed by extensive post-transcriptional processing [Fig. 2(a)–(e)] of primary transcripts of protein-coding genes (Dreyfuss et al., 1993; Madhani and Guthrie, 1994; Moore and Sharp, 1993; Simpson and Emeson, 1991). These initial transcripts are termed heterogeneous nuclear RNAs (hnRNAs). The terms hnRNAs and pre-mRNA are often used interchangeably, although only a subset of hnRNAs actually may be precursors to mRNAs, while the rest turn over in the nucleus (Dreyfuss et al., 1993). From the time hnRNAs emerge from the transcription process, and throughout the time they are in the nucleus, they are associated with proteins. The collective term for the proteins that bind hnRNAs is hnRNP proteins. The full range of functions and mechanism of action of hnRNPs is not yet known, but it may be said that they influence the structure of hnRNAs and facilitate or hinder the interaction of hnRNA sequences with other components that are needed for processing of pre-mRNAs. The hnRNP proteins also may play important roles in the interaction of hnRNA with other nuclear structures, in nucleocytoplasmic transport of mRNA, etc. (Cattaneo, 1991; Dreyfuss et al., 1993; Wu and Maniatis, 1993). All of the hnRNP must be imported into the nucleus, and some of the shuttling proteins involved with nuclear-cytoplasmic transport, must also be exported to the cytoplasm.

The mRNA undergoes various co- and post-transcriptional modifications. The 5' end generally is capped, the 3' end polyadenylated, and up to 98% of the internal sequences can be eliminated by splicing. The RNA editing may involve deletion, insertion, and conversion of residues (Cattaneo, 1991; Hebert, 1996). The snRNAs guide both residue insertion or deletion (Cattaneo, 1991), but nucleotide exchange may require a more complex process, involving the participation of introns and hnRNPs (Hebert, 1996).

Genes in eukaryotes often are interrupted by intervening sequences that must be removed during the processing of mRNA. The RNA splicing is the process by which these intervening sequences, named introns, are removed precisely and the flanking, functional sequences, termed exons, are joined together [Fig. 2(a)–(c) and Fig. 4]. Introns may be divided into different groups depending on mobility within the genome and the kind of splicing mechanism (Baurén and Wieslander, 1994; Blumenthal, 1995; Lambowitz and Belfort, 1993; Larsson et al., 1995; Madhani and Guthrie, 1994; Moore and Sharp, 1993; Yu et al., 1993). Splicing proceeds via two trans-esterification steps. In the first cleavage–ligation step of this reaction, the 2' hydroxyl end of an internal adenosine residue attacks the phosphate at the 5' splice site, releasing the 5' exon (exon 1) and resulting in for-
Intron splicing is a complex chemical process involving the participation of at least five snRNAs (U1, U2, U3, U5, and U6) assembled into a complex called spliceosome. Our major step in this process is to fold the premRNA chain in order to bring the two exons together. The folding is accomplished by recognizing the 5' and 3' splicing sites and the branchpoint region. U1 and U2 are in charge of recognizing these sites. The U6 replacement of U1 is necessary to allow the adequate mRNA folding to be maintained by means of a U2-U6 helix. The role of U4 seems to stabilize the complex U5-U6 before its binding to the complex U1-U2-intron, and U4 is supposed to be released from the spliceosome after U5-U6 binding. U5 plays the role of identifying exon 1 by means of structural relations, whereas the other snRNA/mRNA associations are hypothesized to depend on nucleotide consensus sequences. See text for further details. Modified from Madhani and Guthrie (1994).

Fig. 4. Intron splicing. Intron splicing is a complex chemical process involving the participation of at least five snRNAs (U1, U2, U3, U5 and U6) assembled into a complex called spliceosome. Our major step in this process is to fold the premRNA chain in order to bring the two exons together. The folding is accomplished by recognizing the 5' and 3' splicing sites and the branchpoint region. U1 and U2 are in charge of recognizing these sites. The U6 replacement of U1 is necessary to allow the adequate mRNA folding to be maintained by means of a U2-U6 helix. The role of U4 seems to stabilize the complex U5-U6 before its binding to the complex U1-U2-intron, and U4 is supposed to be released from the spliceosome after U5-U6 binding. U5 plays the role of identifying exon 1 by means of structural relations, whereas the other snRNA/mRNA associations are hypothesized to depend on nucleotide consensus sequences. See text for further details. Modified from Madhani and Guthrie (1994).

Formation of a branched molecule (Fig. 4 and Fig. 5), the lariat intermediate (Madhani and Guthrie, 1994; Moore and Sharp, 1993). During the second cleavage–ligation step, the 3' hydroxyl end of the 5' exon attacks the phosphate at the 3' splice site. This results in the ligation of the two exons and the release of the intron in lariat form (Madhani and Guthrie, 1994). Splicing occurs in a large and dynamic ribonucleoprotein complex, the spliceosome. Five small nuclear RNAs (U1, U2, U4, U5 and U6 snRNAs) constitute the key components of this machine. Coupled to hnRNPs, these snRNAs assemble onto the pre-mRNA substrate (Fig. 4) in an ordered, step-wise fashion, requiring the hydrolysis of ATP in many of the steps (Madhani and Guthrie, 1994).

Initially, U1 and U2 bind to the intron at 5' splice site and the branchpoint region, respectively (Fig. 4(A)). The 5' splice site is characterized by a consensus sequence GUAGUG in the case of yeast and GURAGU (R indicates purine) in the case of mammals, and the branchpoint motif is UACUACA and YNYURAC (Y denotes pyrimidine), for yeast and mammals respectively. The 3' splice motif (YAG) is identical in mammals and in yeast. In the sequence, the complex formed by the assembly of U4, U5 and U6 binds to the initial complex U1–U2 [Fig. 4(B)]. The U5 binds to the 3' exon and it was proposed that their interactions are not base-specific but are dependent on how U1 and U6 locate over the exon 1 (Madhani and Guthrie, 1994). The U6 also binds to the 5' splice site, and because of this it is assumed that it displaces U1 from its initial position [Fig. 4(B)]. The release of U4 from U6 prior to the first nucleolytic event is required in order to form presumptive active site structures, which includes the U2–U6 helix (Fig. 5). This association is important in maintaining the 3' end of exon 1 near the 5' site of exon 2 to allow their fusion into the processed mRNA. The excised intron remains in the nucleus, whereas the mRNA is exported. It has been proposed recently that some of the untranslated pre-mRNAs may function as
gene regulators, which may, for instance, suppress complex interaction between U2 and U6. Reproduced by the U2 binding to the branch consensus sequence and by a retained by means of the coupling of U6 to the 5' splice site; point brings exon 1 close to exon 2. This folding is main-

Fig. 5. The mRNA folding around the branchpoint region UACUACA. The folding of the intron around its branch- point brings exon 1 close to exon 2. This folding is maintained by means of the coupling of U6 to the 5' splice site; the U2 binding to the branch consensus sequence and by a complex interaction between U2 and U6. Reproduced by permission from Madhani and Guthrie (1994).

gene regulators, which may, for instance, suppress tumor formation (Rastinejad et al., 1993).

Splicing is a very important mechanism in generation of protein variability (see e.g. Ichtchenko et al., 1995; Larsson et al., 1995; Ullrich et al., 1995), because different exons and introns may be excised in different moments, given the opportunity for different isoforms of proteins to be produced under different cellular conditions. A remarkable example of such a capacity is the genetic encoding of neurexins. Neurexins are polymorphic cell surface proteins expressed in neurons, and three genes encoding neurexins are known (Ushkaryov et al., 1993). Each neurexin gene has two independent promoters and generates two classes of mRNA. The longer mRNA encode α-neurexins and the shorter mRNAs encode β-neurexins (Ichtchenko et al., 1995). This results in the synthesis of six principal neurexin isoforms, called neurexins 1α-11β (Ushkaryov et al., 1993, 1994). Groups of neurons exhibit different combinations of neurexins, resulting in a combinatorial specificity of neurexin expression that is generated by their cell type-specific transcription from six promoters in three genes and a conserved pattern of extensive alternative splicing. The α-neurexins share five canonical sites of alternative splicing, the last two of which also are present in β-neurexins. At most of these splice sites, two variants are observed: negative and positive inserts. However, some of the splice sites may have more than 10 variants. As a result, the total number of neurexins in brain probably exceeds 2000 forms (Ullrich et al., 1995). It is proposed (Ichtchenko et al., 1995) that different splice versions of neurexins have different ligands and support a role for neurexins in neuronal specificity.

Introns seem, however, to play other important roles in mRNA processing, such as guiding nucleotide exchange at the nearby exons. Double-stranded RNA adenosine deaminase (dsRAD) acts on regions of double-stranded RNA to catalyze the conversion of adenosine to inosine, which is read subsequently as guanosine. This alters the information encoded by the RNA and thus the protein product of a gene (Hebert, 1996). This mechanism is proposed (Hebert, 1996) to explain the substitution of arginine (encoded by the codon CGG) for a glutamine (encoded by CAG) in the protein of the glutamate receptor GluR2, altering its calcium conductance.

The precise location of dsRAD action is provided by an adjacent intron (Fig. 6). First, the intron contains a sequence that pairs with 17 bp of the exon, identifying the arginine to be modified. While this pairing is necessary for editing to occur, it is not sufficient. A second intron sequence that forms an inverted repeat also is required. This inverted repeat probably increases the efficiency of editing by increasing the total length of dsRNA. It is proposed that dsRNA binds to a Z-DNA zone of the transcripted gene and to the intron in order to localize the arginine to be exchanged (Fig. 6). Examination of other glutamate receptor subtypes has shown that these, too, are edited; and many editing sites within their mRNAs often are observed (Kohler et al., 1993; Higuchi et al., 1993; Lomeli et al., 1994). At the moment, there is no consensus as to whether dsRAD or a family of related enzymes edit these RNA, too (Hebert, 1996).

The translated mRNA must be transported to the cytoplasm in order to be translated into proteins. Nucleocytoplasmic transport is mediated by nuclear pore complexes (Fig. 2) and by a protein nuclear-exporting complex (NEC) that involves both a carrier and a protein translocation motor (Davis, 1995; Gerace, 1995; Gorlich and Mattaj, 1995). The RNA substrates for nuclear export probably are all transported as RNA–protein (RNP) complexes. Some proteins, recently characterized as shuttling between the nucleus and cytoplasm, were proposed to have the potential to bear nuclear-exporting signals (NES). Among these shuttling proteins are some RNA-binding proteins, such as the hnRNP A1 protein and the HIV-1Rev protein (Gerace, 1995; Gorlich and Mattaj, 1995). The cAMP-dependent protein kinase PKA has been associated recently to a fast nucleocytoplasmic transportation (Gerace, 1995).

Fig. 6. Nucleotide conversion editing. Double-stranded RNA adenosine deaminase (dsRAD) binds to the Z-DNA of the transcripted gene and to the intron of the produced mRNA in order to promote the replacement of adenine (A) by guanine (G), which may, in the case of the mRNA coding the protein of glutamate receptor GluR2, change its calcium conductance. Modified from Hebert (1996).
4. PROTEIN PRODUCTION, EDITING AND DESTRUCTION

Protein synthesis is an integral part of the pathway of gene expression and the last phase of any signal transduction pathway. Protein production is divided into three steps: initiation, elongation and termination. The reactions in each of these phases are promoted by soluble protein factors which transiently interact with the ribosome, mRNA and aminoacyl-tRNAs (Carter, 1993; Hershey, 1991; Noller, 1991). Cytoplasmic mRNAs are found in two distinctly functional states: those actively being translated by ribosomes, in polysomes; and those that are not active, in mRNP particles. A substantial amount of total cytoplasmic mRNA is found as free mRNP in a wide variety of cells. It is proposed that free mRNPs are repressed by some of their bound proteins and unknown factors are required to bind the first ribosome to an mRNP to begin the formation of a polysome (Hershey, 1991). This phase is called mobilization and currently is poorly understood.

During the initiation phase, two important tasks are achieved: (a) an mRNA is selected from among many available candidates for translation by the initiating ribosome; and (b) the ribosome identifies the initiator codon and begins translation in the appropriate frame (Hershey, 1991; Noller, 1991). The various binding reactions are promoted by at least 10 initiation factors (eIFs) and involve four major steps (Hershey, 1991): (1) ribosome dissociation into 40S and 60S subunits; (2) methionyl-tRNA (Met-tRNA) binding to the 40S ribosomal subunit to form a 40S pre-initiation complex [Fig. 7(I)]; (3) mRNA binding to the 40S pre-initiation complex to form a 40S initiation complex [Fig. 7(II)]; and (4) junction of the 40S initiation complex with the 60S subunit to form an 80S initiation complex [Fig. 7(III)].

Two initiation factors, eIF-1A and eIF-3a, bind to the 40S subunit to dissociate it from the 60S component; while another factor, eIF-3A, binds to the dissociated 60S subunit and prevents it from associating again to the 40S subunit to form the ribosome. The binding of the initiation Met-tRNA to the 40S ribosomal subunit is a step common to the translation of all mRNAs. The initiation factor eIF-2, in a binary complex with GTP, probably is required to bind to Met-tRNA and to activate the pre-initiation complex formed by the 40S subunit and eIF-1A (Hershey, 1991). In general, this activated complex binds to the 5'-terminus of the mRNA, then scans linearly down the mRNA until it recognizes the in-

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![Fig. 7. mRNA Translation](image-url)

M. mRNA translation is processed by ribosome found in the cytoplasm or attached to the endoplasmic reticulum membrane. The process may be divided into the following phases: (a) initiation: characterized by the binding of methionyl-tRNA to the 40S component of the ribosome (I); (b) attachment of the ribosome to the mRNA (II) and its positioning at the initial codon (III); (c) elongation: the protein is synthesized by addition of its amino acids according to the codon sequence read by the ribosome (IV, V and VI), and finally (d) termination: when the ribosome reach the terminal codon and may initiate another translation cycle moving to the initiation site again. Proteins synthesized by reticulum ribosome are transported into the endoplasmic reticulum for further processing, and then packed into vesicles to be delivered at specific cell locations. Proteins produced in the cytoplasm are transported by kinesins to cellular compartments addressed by amino acids labels in the protein itself. See text for further details.
The Brain as a Symbol-processing Machine

...for controlling protein synthesis. It impedes the guanine nucleotide exchange reaction that enables the factor to recycle and promote multiple rounds of initiation. Another alternative mechanism for repressing translation is to sequester RNA into translationally silent mRNPs particles (Curtis et al., 1996). Most mammalian mRNAs are polyadenylated soon after transcription in the nucleus, and carry 200–2500 adenylate residues at their 3’-termini as they are transported into the cytoplasm. The poly(A) tails are metabolized further in the cytoplasm, where in general they are shortened gradually, to about 50–70 residues. It seems that poly(A) and poly(A) binding protein are involved in establishing the distribution of mRNA between mRNPs and polysomes rather than in the initiation rate on polysomes (Curtis et al., 1996; Hershey, 1991).

Other mechanisms for mRNP mobilization are proposed, like e.g. the ferritin control (Curtis et al., 1996; Hershey, 1991). Ferritins are intracellular proteins that bind and store iron molecule. Ferritin mRNA is repressed in iron-deficient cells. It was shown that a conserved 28-nucleotide region in the 5’ UTR of all ferritin mRNAs is necessary for iron regulation. The sequence, called the iron-responsive element (IRE), may bind to a ferritin repressor protein (FRP). Because of this, it was proposed that FRP inhibits the mRNA translation in iron deficient cells. Translation of many mRNAs now is considered to be regulated by a similar regulatory protein paradigm (Curtis et al., 1996).

The rules for gene decoding may be altered temporarily through the action of specific signals built into the mRNA sequences (Gesteland and Atkins, 1996). Many aspects of decoding are subject to redefinition. The meaning of codons can be redefined either as standard amino acids or as the seco-cysteine, the so-called twenty-first amino acid. Recoding can reprogram the meaning of stopcodons either as glutamine at UAG or as tryptophan or seco-cysteine at UGA. The competing reaction to redefinition is termination, which itself is context-dependent. The first base 3’ to the stop codon has a large effect on the efficiency of termination with U>A>G>C in E. coli or A = G> >C = U in mammals (Gesteland and Atkins, 1996). Frameshifting at a particular site allows expression of a protein from an mRNA with overlapping open reading frames, often giving two protein products from one mRNA. Frameshifting may be controlled by the products of the very same reading, such that the concentration increase of protein1 may shift reading to protein2 or vice versa (Gesteland and Atkins, 1996). Non-coding information that disrupts genes is commonly dealt with RNA splicing. The above discoveries revealed that the process of reading out genetic code is itself subject to programmed changes that allow for another level of diversity of gene expression.

A continuing question in protein synthesis refers to the unraveling of those cellular processes that use one-dimensional information in the gene about the...
amino acid sequences of proteins, to produce their three-dimensional structures that give proteins their biological properties. The detailed mechanism of polypeptide chain systems is well established, but it remains to "crack the second half" of the genetic code", which ensures that these chains attain their conformations (Ellis and van der Vies, 1991). It was proposed firstly that each polypeptide chain interacts with itself to assume a folded conformation of lower free energy. This should be a spontaneous process, which requires neither further input of energy nor any steric information intrinsically to the polypeptide itself. However, self-assembly does not provide a full warranty against incorrect folding. Also, protein transport through channels requires, in most instances, the proteins to be unfolded before entering the channel and to be refolded after emerging from this same pore (Davis, 1995; Ellis and van der Vies, 1991; Gorlich and Mattaj, 1995). Finally, it was shown that receptors and other signal transduction molecules have to undergo specific functional conformational changes to promote the actions they are supposed to exercise (e.g. Boehn et al., 1995).

Molecular chaperones are defined as proteins that mediate correct assembly of other polypeptides (Ellis and van der Vies, 1991) and assist folding and unfolding of proteins in many cellular processes (Gerace, 1995; Gorlich and Mattaj, 1995; Weissman et al., 1995; Schatz and Dobberstein, 1995). Interesting enough is the fact that at least some chaperones share a common architecture with proteosome, a proteolic complex in charge of rapidly hydrolyzing marked cytosolic proteins (Weissman et al., 1995). Most proteins in eukaryotic cells are degraded by a soluble, ATP-dependent pathway present in both the nucleus and cytosol. Before proteolysis, proteins usually first are conjugated covalently to multiple molecules of the polypeptide ubiquitin (Goldberg, 1995). This modification marks them as having access to the 19S component of the proteosome. From this component, the marked protein moves to internal ring of the 20S component, where it is destroyed. The 19S component has a small internal ring which prevents non-targeted proteins from entering the proteosome. The opening of the 19S ring is an ATP-dependent process triggered by the binding of ubiquitin to its 19S receptor. The GroEL chaperone has an architecture similar to that of the proteosome, the difference being that the rings of the external components are large enough to allow the protein to move in (unfolded) and out (folded). The internal ring is assumed to be the folding template (Weissman et al., 1995). Chaperones may be considered to be molecules that encode the protein folding rules.

The fate of a protein is dependent mainly on the location of its synthesis. Cytosolic-produced proteins are moved to the nucleus or some other places of the cell, whereas proteins produced by ribosomes associated to the endoplasmic reticulum (ER) are, in general, either constituents of the membranes of exporting vesicles or the contents of such exportation. The Golgi complex is engaged in the biosynthesis of glycoproteins and proteoglycans. It receives its substrates for glycosylation from the ER, transports its raw materials (monosaccharide precursors) in from the cytosol, and distributes its completed protein, lipid and polysaccharide products to a variety of destinations using vesicles as carriers. En route through the Golgi complex, newly synthesized glycoproteins are subjected to a series of post-translational modifications, most notably the ordered remodeling of their N-linked oligosaccharide side chains and biosynthesis of O-linked glycans (Mellman and Simons, 1992).

5. TRANSPORTATION

A protein's function depends critically on its correct subcellular location. Cells therefore have developed elaborate systems for maintaining membrane-limited compartments endowed with specific proteins. Roughly one-third of a cell's protein is composed of membrane proteins and many soluble proteins must travel across one or two membranes to reach their final location, either outside the cell or within an intracellular compartment. According to McAdams and Shapiro (1995), a genetic network is characterized by both a set of genes encoding a family of proteins and set of signal pathways, relating the place where these proteins are produced to the site of their actions. This site-specific biochemical addressing permits many genetic systems to operate in parallel within the same small intracellular volume, without overloading the cell with the complexity of the procedures used in the laboratories to identify the results of such chemical processing. Proteins therefore must be moved from the place where they are produced or activated to the site where they exercise their action (Bennett and Scheller, 1994; De Camilli et al., 1995; Gorlich and Mattaj, 1995; Mallababrenna and Malhorta, 1995; Mellman and Simons, 1992; Schatz and Dobberstein, 1995; Schekman and Orci, 1995; Vallee and Sheetz, 1995; Walker and Sheetz, 1993).

Another way in which proteins can be targeted to discrete subcellular locations is to localize their mRNAs (Johnston, 1996). In principle, localized protein synthesis would seem to be a very efficient way to target proteins to the correct sites, as presumably more energy is need to localize many protein molecules than a single mRNA, which can be translated many times. However, it must be kept in mind that mRNA addressing to the correct subcellular location has also an informational cost. It has been proposed that cis-acting sequences in the 3' UTR may signal these subcellular locations and a specialized transportation system may deliver the mRNA to the target locations (Johnston, 1996).

Intracellular transportation is done by processes whose complexity ranges from: (a) transportation through pore and channels, called here channel protein transport (CPT), which (1) requires the presence of the receptor selecting the cargo, (2) a membrane channel or pore through which the cargo is moved and (3) motor protein in charge of pushing or pulling the cargo; and (b) vesicle transportation, called here vesicular protein transport (VPT), requiring (1) proteins to be loaded into a vesicle which is (2) moved by means of kinesins or kinesin-like mol-
ecules within (3) pathways defined by microtubule (MT) systems. Another attractive hypothesis discussed here is (c) a calcium-guided movement (CGM) of proteins supported by (1) an oriented calcium release to (2) activate motor proteins or kinesins (3) distributed along MTs.

Kinesins are proteins which function as molecular motors in many cellular processes. They are composed by a motor domain, of about 350 amino acids in length, which hydrolyzes adenosine triphosphate; a head and an α-helical coil, with the coiled tail linking the head to the motor domain (Vallee and Sheetz, 1995). The kinesin tail links the motor domain to the structure to be carried and is responsible for regulating the motor activity. Dyneins are another type of motor protein.

Channel protein transport is used to move proteins from the cytoplasm into the other cellular compartments, such as the nucleus, ER, mitochondria, etc. and vice versa. Transportation from and into the nucleus is carried out through the nuclear pore complexes (NPCs). The NPCs are estimated to contain roughly 100 different polypeptides (Davis, 1995; Gorlich and Mattaj, 1995) and constitute a passive diffusion channel about 9 nm in diameter. Small proteins, such as cytochrome c, can diffuse freely through the pore, but proteins above the size limit for passive diffusion can enter the nucleus only in an active way. However, even small nuclear proteins, such as histones, enter the nucleus actively rather than by diffusion. Transport of proteins and RNPs across NPC generally is selective and signal-dependent (Davis, 1995; Gorlich and Mattaj, 1995; Osborne and Silva, 1993).

Nuclear localization sequences (NLSs in Fig. 8) generally are characterized by one or more clusters of basic amino acids, and are used to tag proteins for import, export or shuttling through NPCs. For instance, the α subunit of importin is supposed to bind to the protein NLS in the first stage of its nuclear importation processes. Importin is the heterodimer in charge of directing the protein to NPC, where it docks via its β subunit. Before proteins may be transported through NPC, they may be at least partially unfolded with the aid of chaperones. The energy to drive the protein throughout NPC is provided by the GTP hydrolysis. The RNP is the main nucleus product export, and mRNA must bind to proteins to form RNPs in order to be exported. The RNPs must bind to molecules recognizing export-signaling sequences and docking to NPCs, in order to be exported actively. Small nuclear RNAs are exported rapidly after transcription, to combine with proteins in the cytoplasm and be imported again as snRNPs.

Protein transportation across the reticulum membrane may occur co- and post-translationally. In this latter condition, the protein (Schatz and Dobberstein, 1995) must (1) be unfolded with the help of a chaperone or similar factors; (2) interact with a membrane receptor by means of a signaling sequence; and (3) be translocated through a channel with the help of a peripheral protein translocation motor (Fig. 7). Co-translation translocation requires the nascent protein to bind to a complex (called

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**Fig. 8.** Nuclear transport. Transportation from and into the nucleus involves the following major steps: (a) recognition of cargo signaling sequences (NLS) by special molecules (e.g., importin); (b) binding of the cargo-recognizer to the nuclear pore complex (NPC), and (c) cargo translocation through NPC promoted by the energy obtained from nucleotide hydrolysis (e.g. GTP hydrolysis induced by Ran). See text for further details.
Fig. 9. Calcium guided movement. Ca$^{2+}$ intracellular waves may propagate from the cellular membrane to defined locations in the cytosol, if extracellular Ca$^{2+}$ enters the cell via membrane channels and activates ryanodine receptors in the sarcoplasmic reticulum positioned along the required pathway. The same type of wave may be produced if inositol triphosphate (IP$_3$) activates the corresponding receptor in the endoplasmic reticulum. The elevation of the intracellular Ca$^{2+}$, promoted by Ca$^{2+}$ release from its intracellular pools, may activate calmodulin or another Ca$^{2+}$ binding protein to modulate the activity of kinesins. The organized activation of the kinesins along the pathways defined by microtubules (MtS) may efficiently transport proteins and other types of cargo to defined locations inside the cell.
to move other proteins (e.g. those involved in signal transduction pathways) to defined locations in the cytosol (e.g. toward the nucleus; Fig. 9). Such a molecule's CGM may play an important role in defining the functional pathways associated to many signal transduction-controlled processes.

Eukaryotic cells have an elaborate network of organelles, many of which are in constant and bidirectional communication through a flow of small transport vesicles. For each organelle, a specific mechanism exists to capture and package certain proteins and lipids that are destined for transport to a receiving compartment. In return, the receiving compartment accepts proteins that are meant to remain, or to be passed to another station, and then retrieves for recycling other proteins that belong in the donor organelle (Schekman and Orci, 1995). Synaptic vesicles are particular and important example of such VPT process. The integral membrane components of the synaptic vesicle are synthesized in the cell body and initially follow a secretory pathway, i.e. insertion into the membrane of the ER followed by transport through the Golgi complex to the trans-Golgi network (TGN). It is now widely accepted that vesicles budding from ER and TGN are promoted by cytoplasmic coat proteins (Mallabiabarrena and Malhorta, 1995; Rothman and Wieland, 1996; Schekman and Orci, 1995). Vesicle formation involves a complex process of recognizing and packaging the cargo, which requires the participation of many proteins which may or may not be part of the co-atomer, i.e. of the minimal subunit forming the coat responsible for the vesicle budding (Schekman and Orci, 1995). The initial site of synaptic vesicle formation remains unclear (Bennett and Scheller, 1994; Calakos and Scheller, 1996). One highly probable hypothesis is that the immature synaptic vesicle forms directly from TGN; it is transported to the terminal endings, where they mature and may be recycled in the case of the fast-released transmitters (FRTs) (Bennett and Scheller, 1994; Kuno, 1995). It is assumed (Calakos and Scheller, 1996) that the membrane of the synaptic vesicle contains proteins in charge of (Fig. 10): (a) orienting its traffic toward the terminal endings, as in the case of Rab3; (b) importing the transmitter and other molecules with the aid of a proton pump; (c) anchoring the vesicle at the presynaptic site, and (d) docking the vesicle to the presynaptic membrane to release the transmitter.

Substantial evidence indicates that kinesin is the motor for a number of plus end-directed organelle transport processes (anterograde movement); whereas dyneins are proposed as the motor for minus end-directed transport (retrograde movement) (Bennett and Scheller, 1994; Vallee and Sheetz, 1995; Walker and Sheetz, 1993). On one side, the motor protein must bind to the associated MT (Fig. 10) and on the other side, to the vesicle to be moved. It is assumed that Rab3 is the vesicle membrane protein involved in vesicle transportation and GTP is the nucleotide used to furnish the energy to move the vesicle. Nucleotide binding to the complex MT-kinesin in the presence of Mg is associated with the release of kinesin from the MT, and the hydrolysis of the nucleotide. After or during hydrolysis of the nucleotide, the kinesin rebinds at another site on the MT and is thought to undergo a conformational change (the power stroke) that produces and increment of

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Fig. 10. Vesicle transport. The synaptic vesicle is transported from the cell body to the presynaptic terminal by means of a microtubule motor systems. Kinesin is assumed to be the motor protein in charge of moving the vesicle. Rab3-GTP is considered to be the vesicle protein bound by kinesin and donating the nucleotide which furnishes the required energy. Other membrane proteins are involved with filling the vesicle, anchoring the vesicle at the terminal ending, and docking the vesicle at the presynaptic membrane to release the transmitter. See text for further details. Modified from Bennett and Scheller (1994).
movement (the step). Rebind to the MT stimulates NDP release, and the active site becomes available for Mg-NTP and repetition of the cycle (Walker and Sheetz, 1993).

The mechanism used by synaptic vesicles to take up and store small neurotransmitter molecules is dependent on the electrochemical gradient generated by the a proton pump (Fig. 10), which consists of both peripheral cytoplasmically oriented subunits required for ATP binding and hydrolysis and integral membrane subunits responsible for proton translocation (Bennett and Scheller, 1994; Calakos and Scheller, 1996). The translocation of a proton into the synaptic vesicle generates an electrochemical (pH and potential) gradient that is used to drive the neurotransmitter. Carriers actively move the transmitter into the vesicle. The structure of such carriers currently are poorly understood. The stage in the synaptic vesicle lifecycle at which neurotransmitter uptake occurs has not been perfectly determined. It is likely that it may begin at early endosomal stages.

There are three types of synaptic vesicles that are distinguished morphologically (Calakos and Scheller, 1996): small synaptic vesicles (SSV), catecholamine-containing small dense-core vesicles (SDCVs), and neuropeptide-containing large dense-core vesicles (LDCVs). The SSVs contain the classical neurotransmitters (acetylcholine, glycine, GABA, glutamate, etc.) and when visualized by electron microscopy are electron lucent with a uniform diameter of 50 nm. Dense-core vesicles (DCV), so named by their high electron density under electron microscopy, have larger diameters (80–200 nm), with LDCVs being larger than SDCVs. Biogeneses of SSVs and DCVs significantly differ. The later are loaded with neuropeptides at TGN in the cell body and must be replenished by synthesis of new vesicles at this site. Although membrane proteins of SSVs are synthesized in the cell body, SSVs are loaded with neurotransmitters in the nerve terminal and are recycled locally.

Within the presynaptic nerve terminal, SSVs are clustered near the active zone, the region of the presynaptic plasma membrane located immediately opposite to the postsynaptic cell, where vesicle fusion and neurotransmitter release occurs (Bennett and Scheller, 1994; Burns and Augustine, 1995; Calakos and Scheller, 1996; Edwards, 1995; John and Sudhof, 1994; Kandel, 1992; Kandel and Hawkins, 1992; Kuno, 1995; Matthews, 1996; Verbage et al., 1994). While some of these vesicles are found in close apposition to the presynaptic membrane, the majority are localized a short distance away in the nerve-terminal cytoplasm.
[Fig. 11(A)]. This type of observation and data from studies on neurotransmitter release have led to the proposal that at least two distinct pools of vesicle exist: a readily releasable pool adjacent to the release docking sites, and a reserve pool anchored to the cytoplasmic cytoskeleton (Bennett and Scheller, 1994; Burns and Augustine, 1995; Calakos and Scheller, 1996; Kandel, 1992; Kuno, 1995). Recent studies of SSV recycling [Fig. 11(A)] have demonstrated that newly recycled vesicles are functionally equivalent to the reserve pool and that the entire pool of vesicle can be turned over rapidly with moderate stimulation (Bennett and Scheller, 1994).

The synapsin family (Fig. 10) is proposed as the proteins which anchor the reserve pool vesicles to the cytoskeleton. Synapsins are found in the vesicle membranes associated to calmodulin-dependent protein kinase II (CamK II). It is proposed (Bennett and Scheller, 1994; Calakos and Scheller, 1996; Kuno, 1995) that, upon nerve stimulation, an influx of calcium results in CamK II-mediated phosphorylation of synapsin I, causing its dissociation from the synaptic vesicles and actin filament, thereby allowing the vesicle to join the readily releasable pool [Fig. 11(A)].

Many proteins implicated in synaptic vesicle docking and fusion are common to SSVs and DCVs. However, differences in docking and the kinetics of release distinguish SSVs from DCVs. For example, in electron microscopic studies, DCVs are not seen docked at the active zone, as are SSVs. The secretion of the later therefore is specialized, owing to the accumulation of vesicles in the docked state. The ability of SSVs to accumulate in a 'release-ready' docked state may underlie the rapid exocytotic response of SSVs to a secretion stimulus. They release their contents within 200 msec after calcium influx, whereas DCVs release orders of magnitude more slowly (50 msec). The docking of the vesicle at the presynaptic membrane and the transmitter release are dependent on the calcium influx triggered by the incoming spike. Analysis of the time course of release has demonstrated that the delay between the influx of calcium into the nerve terminal and the initiation of the transmitter release may be as short as 200 msec in the case of FRTs, in contrast to the slow-released transmitter (SRT) dynamics of the neuropeptide release. This fast speed suggests that much of the machinery required for FRT vesicle fusion is preassembled or primed at release sites in contrast to the slow transport of SRT vesicles to the docking sites (Kandel, 1992). Calcium sensors involved in regulating vesicle fusion bind calcium rapidly and with low affinity. It is suggested (Bennett and Scheller, 1994; Verhage et al., 1994) that high calcium concentrations are locally required and that these high concentrations are available near the openings of calcium channel clusters. The low affinity of the sensors associated to the vesicle fusion machinery explains why calcium from these sites may be donated easily to other calcium-binding proteins (e.g. calmodulin; Verhage et al., 1994) and, in the sequence, may control other steps of the vesicle lifecycle; for instance, the vesicle's release from the reserve pool.

A large number of proteins are likely to be involved in regulating the process of synaptic vesicle docking and fusion. It is proposed (Bennett and Scheller, 1994; Calakos and Scheller, 1996; Kandel, 1992; Kuno, 1995; Matthews, 1996) that VAMP (or vesicle-associated membrane protein) and synaptotagmin from the membrane vesicle form a complex with SNAP-25 (25 kDa synaptosomal-associated protein) and syntaxin from the presynaptic membrane, in the first step of the docking process (Fig. 11). The role of synaptotagmin may be to act as a negative regulator of subsequent steps that would, in its absence, proceed rapidly toward fusion. The potential competition between α-SNAP and synaptotagmin for a common binding to syntaxin could explain this negative regulation. Also, it may be hypothesized that calcium influx could facilitate the action of α-SNAP, since synaptotagmin is proposed as a candidate for calcium sensor in the transmitter release process. Once synaptotagmin is displaced by α-SNAP, NSF (N-ethylmaleimide-sensitive factor) can bind and hydrolyze ATP to deliver the energy for membrane fusion.

After exocytosis, the components of the synaptic vesicle membrane are recycled efficiently. It has been suggested that this recycling occurs by the reversal of the exocytic process. However, several lines of evidence suggest (Bennett and Scheller, 1994) that recycling of the synaptic vesicle, at least partially, proceeds by an endocytic mechanism similar to that for vesicle biogenesis. After an indeterminate number of rounds of exo/endocytic cycling, the components of the synaptic vesicle must be turned over, but little is known about this process. Also, it may be the case that the vesicle lifecycle is different for FRT and SRT systems. Local recycling of FRT would be necessary to ensure transmitter availability in high rate message-exchanging systems, in contrast to a stronger dependence of SRT on new synthesis of neuropeptide at the cell body.

Some interesting transmitter-release properties may arise from the fact that low-affinity calcium sensors are involved in vesicle fusion activation, and other high-affinity proteins exist at the presynaptic terminals in charge of controlling other steps of the vesicle lifecycle. It may be the case that high spike frequency is required if a small number of calcium channels exist associated to the docking sites of a given transmitter vesicle, to ensure the high local calcium concentration required to guarantee the vesicle fusion in the presence of an unfavorable competition between fusion sensors and synaptotagmin by other calcium-binding proteins. On the contrary, low spike firing would guarantee the transmitter release at docking sites surrounded by a large amount of calcium channels, even in the presence of high-affinity Ca2+-binding proteins. This could be an efficient way to control the release of different types of transmitter at the same presynaptic terminal. The adequate vesicle addressing by means of VAMP and syntaxin isoforms (Bennett and Scheller, 1994) could distribute different transmitters to docking sites in different calcium channel neighborhoods, such that different spike firing intervals should be required to trigger the release of the transmitter in these distinct neighborhoods. Besides this, calcium
concentrations required to release the contents of SSVs are greater than that necessary to open DVCs (Verhage et al., 1994).

6. SIGNAL TRANSDUCTION PATHWAYS

Changes in cell behavior induced by extracellular signaling molecules (ligands) such as growth factors, cytokines, neuregulators, certain transmitters (e.g. glutamate), etc. require execution of a complex program of transcriptional events, which begins with the binding of the ligand to membrane receptors, followed by the activation of messengers in charge of controlling DNA transcription that results into the synthesis of specified proteins. While the route followed by the intracellular signal from the cell membrane to its transcription factor targets can be traced in an increasing number of cases, how the specificity of the transcriptional response of the cell to different stimuli is determined is much less clear (Hill and Treisman, 1995).

The earliest transduction steps that were elucidated involved massive release of small molecule 'second messengers', originally cAMP, that flooded a cell with information. With the understanding that proteins such as tyrosine kinases and Ras relatives are signal transducers, came the realization that many signaling pathways are more precise, sending controlled and probably weak signals to specific targets. These intracellular signals often are maintained in macromolecular form, rather than being passed to small molecules (Cohen et al., 1995). Signaling proteins are not acting in the classic fashion of enzymes that are designed to modify large number of substrate molecules. These signal transducers, even if they catalyze an event such as phosphorylation, generally affect a small number of target molecules and often have separated their catalytic function from their binding regions, which can bring substrates to the catalytic centers, link the signal transducers to upstream proteins, and localize protein complexes to particular cellular subregions (Cohen et al., 1995). The binding domains are often modular ones, constructed with a common core recognition ability coupled to a fine specificity control. They modulate the interaction of proteins with other proteins and, therefore, determine the paths of signal transduction systems. They are generally controlled also, so that the aggregates they form are transient pathways, forming only when the signal is being transmitted and then desegregating when the signal has passed. The signal transduction protein must be highly integrated, with all of the elements working together to send just the appropriate quanta of signal for the specific need (Cohen et al., 1995).

Two important signal transduction pathways may be recognized, taking into consideration the signaling molecule immediately activated by the ligand binding to the receptor: the G-protein and tyrosine kinase pathways. In the first case, the ligand/receptor binding triggers the GTP coupling to a G-protein, which may in this activated state exercise a catalytic action upon other molecules (e.g. Carter-Su et al., 1996; Kaziro et al., 1991; Neer, 1995; Neer and Smith, 1996). The activation of a protein-tyrosine kinase receptor (PTKR) results in the phosphorylation of tyrosine residues of protein-tyrosine kinases (e.g. Bhat, 1995; Carter-Su et al., 1996; Ihle and Kerr, 1995; Marshal, 1995; Schindler and Darnell, 1995). Both G-proteins and PTks activate other signaling molecules, among them protein kinase A (PKA) and C (PKA, and phospholipase C (PLC) which is a key element in the phospholipid signaling pathways (Carter-Su et al., 1996; Clapham, 1995; Divecha and Irvine, 1995). In this way, both G-proteins and PTks may regulate Ca$^{2+}$ release from endoplasmic reticulum by means of InsP$_3$ (Clapham, 1995; Kuno, 1995). On the other hand, Ca$^{2+}$ entering the cell through voltage-dependent or glutamate-controlled channels may activate PTks and Ras and other signaling molecules using calmodulin (Ghosh and Greenberg, 1995). These findings point to an intricate relationship among distinct signal transduction pathways which, together with the ambiguity of their chemical transactions, support a very complex message exchange within the cell. Both the G-protein and PTk signal transduction pathways and calmodulin signaling are discussed briefly below.

6.1. G-Protein Pathways

The receptors for many hormones, nucleotides, odorants and light span the membrane seven times and activate a group of GTP binding proteins (Fig. 12), called G-proteins, that regulate a variety of enzymes and ion channels, which ultimately lead to the cellular response (Beavo, 1995; Kaziro et al., 1991; Kuno, 1995; Neer, 1995; Sebastião and Ribeiro, 1996; Wickman and Clapham, 1995). Molecular cloning has revealed the primary sequence of more than 300 members of the superfamily of G-protein receptors (Karoor et al., 1996). Every eukaryotic cell contains receptors for many kinds of chemical and/or physical signals, many different types of G-proteins, and many effectors, each with multiple subtypes. A cell only can respond to those signals for which it has a receptor, but the specificity with which the receptor interacts with G-proteins defines the range of responses that a cell is able to make (Neer, 1995). Sometimes, the response is highly specific because the receptor interacts with only one type of G-protein, which in turn activates one or a few effectors. At other times, the receptor interacts with several effectors, each of which can interact with more than one effector, such that the response would be expected to spread over several pathways. A ligand that gives a focused response in one cell may cause a pleiotypic response in another. What is still mysterious is exactly what determines specificity of the response of a cell to an extracellular stimulus. What is the grammar that controls the interpretation of signals (Neer, 1995)?

G-proteins are made up of three polypeptides: an a subunit that binds and hydrolyzes GTP, a b subunit and a g subunit [Fig. 12(1)]. The b and g subunits form a dimer that only dissociates when it is denatured and is, therefore, a functional monomer. The GDP-bound a subunit associates with the bg subunit to form an inactive heterotrimer that binds to the receptor (Kaziro et al., 1991; Kuno, 1995;
Fig. 12. G-protein transduction pathways. G-proteins are associated to specific receptors by means of a binding region of the α subunit (I). Ligand binding to the G-protein receptors promotes the GTP/GDP (II) exchange at the α subunit and the dissociation of the β and γ subunits. The active α subunit may activate (a) adenylyl cyclase to increase the cytosolic contents of cAMP; or (b) PDE which decreases the contents of cGMP; or (c) PLC which stimulates both IP3 and DAG. The augmentation of cytosolic cAMP activates PKA and DAG stimulates PKC. See text for further details.

Neer, 1995; Neer and Smith, 1996). When a physical or chemical signal stimulates the receptor, the latter changes its conformation and the GDP-liganded G-protein decreases its GDP affinity [Fig. 12(II)]. Since the concentration of GTP in cells is much higher than that of GDP, the α subunit now exchanges GTP for GDP. The activated GTP-α subunit dissociates from the receptor and the βγ subunit, until the GTP is hydrolyzed by the intrinsic GTPase of the α subunit. Once GTP is cleaved to GDP the α and βγ subunits re-associate, become inactive, and bind to the receptor. The free (active) α and βγ subunits interact with effectors to exercise their actions. It is important to note that the rate of GTP hydrolysis is the timing mechanism controlling the duration of both α and βγ subunits activation and, because of this, it is assumed to be important to determine the duration of any memory supported by such a mechanism.

Over different 20 α subunits, produced by splicing the products of 16 genes, are divided into four major classes (αs, αi, αq, and α12) according to the similarity of their amino acid sequences that range from 56 to 95% identity (Neer, 1995). With the exception of G-proteins that are found in sensory organs and a few types that are expressed predominantly in hematopoietic cells or in neural cells, most α subunits are widely expressed. Individual cells usually contain at least four or five types of α subunit (Neer, 1995). The α subunit consists of two main domains: (a) a GTPase domain that contains the GTP binding pocket and the receptor and effector binding sites; and (b) a βγ subunit, and a helical domain whose function is not clear (Kaziro et al., 1991; Neer, 1995). The first 25 amino acids of the α subunit are essential for the βγ binding. The βγ-binding surface probably includes a cysteine-containing α2 helix, because this cysteine can be chemically cross-linked to βγ (Thomas et al., 1993). The variability of the receptor-binding site explains the capacity of G-proteins to binding to a large family of receptors, and the variability of the effector domain is responsible for the multiple downstream signals activated by G-proteins.

Activated G-proteins regulate a variety of effectors, including those controlling levels of ubiquitous cytosolic messengers, such as Ca2+ and the cyclic nucleotides cAMP and cGMP. The most studied second messenger-regulated channel is the cGMP non-specific cation channel in the photoreceptor neurons. Stimulation of transducin (a G-protein) by the photactivating receptor (rhodopsin) results in increased cGMP-phosphodiesterase (PDE) activity, decreasing the cytosolic cGMP levels (Beavo, 1995; Wickman and Clapham, 1995). The cGMP-gated channels close in the absence of cGMP, reducing the Ca2+ influx and stopping neurotransmission from the photoreceptor neurons. The homologous cAMP-gated channel of olfactory receptor cells opens in response to the cAMP increase resulting from the G-protein stimulated adenylyl cyclase activity (Beavo, 1995; Berghard and Buck, 1996; Mori and Yoshihara, 1995; Wickman and Clapham, 1995). The duration of this activation is very brief, because the entry of Ca2+ activates calmodulin to increase the activity of the PDE1C to reduce the level of
cAMP (Wickman and Clapham, 1995). The adenosine A2 receptor is a G-protein receptor, whose activation by adenosine may enhance the release of several neurotransmitters. This effect is proposed to be dependent on cAMP increase due to the stimulation of adenylyl cyclase, which may reduce outward K+ currents that result in increases in inward Ca2+ currents and the augmentation of transmitter release (Sebastião and Ribeiro, 1996).

G-proteins activate adenylyl cyclase to augment the cytosolic contents of cAMP that modulates cAMP-protein kinases (Kandel and Abel, 1995; Kuno, 1995; Mochly-Rosen, 1995; Montminy et al., 1990; Moons and Cooper, 1995). For example, the G-protein activation by the ligand results in the stimulation of adenylyl cyclase to enhance the production of cAMP that activates PKA. This activated cAMP-protein may be moved toward the nucleus to phosphorylate the CREB and to control the velocity and the amount of DNA transcription (Alberini et al., 1994; Bailey and Kandel, 1995; Jessell and Kandel, 1993; Montminy et al., 1990; Yin et al., 1995). This mechanism has been implicated in some sort of long-term memory (e.g. Alberini et al., 1994; Bailey and Kandel, 1995; Jessell and Kandel, 1993). The PKA is composed of two regulatory and two catalytic subunits. There are several gene products for each of these subunits, and their combination results in multiple PKA isoforms (Mochly-Rosen, 1995). These multiple isoforms allow PKA to be enrolled by different signal transduction pathways, because they may bind to distinct effector molecules.

Recent studies indicate that specific anchoring proteins located at various sites in the cell compartmentalize the kinases to their sites of action, because inhibitors of the interactions between kinases and their anchoring proteins inhibit the functions mediated by the kinases (Mochly-Rosen, 1995). These data indicate that the location of these anchoring proteins provides some way of reducing the ambiguity of the action of kinases like PKC and PKA. The PKA anchors through its regulatory domain near its protein substrate. In this way, the binding of cAMP to PKA releases its catalytic subunit near the target to ensure a rapid phosphorylation of the substrate. The dissociated catalytic subunits may, however, translocate to new sites to phosphorylate other molecules. It must be remembered that PKA anchors to microtubules near some of its associate substrates, the microtubule-associated proteins (Mochly-Rosen, 1995). In this way, the microtubule system may be used to move the catalytic subunit and associated proteins to their final target. This is another mechanism with which specifically to address messages to defined cellular domains, and to reduce the ambiguity of the chemical transactions activated by signal transduction pathways.

Stimulation of some G-proteins often results in increased intracellular Ca2+ because both their 2 and β subunits stimulated phospholipases (PLC) to cleave phosphatidyl-trisphosphate (IP3) and diacylglycerol (DAG). The IP3 increases the cytosolic Ca2+ by opening ion channels on the surface of internal Ca2+ stores, while DAG stimulates PKC (Divcheva and Irvine, 1995; Clapham, 1995; Wickman and Clapham, 1995). In many neurons, these result in modifying the behavior of K+ channels (Kuno, 1995; Wickman and Clapham, 1995), but PKC translocates also to new subcellular sites in the plasma membrane, cytoskeletal element, nuclei, etc. (Divcheva and Irvine, 1995; Mochly-Rosen, 1995). Before stimulation, PKC is present in the cytosol, whereas its activators are hydrophobic and are present in the membrane. Stimulation of the corresponding signal transduction pathway that increases, e.g. the DAG cytosolic concentration, induces the translocation of PKC to the particulate fraction of the cell (Mochly-Rosen, 1995). The differential subcellular localization of activated PKC isozymes suggest that PKC binds to specific anchoring proteins located at various subcellular sites. Several proteins that bind PKC have been identified and include several annexins, cytoskeletal proteins and at least one nuclear protein.

The functional status of G-protein receptors is dynamic, influenced by physiological signals that can have a profound effect on the fidelity of the signal transduction from ligand to G-protein. Protein phosphorylation plays a prominent role in short-term, agonist-induced desensitization. The attenuation of signaling by proteic phosphorylation following a prior challenge with agonist is a hallmark of G-protein receptors (Karoor et al., 1996). The G-protein receptors are substrates for PKA, PKC, other specific kinases and intrinsic tyrosine kinase growth factor receptors that may be supposed to be activated by competing signal transduction pathways. What is interesting is the finding that growth factor receptors may trigger G-protein receptor phosphorylation at two specific sites that result in creation of binding sites to Grb2 and She (Karoor et al., 1996). This may indicate that interaction between different signal transduction pathways may dramatically change the semantics of the chemical transactions (language) in these pathways. Modification of gene transcription of G-protein receptors is another mechanism involved in long-term agonist-induced desensitization or hormone control of G-protein effects. Different G-protein signal transduction pathways are shown to regulate G-protein receptor gene transcription of co-existing pathways (Karoor et al., 1996), either reducing the synthesis of the receptors associated to these other pathways in a competitive manner, or to augment the production of these receptors, perhaps, in a tentative way, to maintain a fixed ratio of activity between the different signal transduction pathways. Also, a special class of proteins, called regulators of G-protein signals (RGSs), was discovered recently (e.g. Rous, 1996; Siderovski et al., 1996) to exercise a modulatory influence over the G-protein signal transduction pathways. The RGSs are proposed to bind to the z unit in specific G-proteins to attenuate the molecular signals that they usually activate (Dreuy et al., 1996; Koelle and Horvitz, 1996; Rous, 1996; Siderovski et al., 1996). Among the pathways modulated by RGSs are the pheromone mating control in Saccharomyces cerevisiae, regulation of protein exocytosis, and G-protein control of locomotion and egg-laying in C. elegans. All these findings point to the existence of mechanisms to control...
the effectiveness of the G-protein signal transduction pathways, which provides another way to keep the ambiguity of the cellular chemical transactions within boundaries.

6.2. The PTK Pathways

Cell growth, differentiation, migration, and apoptosis are in part regulated by polypeptide growth factors or cytokines (Heldin, 1995; Hessain et al., 1996; Igle and Kerr, 1995; Ip and Yancopolous, 1996; Marshall, 1995; Nagata and Golstein, 1995; Nakao et al., 1996; Naruse and Keino, 1995; Segal and Greenberg, 1996; Schindler and Darnell, 1995; Steller, 1995; Thompson, 1995), but these ligands also may have a functional role on the mature brains (e.g. Li et al., 1996). As these factors are unable to pass the hydrophobic cell membrane, they exert their effects via binding to cell surface receptors with tyrosine kinase activity. The PTKRs consist of single transmembrane domains (Fig. 13) separating the intracellular kinase domains from extracellular domains, which typically contain one or several copies of immunoglobulin-like domains, fibronectin type III-like domains, EGF-like domains, cysteine-rich domains, etc. (Heldin, 1995). Recent results have given ample evidence that such receptors often are activated by ligand-induced dimerization or oligomerization.

Several of the ligands for PTKRs are dimeric molecules, which thus contain two identical receptor-binding epitopes. These ligands form stable receptor dimers by simultaneously binding two receptors. Receptor dimerization brings the receptor kinase domains close together, favoring autophosphorylation [Fig. 13(A)], which mainly occurs by one receptor molecule phosphorylating the other in the dimer (Heldin, 1995). Autophosphorylation occurs on two principally different classes of tyrosine residues: on a conserved tyrosine residue within the kinase domain (e.g. Tyr-857 in PDGF), and at sites normally localized outside the kinase domains that serve the important function of creating docking sites for downstream signal transduction molecules containing Src homology (e.g. SH2 and SH3) domains (Cohen et al., 1995; Heldin, 1995; Marshall, 1995; Overduin et al., 1992; Sonyang et al., 1993). The SH2 domains consists of about 100 amino acid residues folded in such a way that a binding pocket for a phosphorylated tyrosine and the immediately surrounding amino acid residues is formed (Cohen et al., 1995; Sonyang et al., 1993). Of particular importance is the three–six amino acid residue C-terminal of the phosphorylated tyrosine, since different SH2 domains have different preferences for this region (Sonyang et al., 1993; Waksman et al., 1993). Several cytosolic proteins likely to be involved in signaling have been shown to contain SH2 domains. Among these proteins are

![Fig. 13. Protein tyrosine transduction pathways. Ligand binding to the protein tyrosine receptors (PTKRs) causes the receptor dimerization and autophosphorylation of the receptors kinase domain (A). This results into the activation of the Src homology and the cascade stimulation of a group of other kinases with the purpose of controlling DNA transcription cytokine receptors (B) lack the kinase domain, but their dimerization stimulates the Janus kinases (Jaks) to activate signal transducers and activators of transcription (Stats). See text for further details.](image-url)
Ras GTPase activating protein (GAP), phosphatidylinositol 3'-kinase (PIK), phospholipase C-β (PLCβ), etc. Once these proteins are phosphorylated by PTKs, they act as downstream messages to propagate to other subcellular compartments the signal generated by the ligand at the cellular membrane. The binding of a particular SH2 domain to tyrosine-phosphorylated proteins is dependent on the primary sequence around the phosphorylserine (pTyr). For instance, the sequence pTyr-Met/Va/-X-Met was found to be essential to define the binding domain of the phosphatidylinositol 3-kinase. Another important motif is p-Tyr-Glu-Glu-Ile. As a matter of fact, Sonyang et al. (1993) showed that SH2 domains may be divided into four major groups depending on the amino acid occupying the fifth position at their D/β-helix. Two other domains have been proved to be important binding sites in many signal transduction proteins: the SH3 domain and the PH domain (Cohen et al., 1995). Both the structure and the functional properties of these domains are, however, poorly understood at the moment.

The proteins encoded by ras genes serve as essential transducers of diverse physiological systems, and mutationally altered ras products represent important contributors to the neoplastic phenotype (Lowy and Willumsen, 1993; Kaziro et al., 1991). Ras proteins bind guanine nucleotides (GTP and GDP) with high affinity and possess intrinsic GTPase activity. They are encoded by three different genes: H-ras, K-ras and N-ras, which are dispersed to different chromosomes and exhibit a common structure with a 5’ non-coding exon (exon φ) and four coding exons (exons 1–4). In each gene, the corresponding exon encodes the same part of the protein. The K-ras gene encodes two p21 proteins, because it has two alternative fourth coding exons. The introns of the three genes differ widely in size and sequence (Lowy and Willumsen, 1993; Kaziro et al., 1991). The ras genes carry promoters with high GC content that lack a TATA motif. It is proposed also (Lowy and Willumsen, 1993) that expression of these genes involves the first intron as well as sequences located within 150 bp of the transcription start site. The comparison of the structure of the Ras proteins shows that they are homologous in their first 164 amino acids, but their last 25 residues are divergent, except for a cysteine (residue 186) four amino acids from the C-terminus. It is supposed that this variable region participates in mediating appropriate subcellular localization of the protein. The Ras protein is synthesized in the cytoplasm on free ribosomes as pro-p21 and has a half-life of at least 24 hr. The pro-p21 undergoes a series of post-translational modifications at its C-terminus, increasing the hydrophobicity of the protein and resulting in its association with the inner face of the plasma membrane. Ras is a GTP/GDP-binding protein whose biological activity is determined by the bound nucleotide and three sequence motifs are proposed as important for nucleotide interaction (Lowy and Willumsen, 1993). The first, GXXGXGKS (amino acids 10–17) is involved in the binding to the x- and β-phosphates, in the second, DXXG (amino acids 67–60), the aspartate binds the Mg2+ and the glycine binds the γ-phosphate when GTP is bound, and the third, NXXD (amino acids 116–119) is important for binding to the guanine ring. The residues 12 and 61 are important amino acids controlling the Ras GTPase activity that regulates GTP-binding by means of a slow GTP hydrolysis.

Ras activity is proposed to be enzymatically regulated, and the GAP and the Grb2–Sos complex are two examples of such controls (Lowy and Willumsen, 1993; Marshal, 1995). It is assumed that the activation of the PTKR activates the Grb2–Sos complex, leading to binding of GTP to Ras [Fig. 13(A)]. While GTP is bound, the activated Ras interacts with target proteins (e.g. GAP, Raf, MAPK, neurofibromin, etc.) to propagate the signal carried by the ligand (Clark and Brugge, 1995; Lowy and Willumsen, 1993; Marshal, 1995). A region near the N-terminus of GAP encodes two SH2 domains flanking a single SH3 domain, and the Ras binding to GAP is supposed to expose these domains and activates the target function of GAP (Lowy and Willumsen, 1993). Raf is a cytosolic protein kinase that is translocated to the plasma membrane in response to binding of growth factors to their receptors (Mochly-Rosen, 1995). The GTP-Ras activation of Raf is one of the initial steps of a downstream cascade of other protein kinase activations, generically called mitogen-activated protein kinases or MAPKs, which carries the membrane signal toward the nucleus to control cell proliferation and differentiation (Marshal, 1995). Adenylyl cyclase is another firmly established Ras target (Lowy and Willumsen, 1993). It is generally assumed that ligand binding to the PTKR: (1) activates the SH domains to bind the adapter molecule Shc, (2) that may now associate to Grb2 (3) in order to activate the protein Sos (4) that induces RAS to exchange GTP for GDP. The GTP-Ras (5) phosphorylates the Raf protein, which in turn (6) activates the MAPK to control gene transcription.

There is a class of PTKRs that markedly differs from the receptors discussed above, because they lack any tyrosine kinase domain. These receptors are called cytokine receptors [Fig. 13(B)] and they include receptors for many interleukins, colony-stimulating factors, interferons, and certain other factors and hormones (Heldin, 1995; Ihe and Kerr, 1995; Schindler and Darnell, 1995). Class I cytokine receptors are characterized by the presence in their extracellular domains of one or two copies of a conserved domain of about 200 amino acids, which contains two modules of fibronectin type III-like motifs, four conserved cysteine residues, and the conserved motif Trp-SER-Xaa-Trp-Ser. Class II cytokine receptors, including receptors for interferons and interleukin-10, contain another conserved motif of four cysteine residues and lack the Trp-Ser-Xaa-Trp-Ser motif. The intracellular domains of cytokine receptors lack intrinsic enzymatic activities. However, despite the structural difference between cytokine receptors and PTKRs, their mechanism of activation appears to be similar (Heldin, 1995), because ligand binding induces dimerization or oligomerization of receptors, and this activates cytoplasmic PTKs that may associate with the
intracellular domain of the cytokine receptors after the ligand–receptor binding. Recent studies have demonstrated that the members of a novel subfamily of cytoplasmic PTKs, termed Janus kinases (Jaks) are involved in signaling through the cytokine receptor superfamily (Ihle and Kerr, 1995; Ip and Yancopoulos, 1996; Schindler and Darnell, 1995). Jaks are phosphorylated after the ligand–receptor binding, and the activated Jaks phosphorylate and activate members of a family of transcription factors termed signal transducers and activators of transcription (STATs). This signal transduction pathway is known as the Jak-STAT pathway (Ihle and Kerr, 1995). The receptor dimerization, induced by the ligand, brings the Jaks into sufficient proximity to allow cross-phosphorylation and activation of their catalytic activity. The activated kinases phosphorylate a distal tyrosine on the receptor, recognized by the SH2 domain of a STAT protein (Schindler and Darnell, 1995). The activated STAT proteins are now competent for hetero- or homo-dimerization, allowing cross-phosphorylation and activation of their catalytic activity. The activated kinases phosphorylate a distal tyrosine on the receptor, recognized by the SH2 domain of a STAT protein (Schindler and Darnell, 1995). The activated STAT proteins are now competent for hetero- or homo-dimerization, nuclear translocation, and binding to the DNA consensus sequence.

The receptor kinase complex may have both a qualitative and quantitative effect on transcription. The number of Jaks and STATs is far less than the number of cytokine receptors, so each receptor can either have a dedicated kinase or activate a unique STAT. Consistent with this idea, many ligands seem to activate overlapping sets of Jaks and STATs (Schindler and Darnell, 1995). The ability of receptors to interact with only a specific set of STATs indicates that it is the receptor itself that transmits the specificity of the ligand–receptor interaction into the cell. The activating potential of a given ligand depends on the number of receptors present, and on the time the signal continues after a ligand–receptor interaction. So, while two ligands may activate the same STAT, they might not do so at the same level, nor for the same period of time (Schindler and Darnell, 1995). Furthermore, the affinity of a particular STAT for a particular receptor–kinase complex may vary from one receptor to another, so that the combination of a ligand with its receptor will not necessarily generate the same number of active STATs. Of additional importance, some receptors will activate other signals that, along with the Jak-STAT pathway, have an impact on the transcription outcome (Ihle and Kerr, 1995; Schindler and Darnell, 1995). For example, the Ras pathway may be activated by the cytokine receptor through SHC binding and phosphorylation [Fig. 13(B)], which in turn activates Grb2 and Sos (Ihle and Kerr, 1995). So, while complete specificity of response from each ligand–receptor cannot be envisaged, it can be said that significant differences in the signal emanating from different receptors could be expected even though similar STATs are activated.

To complicate issues further, it was discovered recently that MAP kinase from the RAS pathway may phosphorylate STATs activated by the Jak pathways (David et al., 1995). It is proposed that MAPK may phosphorylate a STAT serine residue which may enhance the STAT activity upon the gene transcription. However, the increase of cAMP concentration promoted by other signal transduction pathways, may activate PKA to phosphorylate STATs activated by the Jak pathway (Iyengar, 1996). In addition, cAMP may exercise an opposite control over other signal transduction pathways because of its capacity to inhibit protein phosphatases. This mechanism is proposed to explain the role of cAMP on LPT development (Iyengar, 1996). In this way, the augmentation of Ca2+-intracellular concentration may activate Ca2+-calmodulin-dependent protein kinase (CaMK) to phosphorylate PKA, which may now stimulate a phosphatase inhibitor to amplify the signals conveyed by other phosphorylated proteins.

6.3. Calmodulin Signaling

Ionized calcium (Ca2+) is the most common signal transduction element in cells, but unlike other second messengers, it cannot be metabolized, so cells tightly regulate intracellular levels through numerous binding proteins sequestering the ion and Ca2+ pumps moving it to special cellular compartments (Bootman and Berridge, 1995; Brown et al., 1995; Clapham, 1995; Ghosh and Greenberg, 1995; Kocsis et al., 1995). The ambiguity of the signal carried by Ca2+ may be very high unless its diffusion inside of the cell is perfectly controlled. Calcium entry into the cell from the extracellular space is promoted by numerous ionic channels, which are classified into voltage-dependent and ligand-controlled channels. The NMDA-controlled channels are a special case, since Ca2+ permeability is dependent on both glutamate binding to the channel and on Mg2+ channel control tuning by membrane depolarization. Calcium release into the cell from specialized compartments is promoted by intracellular activation of the ryanodine (RyanR) and IP3 receptors in the membranes of such compartments. RyanRs are assumed to be controlled mainly by the Ca2+ itself, since it opens at concentrations of 100 nM–1 μM, but they are inhibited at Ca2+ concentrations above 1 μM (Ghosh and Greenberg, 1995). The IP3 is the signal produced by the phospholipid transduction pathway, and its concentration may be enhanced, for instance, by G-proteins (Fig. 12). Calcium removal from the intracellular space is promoted by Ca-activated ionic pumps that may sequester it in specialized compartments, or may move it to the extracellular space. Therefore, the adequate spatial distribution of channels, Ca2+ pumps and storage compartments is essential to organize the Ca2+ distribution inside the cell, in order to guarantee its effective role as a second messenger. This may be achieved by orienting Ca2+ waves (Clapham, 1995; Ghosh and Greenberg, 1995; Kocsis et al., 1995) by means of defined spatial distributions of channels and pumps. Calcium moved inside the cell also may bind to special proteins in order to downstream propagate the signal it is in charge of transmitting. Calmodulin
is one of these signal carriers activated by Ca\(^{2+}\). Calcium-bounded calmodulin (Ca\(^{2+}\)-calmodulin or CaM) modulates the activity of a number of enzymes and protein kinases. These include CaMK, adenylate cyclases and protein phosphatases, like calcineurin.

Five CaMK (CaMK I–CaMK V) have been identified. CaMK II has been studied extensively as a potential mediator of Ca\(^{2+}\)-dependent synaptic changes. CaMK IV and certain isoforms of CaMK II may be specifically involved in mediating transcriptional activation of gene expression in response to changes in intracellular Ca\(^{2+}\). CaMK II isolated from the brain contains \(\alpha\) and \(\beta\) subunits in a ratio of about 4:1, and each subunit has a catalytic activity (Ghosh and Greenberg, 1995). In the resting state, an autoinhibitory domain of the kinase keeps the catalytic site inaccessible. This inhibition is relieved by the binding of CaM to the autoinhibitory domain. The kinase thus activated can not only phosphorylate substrates at serine residues, but also undergoes autophosphorylation at a number of sites. Site-directed mutagenesis experiments indicate that of the multiple autophosphorylation sites, phosphorylation at Thr\(^{286}\) is both necessary and sufficient for the generation of Ca\(^{2+}\)-independent activity. Autophosphorylation of Thr\(^{286}\) also increases the affinity of the kinase for calmodulin (Ghosh and Greenberg, 1995).

Nuclear activation by CaMK is proposed to be promoted by two different pathways. On the one hand, cytosolic activated CaMK may be translocated into the nucleus in order to exercise its action upon gene transcription, or CaMK activates other downstream signals which are moved into the nucleus. On the other hand, Ca\(^{2+}\) waves directed toward the nucleus may increase the Ca\(^{2+}\) nuclear concentration and promote activation of local CaMK (Ghosh and Greenberg, 1995; Kocsis et al., 1995). Among the non-nuclear substrates activated by CaMK II are MAP2, synapsin I, the metabotropic glutamate receptor GluR1, etc. (Ghosh and Greenberg, 1995; Swope et al., 1992). MAP2 is a microtubule-associated protein and both synapsin I and GluR1 are involved in synaptic transmission. As discussed before, the phosphorylation of synapsin I may release transmitter vesicles from their anchoring sites at the presynaptic terminal, and phosphorylation of ligand channels by CaMK and PKA is proposed as a paradigm for synaptic plasticity involving the postsynaptic receptor (Sigel, 1995; Swope et al., 1992).

Although CaMKs are important transducers of Ca\(^{2+}\) signals, CaMs also may activate specific adenylyl cyclases to influence cAMP levels at definite cellular sites. The augmentation of cAMP levels may activate other protein kinases, e.g. PKA, to act as downstream signals. Of particular interest is type I Ca\(^{2+}\)-sensitive adenylyl cyclase (I-AC), which is highly expressed in the hippocampus and neocortex, regions associated with activity-dependent synaptic plasticity (Ghosh and Greenberg, 1995). It is interesting to note that adenylyl cyclases may be activated synergistically by both Ca\(^{2+}\) and G-protein receptors, such that calcium may serve to amplify neurotransmitter-induced increases in cAMP. This is of particular interest, since CREB is a cAMP-activated protein controlling early gene transcription involved in a number of neural activities. CaMK IV and certain isoforms of CaMK II were shown to phosphorylate CREB Ser\(^{133}\), and the phosphorylation at this site is known to be important for the action of CREB upon the complex machinery involved in DNA transcription. The CREB activity is known to be reduced by phosphorylation of Ser\(^{32}\), and it was shown that CaMK II is able to phosphorylate both Ser\(^{133}\) and Ser\(^{32}\), whereas CaMK VI seems to phosphorylate only Ser\(^{133}\) (Ghosh and Greenberg, 1995). However, the meaning of such findings remains to be established.

Increased protein phosphorylation, following the stimulated entrance of calcium into presynaptic terminals and associated with changes in the efficacy of transmitter release, is accompanied by the simultaneous dephosphorylation of a subset of nerve terminal phosphoproteins (Nichols et al., 1994). Dynamin is one of these molecules undergoing dephosphorylation induced by Ca\(^{2+}\). Dynamin GTPase activity was shown to be regulated dramatically upon its phosphorylation by PKC, and CaM-dependent protein phosphatase calcineurin was shown to be involved in dynamin dephosphorylation. It was proposed also that calcineurin activation may limit neurotransmitter release (Nichols et al., 1994), although the mechanism by means of which it exercises this action remains unknown. It is interesting to remark that transmitter release inhibition by protein dephosphorylation may be an important mechanism to relate different spike frequencies to the release of distinct transmitters.

7. NEUROTROPHIC AND DIFFERENTIATION FACTORS

Neurotrophic factors (NTFs) are required for growth, differentiation and survival of neurons. They are particularly important during embryonic development of the nervous systems, by they also play a significant role in the physiology of the mature neuron. The NTFs are produced in small amounts by target cells and are taken up the neuron enervating such cells. As a normal part of development, the neurons which do not make proper connections do not receive sufficient NTFs and die. The NTFs guarantee the survival of the mature neuron and contribute to synaptic plasticity (Cellerino and Maffeì, 1996; Hosain et al., 1996; Ip and Yancopoulos, 1996; Kuno, 1995; Lewin and Barde, 1996; Miller, 1994; Nakao et al., 1996; Patterson and Nawa, 1993; Ross et al., 1994; Segal and Greenberg, 1996). The nerve growth factor (NGF) was the first recognized NTF, followed by brain-derived NTF (BDNF), and more recently by Neurotrophins 1–6 (NT3-6).

The NTF actions are thought to be mediated by two surface receptors. The first NTF receptor is the low-affinity p35\(^{NTR}\) receptor, a 75,000 Da protein with a cystein-rich extracellular domain, a single transmembrane domain and a 155-amino acid cytoplasmic domain (Bothwell, 1996; Kuno, 1995; Ross et al., 1994). The relative short cytoplasmic C-termi-
nus domain suggests that the cytoplasmic region of the \( p35^{NTR} \) may not serve signal transduction directly (Kuno, 1995). The second NTF receptor is a 140 000 Da transmembrane protein (Trk), with an intracellular tyrosine-specific kinase domain. Different NTFs have distinct affinity to a set of at least three Trks (TrkA, TrkB, and TrkC). It is proposed that NTF binds the two receptors generating an heterodimer composed by one Trk and \( p35^{NTR} \) (Bothwell, 1996; Enfors et al., 1994; Kuno, 1995). It is also assumed that \( p35^{NTR} \) may enhance the Trk activity, because Trk can mediate many responses in an heterodimer composed by one Trk and \( p35^{NTR} \). The second NTF receptor is the \( p35^{NTR} \) that may not serve signal transduction directly (Kuno, 1995). The second NTF receptor is the \( p35^{NTR} \) that may not serve signal transduction directly (Kuno, 1995). It has been shown recently that \( p35^{NTR} \) may be involved in other signal-transduction pathways commanding apoptosis (Bothwell, 1996; Carter et al., 1996). This seems to explain some previous discussion in the literature about the role played by \( p35^{NTR} \).

It becomes clear now that \( p35^{NTR} \) may trigger cellular responses without the participation of Trk receptors at all. Understanding of this mode of \( p35^{NTR} \) action has been substantially from studies of the signaling mechanism of the tumor necrosis factor (TNF) and CD40 receptors and reas, that are receptors of the same family of the NGF receptor (Bothwell, 1996; Nagata and Golstein, 1995). The TNF, CD40 and Re as couple, to varying extents, to two parallel signaling pathways leading, respectively, to apoptotic death or activation of the transcription factor NF-kB. The recognition of a death domain motif within \( p35^{NTR} \) was the first step in a series of experiments showing that \( p35^{NTR} \) may promote apoptotic death. Enhanced conversion of sphingomyelin to ceramid, which accompanies TNF-induced apoptotic cell death, has been demonstrated in response to activation of \( p35^{NTR} \) by NGF, BNDNF or NT-3 (Bothwell, 1996). Carter et al. (1996) provided evidence that NGF-induced tyrosine kinase activity of the TrkA receptor negatively regulates the capacity of \( p35^{NTR} \) to mediate NGF-induced ceramide production. In this way, NTFs may not only promote growth but also inhibit apoptosis. The NF-kB is a potent transcriptional activator that resides in latent form in the cytoplasm complexed to its inhibitor I-kB. Phosphorylation of I-kB by PKC releases NF-kB and enables its translocation to the nucleus, where it may contribute to alterations in target gene expression that accompany activity-dependent synaptic plasticity in a combinatorial fashion with other transcription factors (Bhat, 1995), for instance NTFs.

The NTFs regulate genes involved in many of the aspects of cellular growth and differentiation, including those encoding \( p35^{NTR} \) and its modulators, and tyrosine hydroxylase. These induced alterations are not limited to developing neurons, but can be elicited in mature neurons in vivo (Miller, 1994). However, these effects upon gene regulation are dependent on the site of NTF release. On the one hand, the injection of NGF in the nucleus or cytoplasm fails to trigger its gene-regulation action (Kuno, 1995; Miller, 1994; Ross et al., 1994). On the other hand, the magnitude of the gene activation is less when NGF is applied to cell bodies and proximal axons than to distally axonic terminals (Miller, 1994). All of this implies that NTFs must bind to their receptors in order to be internalized by means of endocytosis, and to be transported to the nucleus to exercise their actions (Kuno, 1995; Miller, 1994; Ross et al., 1994). Different studies demonstrated that the complex NTF-receptor is necessary for gene activation and the complex is also transported to the nucleus (DiStefano and Curtis, 1994; Kuno, 1995). It is known that dimerization of the \( p35^{NTR} \) is required in order to phosphorylate the tyrosine in the receptor kinase domain, and that this phosphorylation triggers the cascade activation of downstream signals. It may be proposed that the heterodimer composed by \( p35^{NTR} \) and Trk lacks the capacity of favoring such tyrosine autophosphorylation because of the reduced \( p35 \) intracellular domain, and that this preserves the complex NTF-\( p35^{NTR} \)-Trk during the retrograde transportation as a signal to be transduced at its arrival at the cell body.

In addition to neuronal growth, target tissues also can control the phenotype of the neurons that enervate them. Phenotypic traits that are regulated in a qualitative fashion include neurotransmitters, neuropeptides, membrane receptors, etc. Such qualitative alterations in phenotype can be regulated by the neuron differentiation factors, whose effects can be distinguished from the classical survival and growth activities. Differentiation factors characteristic in neuronal gene expression and phenotype and include, besides NTFs, many other cytokines and neuropeptides (Cellerino and Maffei, 1996; DiStefano and Curtis, 1994; Ip and Yancopoulos, 1996; Lennon, 1994; Lewin and Barde, 1996; Li et al., 1996; Patterson and Nawa, 1993; Pacl, 1995; Tong et al., 1996; Waschek, 1995).

It is now clear that the same protein can act instructively as a differentiation factor or permissively as a growth factor, depending on the responsive cell population (Patterson and Nawa, 1993). For instance, BNDNF also can selectively induce the expression of the neuromodulating factor (SOM) and neuropeptide Y (NPY). Cholinergic differentiation factor (CDF) initially characterized for its ability to regulate gene expression in post-mitotic sympathetic and sensory neurons, has been found also to act as a survival factor for sensory and motor neurons. Also, CDF and other factors may be responsible for the transmitter switching of sympathetic neurons changing a noradrenergic phenotype into a cholinergic one (Patterson and Nawa, 1993). Ciliary neurotrophic factor (CNTF) may control such switching too, but does not appear to be a target-derived cytokine, it is expressed predominantly in the glial cells of the peripheral and central nervous systems (Stockley et al., 1991). A key feature of differentiation factors acting in retrograde and anterograde pathways is that these trans-synaptic exchanges of factors make use of the intricate circuitry of the nervous systems (Patterson and Nawa, 1993). The importance of this is two-fold. First, since the circuitry is designed for discrete, cell-to-cell interactions, cytokines can regulate neuronal phenotype and gene expression with the same degree of precision that is inherent in the wiring. Second,
8. CHEMICAL TALK AT THE SYNAPSIS

It is now clear that chemical transactions at most, if not all, synapses are very complex and involve a large number of transmitters, neuropeptides, trophic or differentiation factors, cytokines, etc., released by both the same or different pre-synaptic neurons, as well as other types of cells located nearby (e.g. glial elements) or at different places in the organisms (e.g. hormones) or belonging to the immunological system (e.g. cytokines). Also, different families of post-synaptic receptors are activated by ligand binding or modulated by phosphorylation or dephosphorylation promoted by neuropeptides or differentiation factors. As a general feature, distinct types of receptors for the same transmitter are located at distinct postsynaptic sites of the same cell and different ligand-gated ionic channels may be activated by the same ligand. Information normally flows from pre- to postsynaptic cells, but signals also are transmitted from post- to presynaptic neurons. The very complex chemical talk taking place at the synapsis between pre- and postsynaptic cells as well as other neighboring cells, results not only in the postsynaptic cell decision of firing or not axonic spikes, but also in the decision of propagating chemical signals which may determine the way genes are transcribed at both the pre- and postsynaptic cells or may change other cellular activities.

As an example to point out some important characteristics of this chemical talk, the organization and the physiology of some sensory synapses at the thalamus and cortex will be discussed briefly below. The reasons for the decision to choose these synapses are two-fold. First, there is now available in the literature an interesting body of knowledge about the chemical transactions related to very important sensory processings, which may in the future shed light upon one of the most intriguing qualities of sensations: the way we consciously acknowledge the results of a sensory processing or what commonly is known as the quale of the sensory information. Second, there is also a sound set of data about the distributed characteristics of sensory processing, which may help in the understanding of how the coherent behavior of a huge set of neurons may be obtained by means of hierarchy and synchronization.

8.1. Excitatory Amino Acids

There is ample evidence to suggest that amino acids form the major class of excitatory transmitters in the sensory cortex and thalamic relay nuclei, and among them glutamate plays the most important role (see Broman, 1994; Johnson and Burkhalter, 1994; Cauler, 1995; McCormick, 1992; Salt and Eaton, 1996). Glutamate receptors are classified into ionotropic and metabotropic receptors, according to their capacity to control ionic channels or activate a cascade of biochemical events that eventually may control some ionic currents. The ionic receptors classically are classified into AMPA/kainate and NMDA receptors based on responses evoked by the selective agonists AMPA, kainate and NMDA, respectively (Kuno, 1995; Salt and Eaton, 1996).

Four glutamate receptor subunits (GluR1–GluR4) can be regarded as AMPA receptor subunits and five other subunits (GluR5–GluR7, KA1 and KA2) can be regarded as kainate receptor subunits. Both of these subunit groups can form homomeric and heteromeric channel assemblies with other members of their groups (Hollman and Heinemann, 1994; Kuno, 1995; Salt and Eaton, 1996). Apart from GluR2, the cloned AMPA receptors have a non-linear voltage relationship and are relatively
Ca$^{2+}$ impermeable. However, in heteromeric AMPA receptors, the linear voltage properties and Ca$^{2+}$ properties of GluR2 are predominant. These properties of GluR2 are dependent on the presence of Arg in its second transmembrane segment M2, that is replaced by Gln in all other AMPA subunits.

As discussed before, the presence of Arg in GluR2 is the result of an mRNA editing promoted by dsRAD (Fig. 6) (Hebert, 1996). The above dependence of the result of a mRNA editing promoted by dsRAD indicates that the M2 segment of these receptors is involved in the formation of the wall lining the ionic pore (Kuno, 1995). Both GluR5 to GluR7 are thought to correspond to the low-affinity kainate receptors, whereas KA1 and A2 correspond to the so-called high-affinity kainate receptors. It is noteworthy that KA2/GluR6 receptors show a substantial response to AMPA (Hollman and Heinemann, 1994; Salt and Eaton, 1996).

The NMDA receptors have relatively high Ca$^{2+}$ permeability, controlled by Mg$^{2+}$ in a voltage-dependent manner, and require glycine (or similar ligand) as co-agonist. They also have modulatory sites for polyamines, reducing agents, Zn$^{2+}$ and protons (Salt and Eaton, 1996). The NMDA receptor-channel complex comprises two subunits: NR1 and NR2. There are eight splice variants of NR1, and it is thought that NR1 is a component of all native NMDA receptors. There are four NR2 subunit types, which appear to confer different physiological and pharmacological properties to the receptors: e.g. NR1–NR2C channels are more sensitive to Mg$^{2+}$-blockade and display the highest affinity sites for glycine binding compared to other heteromeric channels (Salt and Eaton, 1996). Interestingly, NR1 has an uncharged asparagine (Asn) at the Arg/Gln site of the M2 segment. The replacement of the Asn by Gln in NR1 decreases Ca$^{2+}$ channel permeability as well as the blocking effect of Mg$^{2+}$. Once again, the M2 segment seems to line the ionic channel of the receptor (Kunc, 1995). The NMDA receptors received much attention because of their association with the phenomenon of long-term potentiation (LTP) (Bartsch et al., 1995; Jessell and Kandel, 1993; Kuno, 1995; Mayford et al., 1995; Tsuno. 1992). The NMDA receptor-channel complex normally is blocked by Mg$^{2+}$ at the resting potential. For Ca$^{2+}$ influx to occur through the NMDA channel, the receptor must be activated associatively by glutamate and a co-agonist (e.g. glycine) and the membrane must be depolarized to remove the Mg$^{2+}$-block (Nicoll et al., 1988). Thus, the function of the high-frequency train of impulses in the presynaptic cells required by LTP, is simply to depolarize the postsynaptic cell to an extent sufficient to relieve the Mg$^{2+}$-block. This critical depolarization normally is achieved through the synchronous firing of many presynaptic neurons, activating many non-NMDA receptor-channels on the postsynaptic cell. The Ca$^{2+}$ influx by the now unlocked NMDA receptor activates at least three different kinases: CaMKII, PKC and one or more tyrosine kinases (Jessell and Kandel, 1993; Kuno, 1995; Tsuno, 1992). This activates signal transduction pathways responsible for the short- and long-term effects of LTP by means of phosphorylation of membrane proteins and the control of DNA transcription.

Eight metabotropic glutamate receptors (mGluR1–mGluR8) can be placed into three groups on the basis of sequence homology, agonist pharmacology, and coupling to intracellular transduction mechanisms. Group I comprises mGluR1 and mGluR5 that are coupled to postsynaptic inositol phosphate metabolism. Group II comprises mGluR2 an mGluR3, and Group III comprises mGluR4, mGluR6, mGluR7 and mGluR8. Both groups can couple to an inhibitory cAMP cascade but also to other signal transduction pathways (Salt and Eaton, 1996). The mGluR6 is assumed to be responsible for synaptic transmission from photoreceptors to ON-bipolar cells in the mammalian retina (Nakanishi, 1995) by means of the following mechanism. A photoreceptor absorbs photons, and decreases the intracellular concentrations of cGMP through the stimulation of phosphodiesterase via transducin. The decrease in the concentration of cGMP leads to the closure of cGMP-gated ions channels, and lowers the release of glutamate. In the absence of glutamate, mGluR6 remains inactive, and cGMP modulates cation-selective channels, and depolarizes ON-bipolar cells, resulting in excitation of the subsequent ON pathway. Therefore, the key role of mGluR6 in ON-bipolar cells is to mediate inversion of responses between photoreceptors and bipolar cells, the hyperpolarization of presynaptic photoreceptors is converted to depolarization at the postsynaptic bipolar cells (Nakanishi, 1995). In OFF-bipolar cells, the AMPA receptor is used as the postsynaptic receptor, thus preserving the response of the photoreceptors. Glutamate metabotropic receptors also are proposed to be responsible for inducing synaptic morphological changes associated with LTP (Edwards, 1995).

8.2. The Thalamic Relay Neuron

Intra- and extracellular recordings in vivo and in vitro have revealed that thalamic relay neurons (TRNs) have two basic modes of action potential generation: single-spike activity and rhythmic burst generation. Single-spike activity is prevalent during 'brain-activated' states, characterized by EEG desynchronization, such as in awake and attentive animals or rapid eye movement (REM) sleep. Rhythmic burst firing is prevalent during periods of synchronized slow waves in the EEG, such as during slow wave sleep (SWS) and deep anesthesia (McCormick, 1992; Munk et al., 1996; Steriade, 1996). McCormick (1992) and Salt and Eaton (1996) published excellent reviews about the electrophysiology and the biochemistry of TRN and the way in which its different physiological states are controlled by acetylcholine, norepinephrine, serotonin and histamine. Most of the discussion in the following two sections is supported by data reviewed by these authors.

Burst firing is due to the activation of low-threshold Ca$^{2+}$ spikes, which are generated by the low-threshold Ca$^{2+}$ current or T-current (I_T). This T-current is, in turn, activated by depolarization of the membranes up to approximately −80 mV and
becomes progressively inactivated by depolarization, such that inactivation is complete at around -60 mV. Owing to this, it is proposed that $I_f$ is dependent on both activating (m) and inactivating (h) gates: the m gates begin to open at a membrane potential around of -80 mV and reach the full opened state at a potential around of -40 mV, and h gates change from a full opened state at -100 mV to a closed one at membrane potentials near -60 mV. The much greater rate of activation than inactivation of $I_f$ allows depolarization from hyperpolarized membrane potentials to generate low-threshold Ca$^{2+}$ spikes. Single-spike activity is assumed to be supported by the classical Na/K system, such that depolarization of the membrane to adequate levels results in the generation of spike trains. The rhythmic activity triggered by the activation of $I_f$ may produce depolarizations to activate the Na/K system and to generate oscillatory spike trains. This rhythmic activity, called intrinsic rhythm, occurs in the range of 0.5-4 Hz.

Each high-frequency burst of action potentials is generated by the occurrence of a low-threshold Ca$^{2+}$ spike. In between Ca$^{2+}$ spikes is a slowly depolarizing 'pace-maker' potential generated by the hyperpolarizing cation current known as $I_{h}$. This current is carried by both Na$^+$ and K$^+$ and therefore has a reversal potential of around -40 mV. In voltage clamp experiments, hyperpolarization of the membrane potential negative to approximately -60 mV results in activation of $I_{h}$, that appears as a slowly activating inward current, largely carried by the inward movement of Na$^+$. This inward current is responsible for the membrane depolarization which activates the next Ca$^{2+}$ spike. The rate with which $I_{h}$ activates therefore can determine the time period between successive low-threshold Ca$^{2+}$ spikes, and consequently the amplitude of each Ca$^{2+}$ spike. Slow rhythmic burst firing occurs only in a limited range of membrane potential of -85 to -70 mV. During the appearance of rhythmic bursts, the fast and transient Na$^+$ current $I_{Na}$, the delayed rectifier K$^+$ current $I_K$, the transient K$^+$ current $I_{A}$, and the leak currents of K$^+$ and Na$^+$ are responsible for the generation of the fast action potentials.

Depolarizations above -50 mV change the TRN firing behavior from burst rhythmic activity to single-spike activity, promoted by the Na$^+$ and K$^+$ currents, because $I_{h}$ and $I_{f}$ are deactivated. The TRN activity in the range between -70 and -50 mV therefore is characterized by complex firing behavior, and its response to phasic depolarization differs not only in the amplitude of inputs required to reach spike threshold, but also in the pattern of action potentials generated. For example, intracellular injection of constant current pulses at -70 to -80 mV results in trains of action potentials that are unique in that there can be a prolonged delay onset of spike firing. Once generated, however, the train of action potentials demonstrate a steady rate of discharge with a marked lack of spike frequency adaptation. This is due to the presence of a least two distinct types of transient outward K$^+$ currents known as $I_{A}$ and $I_{Kh}$, that are inactivated by steady depolarization. In addition to controlling the spike generation onset, these currents also cause TRN to display marked rectification current properties in the range of -70 to -50 mV. Further TRN depolarization abolishes the onset activity delay and results in a steady rate of discharge of action potentials. It is possible to conclude from the above that distinct and complex neural encodings are available at TRN, which may be used to transmit differently sensory information to the cortical areas, depending on the behavioral state of the animal. It is now believed that spike firing encoding is more complex than simply correlating firing frequency to stimulus intensity (Kohn et al., 1981; Rocha, 1980a, 1992; Rocha and Butto, 1985), it is also dependent on the way spikes are organized in defined firing patterns.

Repeated stimulation can either increase or reduce the spike firing in sensory neurons (Rocha, 1980a, 1992). This phenomenon is called response sensitization in the first case and response attenuation in the latter.

Figure 14 illustrates the response attenuation obtained by repeated stretching of the fast (phasic—Fig. 14[A]) and slow (tonic—Fig. 14[B]) adapting stretch receptor organ of the crayfish at a rate of 2 Hz. Similar response attenuation was described by Rocha (1980a) for the midbrain reticular sensory neurons in the case of repeated touch taps in the cat skin. A very specific pattern of spike disappearance is disclosed by careful analysis of the spike-firing epochs in the spike trains elicited in the sequentially repeated stretches (Fig. 14). Briefly (Rocha, 1992): (a) the histogram of the spike trains shows the existence of distinct time epochs $t_i$ of increased possibility of spike occurrence; (b) spikes generated near the transition from the dynamic to the static phase of the stretching are less likely to disappear during the response attenuation than those spikes triggered at the beginning or end of the stimulation; and (c) a resistant spike may disappear occasionally during the attenuation sequence to reappear later after a less resistant spike being eliminated from the spike train by the attenuation. Rocha (1992) conclude from these data that the spike distribution in the encoding spike train (or codewords) $w_i$ is not a continuous distribution over the time continuum, but a fuzzy distribution over defined epochs $t_i$ of this continuum. In this way, given a cover $T$ of the time continuum constituted by a family of discrete time epochs $t_i$, and the binary dictionary D associated with the decision-making about the axonic spike firing, the possible axonic codewords (spike trains) are generated by a fuzzy point process $\Pi$ (Rocha, 1980b) associating a possibility distribution $\pi_{\Pi}(D)$ of action potentials in $w_i$ to the possible energy profiles $s_i$ of a set $S$ of sensory stimuli. It was proposed also that each $w_i$ is composed of two strings $w_{a}$ and $w_{h}$, describing the encoding in the dynamic and static phases of the stretch, respectively.

The TRN may exhibit two other rhythmic activities in the range of 7-12 and 30-50 Hz, which are consequences of the intra-thalamic circuitry and cortico-thalamic feedback (Fig. 15), respectively. Intracellular recordings in TRN during the generation of EEG spindle oscillations reveal barrages of inhibitory postsynaptic potentials arriving at a fre-
The complex TRN electrical behavior has important implications for the manner in which these neurons respond to phasic synaptic inputs, such as those arising from the retina. Rhythmic firing during SWS or drowsiness is associated with a markedly reduced responsiveness to receptive field stimulation. In contrast, awakening from sleep is associated with an abolition of rhythmic burst firing, presumably due to the Mg$^{2+}$ blockade of NMDA channel dependency on the membrane depolarization. The NMDA antagonists applied by various means, both in vivo and in vitro, can reduce EPSPs evoked by stimulation of presumed corticothalamic afferents, thus providing evidence in favor of NMDA receptor participation in the mediation of cortical information to TRN. In addition to ionotropic receptors, there is also evidence suggesting that postsynaptic mGluRs may participate in TRN responses. For instance, it was shown that the agonist trans-ACPD can depolarize thalamic neurons via a reduction in a K$^+$ conductance, in a similar manner to the slow EPSP promoted by corticothalamic stimulation.

Glutamate is assumed to be the neurotransmitter released by both retinal ganglion cell axons and corticothalamic axons in mammalian lateral geniculate nucleus (LGN) (Broman, 1994; McCormick, 1992; Salt and Eaton, 1996). Cortical inputs are assumed to reach more distal dendrite locations, and probably to activate more mGluRs and fewer AMPA/kainate receptors than sensory afferents (Fig. 15). Intracellular recordings, both in vivo and in vitro, together with selective antagonists, indicate that TRN postsynaptic response comprises an initial non-NMDA receptor-mediated component followed by an NMDA-associated response. This compound EPSP typically is followed and curtailed by a GABAergic IPSP. It seems to be the case that NMDA receptor-mediated component becomes more apparent upon repetitive activation of afferents, maybe due to the Mg$^{2+}$ blockade of NMDA channel dependency on the membrane depolarization.

The GABA neurons form two distinct groups in the thalamus: local circuit interneurons and neurons belonging to nRT (Fig. 15) (Broman, 1994; Huguenard and Prince, 1994; McCormick, 1992; Salt and Eaton, 1996). Local circuit cells are innervated by axons from the retina, cerebral cortex and nRT. In addition, they give rise to two different types of synaptic contacts onto thalamocortical relay cells: dendrodendritic connections and axon terminals. Dendrodendritic connections are present in synaptic glomeruli in which a retinal terminal makes synaptic contacts upon both the TRN dendrites and the GABAergic interneurons. The dendrite of the GABAergic interneuron, in turn, forms a synaptic contact with TRN, thereby forming a tri-synaptic relation which is a typical feature of thalamic circuitry (Fig. 15). The GABAergic neurons of nRT receive massive innervation from collaterals of
Fig. 15. The thalamo-cortical visual cells. The thalamic relay neuron (TRN) receives (1) Glutamate connections from the optical neuron; (2) Cholinergic (Ach) input from Midbrain Reticular Formation (MFR); (3) Noradrenergic (NA), Histaminergic (HA) and Serotonergic (5-HT) terminals from the Locus Coeruleus (LC), Raphe Nucleus (raphe) and tuberomamillary nucleus (TMN); (4) GABAergic inhibition from the Nucleus Reticularis (nRT) and Perigeniculate Nucleus (PGN); (5) enervates and is enervated by the triadic GABA neuron. Glial cells are influenced by the incoming information to TRN and also modulate the activities in many of the above synapses. TRN indirectly activates the Pyramidal cortical neurons (PCN), which also receive information from other cortical areas and from the same Ach, NA, HA and 5-HT systems. PCNs from cortical layer 5 reciprocally enervates TRNs. PCNs from layers 2 and 3 send their axons to the other visual cortical areas, and those of layer 6 provide outputs to the Superior Colliculus and the Brain Stem. Glutatione (GSH), L- arginine (l-arg), D-serine (D-ser), glutamate (glu) and L-homocysteic acid (HCA) may be released by glial cells to act upon several of the above synaptic processes. See text for further details.
sumably owing to the large hyperpolarizations of the membrane potential that they induce. It is clear, from the above, that responses triggered by excitatory amino acids and GABA involve two distinct components characterized by fast and slow conductance changes, respectively. It seems, therefore, that TRN is in charge of processing two different types of codewords, \( w_f \) and \( w_s \), associated with distinct (fast or slow) features of the incoming sensory information.

Application of acetylcholine (Ach) to TRN or stimulation of MFR cholinergic neurons results in a pronounced inhibition of rhythmic burst activity and the appearance of single-spike activity, whereas Ach markedly inhibits the neuronal discharge of GABAergic neurons in nRT. The switch of TNR activity is achieved by depolarization of the neuron through activation of both nicotinic and muscarinic receptors, the first promoting a rapid TRN depolarization and the second being responsible for a more prolonged but later response. While the nicotinic response seems to be due to an increase in membrane conductance, the muscarinic effect results from a block of a resting K⁺ conductance. Voltage clamp analysis of the slow depolarizing response to Ach has revealed that it is due largely to the reduction of a relatively linear potassium current, which contributes substantially to the resting ‘leak’ conductance and, therefore, has been termed \( I_{KL} \). This Ach effect appears to be mediated by a non-pertussis toxin-sensitive G-protein, and is non-additive with the slow depolarizing responses mediated by \( \alpha_1 \) and \( \beta_1 \) receptors, suggesting that all three of these receptors are coupled to the same postsynaptic second messenger system or ionic channels.

The mammalian thalamus is enervated by histaminergic (HA) axons, presumably arising from tuberomammillary nucleus (TMN) of hypothalamus. Application of histamine to TRN results in a slow depolarization due to the reduction of \( I_{KL} \), promoted by the activation of a G-protein. Like the Ach-induced slow depolarization, the HA-triggered response can completely switch TRN from the rhythmic oscillatory mode to the single spike mode of action potential generation. Application of HA to TRN in the presence of \( \beta_1 \) antagonists results in a small depolarization of the membrane potential and a substantial decrease in the response of the neuron to hyperpolarizing current pulses. Examination of \( I-V \) relations in voltage clamp reveals that this action is associated with a voltage-dependent increase in \( I_{HL} \) through a shift in the activation curve of this current to more positive membrane potentials. This effect is supposed to be mediated by the activation of adenyl cyclase.

Stimulation of the LC or iontophoretic application of norepinephrine (NE) results in prolonged enhancement of TRN responses to excitatory inputs through activation of \( \alpha_2 \) adrenoceptors, due to a decrease of \( I_{KL} \), mediated by a non-pertussis toxin-sensitive G-protein. The \( \beta \) adrenoceptors, in turn, are shown to enhance \( I_{HL} \) in a similar way to HA. The TRNs respond to iontophoretic application of 5-HT or stimulation of the raphe with slow and prolonged inhibition and a small depolarization associated with an enhancement of \( I_{HL} \). One possibility is that this inhibition is indirect and mediated by excitation of neighboring interneurons.Activation of adenosine \( A_1 \) receptors results in inhibition of single-spike activity through the activation of a potassium conductance, in addition to a marked decrease in the amplitude of \( f_{HL} \), probably due to the inhibition of adenyl cyclase. The modulatory site on the NMDA receptor, which is sensitive to sulfhydryl redox agents, may be used by glial cells to control some of the TRN NMDA receptors through the release of glutathione. Homocysteic acid is another ‘gliotransmitter’ which may be involved in a presynaptic control of TRN.

It is now evident that glial cells play an important role in information processing, being activated by transmitters and accumulating certain substances relatively selectively (Bhat, 1995; Salt and Eaton, 1996; Vernadakis, 1996). For instance, it is proposed that glial cells control the efficiency of the glutamatergic synapses, because they are in charge of removing the released transmitter and transforming it into glutamine, which are then moved back to the neuron to be used in new synthesis of the transmitter (Vernadakis, 1996). The action of glutamate is terminated by an efficient glutamate uptake system located primarily in astrocytes and controlled by arachidonic acid (AA). Augmentation of the AA level, triggered by noradrenaline, somatostatin, adenosine, etc., reduces the glial glutamate uptake, increases the transmitter presynaptic concentration and augments the duration of its action upon the postsynaptic neuron. Also, glial cells may release \( \delta \)-serine to control allosterically the NMDA receptor (Fig. 15) and it was shown that these glial elements contain both AMPA/Kainate receptors and mGluR. It is possible to assume that activation of AMPA/Kainate receptors on astrocytes can release \( \delta \)-serine to enhance NMDA receptor-mediated responses. Another important role of glia in the TRN physiology is related to the nitric oxide (NO) role in the thalamus. Nitric oxide is a free-radical gas which can diffuse across membranes rapidly, thus acting on neural elements which are at some distance from the site of production. One of the modes of action of NO is to stimulate soluble guanylate cyclase, leading to an increase of intracellular cyclic GMP in target cells. The NO is synthesized from l-arginine by the action of NO synthase (NOS) with the production of l-citruline. There is evidence to suggest that NOS in the thalamus is located in the terminals of cholinergic brainstem afferents, and arginine is available from glia. It may be assumed (Fig. 15), therefore, that activation of glia cells by sensory afferents releasing glutamate could liberate arginine to be used by cholinergic terminals to produce NO, with the purpose of controlling the activation of TRN receptors. The NMDA receptors are involved also in regulation of NOS expression (Akaike et al., 1994; Baader and Schilling, 1996; Dawson and Snyder, 1994; Schumann and Madison, 1994).

The functional consequences of the complex chemical talk taking place around the TRN is becoming to be understood. Sensory information from periphery uses both AMPA/kainate and NMDA receptors to influence TRN activity in a dependent manner on its electrophysiological state,
which is, in turn, determined by the activity of the cholinergic, noradrenergic, histaminergic and serotonergic functional systems arising from the brain stem and hypothalamus. The state of these systems is determined mainly by the emotional and arousal/sleep conditions of the animal. Intracellular recordings in vitro have revealed two basic modulatory responses associated with these animal states: (1) a decrease of the potassium conductance due to the action of \( z_1 \), \( H_1 \), muscarinic, 5-HT\(_2\) and glutamate metabotropic receptors or an increase of this conductance promoted by muscarinic, GABA\(_A\) and A\(_1\) receptors; and (2) an increase in \( I_{hi} \) induced by \( \beta \), H\(_2\), and 5-HT\(_1\) receptors or a decrease of this current due to the activation of A\(_1\) receptors.

Functionally, decreases or increases in membrane potassium conductance are well suited to change the TRN firing mode. In this way, tonic depolarization of thalamic TRN and nRT cells leads to complete or near-complete inactivation of \( I_h \), thereby inhibiting burst discharges. In addition, tonic TRN depolarization lessens the bias of these cells against EPSPs. The enhancement of the activity of cholinergic systems arising from MFR (e.g. Castro-Alamancos and Connors, 1996; Kinomura et al., 1996; Steriade, 1996; Williams et al., 1994) during alert/wake states; REM sleep may be assumed to promote such changes. Intracellular and extracellular recordings in vitro indicate that strong enhancement of \( I_{hi} \), through activation of serotoninergic, \( \beta \)-adrenergic or H\(_2\) histaminergic receptors, result in an abolition of slow rhythmic burst discharge and a small enhancement of single-spike activity. These effects may be determined by the augmentation in the activity of these systems in the awake state. In this way, the alternation of activity in the cholinergic, serotonergic, adrenergic and histaminergic systems, accompanying the changes of behavioral states in the cycle sleep/alertness, is associated with the switch of the TRN firing mode, from an oscillatory one associated to SWS and unconsciousness to a non-bursting firing accompanying REM sleep and supporting mental alertness and consciousness in the awake state. It is possible to assume that low burst rhythmically and single-spike firing provide different neural encodings of sensory information, the first one resulting in a poor message transmission and the second one supporting a detailed description of the sensory environment.

Monotonous sensory information was shown to reduce the activity of reticular sensory neurons (RSN) (Rocha, 1980a), which may be associated to a decrease of cholinergic activity upon the sensory thalamus correlated with the sensory field of the monotonous stimulus. On the contrary, stimulus novelty recovers RSN sensitivity and may be responsible for switching the corresponding TRN neurons from burst rhythmically firing to single-spike activity accompanying the focusing of attention upon the new event. In a similar way, emotional states would be supposed to modify the thalamic encoding of the sensory information and to change the quality of the perceived information. It may be concluded, therefore, that the receptors of ACh, NA, HA, 5-HT, etc., are to set the semantic of the codewords \( w_i \) being processed by the TRNs.

8.3. The Cortical Circuits in Primary Sensory Areas

Cortical neurons display a variety distribution of electrophysiological properties that result in four major neuron types (McCormick, 1992): regular spiking cell, burst rhythmic cells, thin spiking cells and tonic firing neurons. Regular spiking neurons generate a train of action potentials in response to intracellular injection of a depolarizing current pulse, that in absence of transmitter actions, typically slows down in frequency over a period of several hundred milliseconds, due in large part to the activation of two distinct potassium currents \( I_{A} \) and \( I_{AHP} \). Regular spiking neurons are found in layers II–VI of the cerebral cortex and typically are pyramidal cells in morphology. They respond with spike trains of up to 200–300 Hz and show a marked spike-firing adaptation, they are the most common pyramidal cells. Burst-generating neurons are pyramidal neurons and generate a burst of from three to five action potentials in response to the intracellular injection of current. The possible involvement of a low-threshold \( Ca^{2+} \) current has been proposed recently to explain this bursting activity. Burst-generating pyramidal cells are located predominantly in a subportion of layer V and possess unusually thick apical dendrites that rise to layer I and bifurcate extensively. In addition, burst firing cells also can shift their mode of spike firing to generate trains of single action potentials upon tonic depolarization. Thin spiking cells are characterized by unusually short duration action potentials, an ability to fire tonically at rates higher than 250 Hz, and a relative lack of firing adaptation. It seems that most of these cells are GABAergic neurons. Tonic pyramidal cells are found also in layer V and the majority of these cells generate trains of action potentials which show little spike frequency adaptation and which have the ability to oscillate endogenously at a frequency of between 5 and 12 Hz. The intrinsic oscillation of tonic firing pyramidal cells appears to depend critically upon Na\(^+\) currents and can become synchronized with other layer V pyramidal cells.

The EEG displays a number of different frequencies which become more or less prevalent during different periods of the sleep–wake and behavioral continuum (Castro-Alamancos and Connors, 1996; Contreras et al., 1996; McCormick, 1992; Munk et al., 1996; Nicolelis et al., 1995; Salt and Eaton, 1996; Steriade, 1996). Slow waves (0.5–4 Hz), known as delta waves, and spindle waves (7–12 Hz), are prevalent during SWS and disappear upon arousal. Higher frequency rhythms (30–60 Hz), called beta waves, have been described in many areas in conditions requiring attention to be paid to defined pieces of information.

Traditionally, spindle waves and alpha waves have been associated with a thalamic origin, while delta and beta waves are assumed to be cortical in essence (Castro-Alamancos and Connors, 1996; Contreras et al., 1996; Munk et al., 1996; Nicolelis et al., 1995; Steriade, 1996). Delta waves are related to the capacity of pyramidal cells of layer V to produce rhythmic activity endogenously. Interest in the origin of fast (30–60 Hz) oscillations has risen since the demonstration that these rhythms are associated...
with the synchronous firing of cortical neurons sensitive to similar stimulus features, even if these neurons are separated spatially by up to a few millimeters. Cortical synchronization also is proposed to occur during language processing of verbal information (Rocha, 1990). Intracellular recording from layer IV sparse spiny neurons in vitro reveals an intrinsic propensity for generating trains of action potentials at rates of around 35–50 Hz, that can be self-sustained for brief periods and appear to depend upon the activation of voltage-sensitive Na⁺ currents. Llinás et al. (1991) proposed that these layer IV neurons may be capable of coordinating the activity of local populations of pyramidal cells in other layers.

Glutamate and aspartate have been proposed to be major excitatory transmitters in the cerebral cortex (Aoki et al., 1994; Edwards, 1995; Hasselmo, 1995; Johnson and Burkhalter, 1994; McCormick, 1992; Salt and Eaton, 1996). Intracellular or extracellular in vivo recordings demonstrate that activation of thalamocortical fibers results in monosynaptic EPSPs in cells in layers III, IV, V and VI, which possess dendritic elements in layer IV, the major terminal lamina of LGN efferents (Figs 15 and 16). Cells immunoreactive for glutamate or aspartate are found in abundance throughout layers II–VI. Also, it seems that all pyramidal cells use glutamate or aspartate as neurotransmitters independently of the final destinations of their axons, whether intracortical or extracortical. Both AMPA/kainate and NMDA receptors are proved to be involved in the glutamate/aspartate transactions in the sensory cortex, the first ones being responsible for fast response and the latter involved with a somewhat slower and highly voltage-dependent component of EPSPs. In addition, cortical responses to NMDA receptor activation are controlled by extracellular glycine, as in other neuronal systems. Activation of mGluR on some types of cortical pyramidal cell, such as the burst-generating neurons of layer V, results in a marked and prolonged depolarization of these cells. In the burst-generating cells, this action typically results in a shift in the firing in mode of the cell from one of rhythmic burst firing to one of single-spike activity (McCormick, 1992).

Different sets of thalamic neurons are assumed to enervate the visual cortex (Fig. 16): the neurons

Fig. 16. Organization of the primary visual cortical areas. Visual information arrives from thalamus through two major pathways: the Magnocellular (M) and Parvo (P) cellular systems. A special P component gives rise to the Blob system in cortical layer 2, whereas the remaining P and M elements enervates the spiny Stellate Cells in the cortical layer 4. The smooth Stellate Cell is enervated by Pyramidal neurons from layer 6. Stellate neurons provide a major input to all pyramidal cells at layers 2 and 3. Pyramidal neurons from layers 5 and 6 send their axons predominantly to other visual cortical areas. Information from these areas re-enter the visual primary cortex to innervate pyramidal neurons reaching layer 1. Fibers from the Reticular Activating System (RAS) as well as Noradrenergic (NA), Dopaminergic (DA) and Serotonergic (5-HT) axons enervate pyramidal cells and are numerous at the superficial layers.
from the parvocellular system (P) carry information predominantly about color and spatial relations, while neurons from the magnocellular system (M) transmit information about movement and coarse spatial distribution. A special P component reaches layer II and give rise to the blob system in charge of color analysis (Fig. 16). Spiny stellate neurons are in charge of distributing sensory information arriving at layer IV to other layers. All these anatomical details explain the complex and wide distribution of glutamate/aspartate receptors in the visual cortex.

The GABAergic neurons in the visual cortex have been shown to form a heterogeneous population with multiple subtypes including, but not limited to, basket cells, chandelier cells, and double bouquet cells (Hasselmo, 1995; McCormick, 1992). Exogenous application of GABA to the sensory cortex results in a potent inhibition and a large increase in membrane conductance, which appear to involve a least distinct ionic responses. Application of GABA \_A receptor agonist results in a selective increase in Cl\^- conductance with a reversal potential of around \(-75\) mV, while application of the GABA \_B receptor agonists results in an increase in K\^+ conductance, which exhibits a reverse potential of around \(-100\) mV. Interestingly, maximal increases in Cl\^- conductance are much larger than maximal increases in K\^+ conductance, suggesting that GABA \_A-mediated IPSPs may work more through 'shunting' inhibition while GABA \_B-mediated IPSPs inhibit neuronal activity largely through changes in membrane potential (McCormick, 1992). Activation of different fibers results in a two-phase response. The fast IPSP peaks at about 30 msec and lasts for approximately 100 msec and is associated with a maximal 40–100 nS increase in Cl\^- conductance. The late IPSP activates more slowly, peaking at about 135 msec, lasting for 300–400 msec and is associated with a maximal 5–20 nS increase in K\^+ conductance. Of the different response properties of visual cortical neurons, the ones in which a role for intracortical GABAergic mechanism is best supported is the antagonism between subfields of the receptive field and the formation of direction selectivity.

Intracellular recordings in vivo revealed that Ach induces a depolarization of cortical pyramidal cells, that is due to a decrease in K\^+ conductance. This seems to be a consequence from the block of the voltage dependent K\^+ current \(I_{M} \), the Ca\(^{2+}\) activated K\^+ current \(I_{AP} \) and a variable block of the K\^+ leak current \(I_{L} \) (Hasselmo, 1995; McCormick, 1992; Sah, 1996). The \(I_{M} \) is activated by depolarization of the membrane potential positive to approximately \(-65\) to \(-75\) mV, it is non-inactivating, and activates and deactivates over approximately 100–200 msec. The analysis of the \(I-V \) plots of \(I_{M} \) reveals its selective block by the muscarinic receptors. Since \(I_{M} \) is activated by depolarization and does not inactive, it acts as a 'break' upon tonic depolarization and contributes to the initial portions of the process of spike frequency adaptation. The \(I_{AP} \) contributes substantially to the slow afterhyperpolarization (hence its name) that appears after a train of action potentials (McCormick, 1992). The studies of iontophoretic application of ACh in the cerebral cortex shows that the effect of ACh is facilitation of the response of the cortical neuron to stimulation of its receptive field, accompanied by relatively small increases in background firing rate.

Noradrenergic fibers are abundant throughout all layers in the neocortex and are provided by neurons of the locus coeruleus, however, \(\alpha_1 \) receptors predominates in layers I–III. Extracellular application of noradrenaline to cortical pyramidal cells in vivo results in both inhibitory and excitatory responses, the first one due to activation of \(\beta \) receptors and the latter being attributed to the activation of \(\alpha \) receptors (McCormick, 1992; Milheusheva et al., 1994). The exact proportion of activated cells vs inactivated cells is difficult to be determined experimentally, but electrical stimulation of the LC results in largely suppressive effects in the superficial layers of the visual cortex (II, III and IV) but facilitatory or excitatory effects in the deeper layers V and VI.

Application of 5-HT to pyramidal cells results in three separate responses: inhibition through activation of a potassium conductance (\(I_{KG} \)) and excitation of enhanced responsiveness through reduction of \(I_{AP} \) and \(I_{M} \). Also, 5-HT excites a subset of superficially located GABAergic neurons. It seems that 5-HT may modulate the excitability of cortical neurons in a number of different manners, including simple inhibition, excitation, or voltage-dependent facilitation (McCormick, 1992). The cerebral cortex is heavily enervated by histaminergic axons and displays the presence of \(H_1 \), \(H_2 \) and \(H_3 \) receptors, but the role played by HA in the modulation of the cortex is not well understood.

The modulatory transmitter responses revealed in the cerebral cortex are of three main types: (1) increases (adenosine, GABA_A, 5-HT_1) or decreases (muscarnic, 5-HT_2, \(\alpha_1 \)) in membrane potassium currents, (2) decreases in the Ca\(^{2+}\)-activated \(I_{AP} \) (muscarnic, \(\beta \) adrenergic, \(H_2 \), 5-HT_1), and (3) decreases in the depolarization-activated potassium current \(I_{M} \) (muscarnic, 5-HT, mGluR). Increases in potassium conductances are associated with inhibition of neuronal activity through hyperpolarization of the membrane potential. Decreasing in resting potassium conductance in regular spiking cells results in an increase in excitability, owing to the decreased distance to the firing threshold. In burst firing neurons, on the other hand, depolarization result in a shift in the firing mode from one of rhythmic burst firing to one of tonic single-spike activity. Such alterations in the intrinsic firing mode of cortical neurons could contribute substantially to the suppression of slow wave rhythms during periods of increased arousal and attentiveness. In addition, the switch to single-spike mode of action potential generation is associated with an increased ability to respond to excitatory inputs which arrive at high frequencies. Decreases in \(I_{AP} \) will result in a selective increase in responsiveness of cortical neurons to trains of EPSPs, with little effect on the resting membrane potential or response to IPSPs. The M current can be viewed as a K\(^+\) current which biases neurons from being depolarized for more than a few milliseconds, therefore restricting the length of any codeword \(w \), defined by the spike-firing distribution over the pyramidal spike train.
The IAHp modulation is another mechanism to control codeword spacing, since it is a key element in determining the size of afterhyperpolarization following pyramidal spike firing.

Sensory information is assumed to be directed from thalamus predominantly to layer IV, where it may activate spiny stellate cells in charge of distributing information upon pyramidal cells distributed in all other layers (Fig. 16). Monosynaptic activation of pyramidal cells also may occur. The final result is the activation of AMPA/kainate receptors to produce a fast EPSP response which may be followed by a NMDA component. It must be remembered that magnitude of this response is dependent on the Mg2+ blockade that is voltage sensitive. The output of pyramidal cells in layers II and III is directed mainly to secondary sensory areas, which comprise a huge set of areas in the case of visual systems. The purpose of the analysis in these secondary areas is to process stimulus features whose complexity increases along the hierarchy established among the many secondary or association cortical areas. The result of such a processing is the recognition of complex relations among the incoming stimuli, which may result in the recognition of highly informational sensory patterns. The activity of these upper areas in the sensory hierarchy is fed back to the primary visual areas, activating the dendrites of the pyramidal cells reaching layer I (Fig. 16). The mGluR and NMDA receptors are in charge of transducing this incoming activity into a modulation of the activity of the pyramidal cells already triggered by the original sensory information because, in general, the corticocortical enervation is established at the most distal dendrite locations compared to the thalamocortical synapses. It is interesting to remember that Ca2+ inward currents carried by NMDA channels may be used to tune calmodulin signal transduction pathways and that mGluR may activate other signal transduction pathways.

The result of this may be that the returning cortical activation may now be associated to events other than ionic conductance-modulated pyramidal responses. Worth noting is the dependence of sensory consciousness upon the re-entrance of information from secondary cortical areas around 100 msec after the arrival of the original sensory activation of the primary pyramidal neurons, that may be associated with the activation of the above signal transduction pathways. The information re-entry in the primary sensory areas is recorded as negative components in the EEG (Cauller, 1995). Figure 17 shows EEG-averaged responses to a sequence of noise clicks regularly presented at 2 Hz frequency to human volunteers, followed by a silent period in which EEG epochs were selected for averaging according to the same 2 Hz signal used previously to synchronize the noise click production and used now to mark the epoch of the missing stimulus. This silent period occurred between two series of stimulation with different click frequencies, and the volunteer was instructed that it would be required to estimate the relation between the frequency on both series of stimuli. Comparison of EEG activity during the perception of the real clicks to that associated to the click mental images during the silent period clearly shows that consciousness of the real sound is associated with an EEG activity composed of waves more negative than those related to the click mental images over the temporal but not the parietal areas. These pieces of information seem to point to a dependence of sensory qualia upon the activation of some specific signal transduction pathways (e.g. Ca-calmodulin or glutamate metabotropic pathways), in some defined (e.g. layer V pyramidal neurons) cortical locations. Another important implication of the sensory re-entry at layer I may be the editing of the original sensory information provided by peripheral systems, taking into consideration pattern recognition by high-order neurons in the sensory hierarchy. The image edition may fill in missing details or sharpen fuzzy data to improve the quality of the perceived information. The edited information may be retransmitted to the thalamic relay station by means of the precisely reciprocal enervation to enhance further edited features and to other cortical or subcortical areas in order to support other decisions being made (Fig. 16).
9. DISTRIBUTED CELLULAR SYSTEMS

Undoubtedly, neurons are complex processing units taking profit from both electrochemical and biochemical transactions, to organize themselves into complex hierarchical systems, in charge of adapting the behavior of the entire organism to the demands of the surrounding environment. The high complexity of the neural systems, pointed to in the recent literature, claims for proposals of more powerful theoretical models about the brain functioning other than simple formal constructs based on the notion of electrical inhibition and facilitation of the axonic decision-making about spiking or not spiking. The purpose of the following sections is mainly to rewrite the knowledge discussed in the previous sections in a more formal way, in order to prepare the reader to accept that fuzzy formal languages (FFLs) may provide an adequate mathematical tool for describing a neural system as a distributed intelligent processing system (DIPS), where intelligence is achieved both by the way neurons specialize to solve particular tasks and by the way specialized neurons combine themselves to provide solutions to complex problems. Most of what is discussed below is derived from the work developed by our group following these guidelines (Pedrycz and Rocha, 1993; Pedrycz et al., 1995; Rocha et al., 1980, 1992, 1993, 1996a; Rocha, 1982a,b, 1992; Serapião et al., 1996).

9.1. Signal Processing

The set \( P \) of proteins encoded by a set \( G \) of genes, may be organized into different ordered sets of chemical interactions, each one associated to a signal transduction pathway. Some proteins act as triggers of these biochemical chains, while other subsets of proteins are activated at their intermediate steps or as end-products of the corresponding pathway. Also, the chemical transactions will involve chemical products \( C \) other than proteins. Given \( P = C \cup P \), i.e. the set \( P \) defined as the union of the sets \( C \) and \( P \), then a biological system \( BS \) (virus, mono or multicellular organism) is supported by a set of signal transduction pathways (Rocha et al., 1996b):

\[
BS = \{P, P_n, P, B, G\} \quad (5)
\]

where

(a) \( P \) is the set of initial chemical products \( C \cup P \);
(b) \( P_n \) is the set of intermediate chemical products \( C \cup P \);
(c) \( P_t \) is the set of terminal chemical products \( C \cup P \);
(d) \( G \) is the set of genes encoding the set \( P = P \cup P_n \cup P_t \);
(e) \( B \) is the set of biochemical reactions of the type:

\[
P_k \oplus \cdots \oplus P_l \rightarrow P_m \quad (6)
\]

denoting that the interaction \( \oplus \) among the products \( P_k \cdots P_l \) produces (or activates) \( P_m \), such that:

(f) a signal transduction pathway \( s(p_0, p_p) \) is characterized as the ordered set of reactions required to produce (or activate) \( p_p \), whenever \( p_0 \) is available, i.e.:

\[
s(p_0, p_1) = p_0 \oplus \cdots \oplus p_i \rightarrow p_{i+1} \oplus \cdots \oplus p_p \quad (7)
\]

A basic property of any \( BS \) is the closure of \( G \), meaning that the genes \( g \in G \) are also products defined in \( P \). That is, \( G \) is contained in \( P \), and \( G \cap P \) is reproduced by a copying process. A particular type of product, \( p \in P \), is obtained by the following type of biochemical chain:

\[
s(p, pr) = (p_1 \oplus \cdots \oplus P_l)_{m} \cdots (p_i \oplus \cdots \oplus p_j)_{m} \rightarrow p_r \delta
\]

In other words, \( pr \) is a repeated association of \( n \) strings \( (p_1 \oplus \cdots \oplus p_j)_m \) of size \( m \). Let \( p_0 \) be called a regular product. If the symbols \( p_1 \cdots p_j \) of \( (p_1 \cdots p_j)_m \) are the same \( (p_1 = \cdots = p_j) \), then \( pr \) is called the simple regular product, otherwise it may be called the complex regular product. A typical example of a regular product is a polymer. The cellular membranes, DNA strands, etc., are examples of complex \( p \). An enclosed \( BS \), denoted here as \( BS \) for cell, is defined as (Rocha et al., 1996b):

\[
C = \{P, P_n, P, M, B, G\} \quad (9)
\]

where \( M \) is a set of complex \( P \), enclosing the components of \( C \) into a defined (internal) space. In other words, \( M \) is a set of membranes defined by \( G \), each \( M_m \) partitioning \( P \) into:

(a) \( P^o \): the set of chemical products located outside the enclosure provided by \( M_m \);
(b) \( P \): the set of chemical products located inside the enclosure provided by \( M_m \); and:
(c) \( M^m \): the set of chemical products located at membrane \( M_m \).

If there exist one \( M_m \), called external membrane, defining an internal space containing all other membranes, then \( M_m \) partitions \( C \) into a family of partially ordered chemical spaces.

Three special subsets of elements of \( P^o \) are:

(a) the set \( R^m \) of membrane receptors: composed by those elements \( p_1 \) in \( s(p_0, p_1, \cdots) \) activated by \( p_0 P_{p_0}^o \), i.e. activated by initial products (ligands) available outside of the \( M_m \) encirclement;
(b) the set \( T^m \) of membrane carriers: composed by those elements \( p_1 \) in \( s(p_0, p_1, \cdots) \) moving \( p_0 P_{p_0}^o \) from the outside to the interior of the \( M_m \) enclosure, or by those elements \( p_n \), in \( s(p_0, p_1, \cdots, p_0) \) moving \( p_0 P_{p_0}^o \) from the interior to the outside of the \( M_m \) enclosure; and:
(c) the set \( A^m \) of membrane anchors: composed by those elements \( p_1 \) in \( s(p_0, \cdots, p_1, \cdots) \) located at specific sites \( k \) of \( M_m \), determining that the chemical transactions \( p_1 \oplus \cdots \oplus p_1 \) are to occur at the neighborhood of the site \( k \).

Thus, \( M_m \) organizes \( C \) into a set of chemical processing spaces supporting chemical transactions of the type:

\[
d(p_0, \cdots, p_n) = s(p_0 P_{p_0}^o, \cdots, p_n P_{p_n}^o) \quad (10)
\]

where \( p_0, p_0 P_{p_0}^o, p_1 P_{p_1}^o \) or \( R^m, p_n A_m \) and \( p_n T_m \).
defined by each \(M_{n}\) of \(M\). Here, \(d(p_0, \ldots, p_n)\) is defined as the signal pathway transducing \(p_0\) into \(p_n\).

There exists a family \(I_m\) of sets \(I^1, \ldots, I^m\) of a given \(M_m\), composed by a complex \(P\), whose function is to move chemicals of \(P\) inside the \(M_m\) encirclement from one place, \(k\), to another one, \(i\). These \(p_i\) define the so-called intracellular transport systems, like the axonic anterograde and retrograde systems, moving chemicals from the cell body to the axonic terminals and vice versa, respectively. Since membranes are also chemical products of \(P\), then some \(I^k\) of \(M_m\) may specialize in moving the entire encirclement defined by a given membrane \(M_k\) and contained in the encirclement defined by \(M_m\). These transport systems are specialized in moving vesicles inside the different intracellular spaces. Thus, \(I_m\) organizes the chemical transactions of \(C\), by distributing the chemical reactions \(P_0 \oplus \cdots \oplus P_n\) over the different chemical spaces defined by \(M\). Therefore, the cell \(C\) may be considered to be a very organized set of chemical spaces, each one specialized in supporting a defined set of biochemical chains of a given signal transduction pathway.

Two different \(C_i, C_j\) supported by the same genetic \(G\) are said to be functionally associated if they share a subset of products \(P\), which are terminal products of \(C_i\) and initial products of \(C_j\) (or vice versa), i.e.:

\[
\begin{align*}
(a) & \quad P_i \cap P_j \neq \emptyset \quad \text{at} \quad C_i; \quad \text{and} \\
(b) & \quad P_i \cap P_j \neq \emptyset \quad \text{at} \quad C_j
\end{align*}
\]

where \(\cap\) means the set intersection, \(\neq\) stands for different, and \(\emptyset\) denotes the empty set. Since elements of \(P_i\) may be promoters, inducers or repressors of genes of \(G\) at \(C_i\), the functional interaction between two different \(C_i, C_j\) may result into the specialization of \(C_j\) to produce (activate) a defined subset \(P_i\) from the possible set of final products \(P\), defined by \(G\). The specialization of \(C_j\) to produce \(P_i\) is accomplished by the selection of a subset \(G_k\) of \(G\) as the readable genes at this very same \(C_j\). A distributed biological system or organism (O) is a family of specialized cells sharing the same genetics \(G\).

### 9.2. Genetic Network

A remarkable characteristic of the biochemical cellular processing is its distribution over different cellular sites (e.g. membranes, cytoplasm, etc.) and compartments (e.g. nucleus, ribosome, Golgi complex, etc.), with the purpose of avoiding expensive separation procedures in a high homogeneous chemical space, necessary to isolate defined end products. Diffusion barriers and chemical sequestering are also tools to organize sets of chemical reactions into coherent and purposeful biochemical networks subserving an efficient cellular physiology. Evolution improved this distributed chemical processing from prokaryotes to multicellular organisms, by specializing organelles, cells, systems and organs. Even a virus needs an organized host environment to reproduce itself. Event sequencing is another basic property of life, supported by a hierarchical genetic control of the cellular biochemistry. Upstream genes are used to activate downstream reading of the information necessary to guide cellular reproduction, embryonic development, etc. An entire cellular system, the nervous system was created by nature to help both the spatial and sequential organization of information processing subserved by the more complex genetic networks of high-order animals.

A genetic network may be considered in its most primitive definition as a set of genes encoding a family of proteins and set of signal pathways to organize gene reading and protein synthesis. The reduction of the chemical language ambiguity may be achieved by means of a non-homogeneous distribution of chemicals and strings of amino acids (proteins) over a given processing space. In this way, proteins are produced (or activated) at defined places to be used at some other specific or broader sites. This implies moving chemical strings in a defined space through more or less specific carrier systems, supporting from mail to broadcasting systems as information channels.

Here, a genetic network \(GN_k\) supported by a genetic \(G\) is defined formally as (Rocha et al., 1996b; Serapião et al., 1996):

\[
GN_k = \{P_i,P_n,P_t,B,G,M,N\}
\]

where \(P\), \(P_n\), \(P_t\), \(B\), \(G\) and \(M\) are defined as in Equation (9) and \(N\) is a network defined by:

(a) a set \(A\) of discrete elements \(a_k\) called agents (also, organelle or operator), each of which has a defined set of spatial or logical addresses (or direction) \(D_k\) and it is specialized in processing a set \(B^k\) of one or more chemical reactions by \(B\). Thus:

\[
a_k = \{P_i \subset P_n \subset P_t \subset B, D_k\}; \quad (12)
\]

(b) a set \(I\) of information (mail or broadcasting) channels (Shannon, 1974) supporting a message (chemical) exchange among the elements of \(A\).

Given \(S\), as the set of strings or messages produced by a set \(A_j\) of agents, the information channels \(I_{ij}\) supporting the communication between a subset of agents (senders) \(A_i\) and another set of agents (receivers) \(A_k\) are specified by:

(c) a set \(D_{i,k}\) of physical or logical addresses \(d_{i,k}\) referring to the agents \(a_i\) producing (sending) messages to be delivered to (received by) \(a_k\) of \(A_k\):

\[
d_{i,k} \subset \{P_i \subset P_n \subset P_t \subset B, D_k\};
\]

(d) a family of cost function \(A_{i,k}\) describing time and space restrictions in transmitting messages throughout the corresponding channel:

(e) a mail system is defined when the sender (e.g. presynaptic neuron) knows the physical direction of the receiver perfectly (e.g. postsynaptic cell), to which a set of strings or messages (transmitters) \(S_i S_s\), in which the receiver is interested (has the receptor for), must be delivered. A broadcasting system is defined whenever the receiver (e.g. target cell) selects the set \(S_s\) of strings or messages in whose contents it is interested (e.g. hormones), from the set \(S_i\) produced by \(A_i\), and transmitted by a less selective channel (e.g. bloodstream).
channels operate, whether by mail or broadcasting. Defined, depending on the way the information, different spatial locations. From the formal point of view, may be either physically or logically organized, enhancing the computational power of the fuzzy language defined by their common genetics G: 

\[ \text{NN} = [C_\alpha, C_n, C_t, G, N_n] \]  

where:

(a) \( C_i \) is the set of input (e.g. sensory) cells recognizing the set of initial symbols \( P_i \) of \( G \);

(b) \( C_n \) is the set of intermediate (associative) cells producing the set of non-terminal symbols \( P_o \) of \( G \);

(c) \( C_t \) is the set of output (e.g. efferent neurons) cells associate with the set of terminal symbols \( P_t \) of \( G \); and:

(d) \( N_n \) is the communication network supporting the message exchange among these cells.

Any communication network \( N \) (either an intracellular \( N_c \) or intercellular \( N_n \) communication network) is supported by a set of information channels \( I \) (either intracellular \( I_c \) or intercellular \( I_n \) channels) in charge of transmitting a set of messages \( S \) supported by a grammar \( G \). The information capacity of each channel \( i \in I \) is measured by the entropy \( h(S_i) \) of the set of messages \( S_i \) it may transmit (Shannon, 1974) and \( h(S_i) \) is assumed to be dependent on the variability of \( S_i \), i.e.:

\[ h(I) = h(S_i) = -\sum_{p_i} m\log_2 p_i \]  

where \( p_i \) is the probability of \( s_i \) in \( S_i \), and \( m \) is the number of possible messages in \( S_i \). Also, the total entropy \( h(I) \) of \( I \) is defined as:

\[ h(I) = \sum h(I_k) \]  

where \( n \) is the number of channels in \( I \). Consequently, the entropy \( h(N) \) of the communication network \( N \) is calculated as:

\[ h(N) = -\sum_{k=1}^{n} p_i \log_2 p_i \]  

which means that \( h(N) \) depends both on the complexity of the set \( S \) of messages, as well as on the complexity of the set \( I \) of communication channels. On the one hand, the complexity of \( S \) is dependent on the complexity of its supporting grammar \( G \), which signifies that it depends on the complexity of the genetics \( G \) defining the signal transduction pathways supporting \( N \). On the other hand, the com-
plexity of I is determined by the complexity of the addressing system D of directions D_{ij} specified to construct I.

In the case of broadcasting systems (e.g. hormones), h(N) tends to be equal to h(S_k) because n in (17) tends to = 1. This implies that communication has to rely on a set of complex molecules providing the entropy required by the intended control of a complex set of signal transduction pathways. In the case of NNs, h(I) is a measure of the intricacy of the complexity of the family of receptors and downstream signal transduction pathways involved with the synaptic processing. However, transmitters tend to be simple molecules (e.g. amino acids) having low encoding power, then h(S_k) remains characterized mostly by the complexity of the family of receptors and downstream signal transduction pathways. In the case of ligand-gated ionic channels, h(S_k) greatly depends upon the entropy of the membrane electrical encoding, i.e. on the variability of spike train generation. Because of this, h(I) is assumed to be the main determinant of h(N). Neurmodulators support an intermediate system between hormones and NNs, depending almost equally on h(I) and h(S_k).

The real brain combines these three different approaches: hormone control, neurmodulation and axonic mail systems (commonly named NNs) to optimize h(N) concerning the costs of wiring and molecular synthesis. Broadcasting systems require the same messages to be produced in high amounts to be widely distributed, with no warranty of each message copy reaching the intended receiver. On the contrary, NNs trade numbers of message copies for numbers of axonic channels, in order to guarantee that the messages are delivered to the receivers correctly. The decision to organize a message system supported by hormones, neurmodulators or NNs must be based on the trade-off between the genetic cost of encoding and producing h(S_k) and the costs of replicating and addressing axonic channels.

Another important factor influencing the blackboard vs mail system decision is the temporal cost of message transmission. Broadcasting (either hormone and neurmodulators) heavily depends upon moving molecules by means of bloodstreams or intracellular transportation, whereas messages are transmitted rapidly either as (a) electrical signals through axons to release transmitters stored at the axonic terminals in the vicinity of the receiver; or by (b) small second messengers, e.g. like Ca^{2+} waves, moves along defined cellular pathways. It must be remembered that neuromodulators are molecules more complex than transmitters, the former being synthesized mainly at the cell body and transported to the axonic terminals, whereas transmitters are resynthesized mainly at the axonic terminals from products provided by the cell bodies of the pre- and postsynaptic cells, but locally recycled. Because of this, transmitters and neurmodulators are used by channel systems distinguished by different temporal cost for message transmission.

The main characteristics of broadcasting and mail systems, organized at the organic level, are similar to those systems associated to the communicative processes organized at the cellular level. Ions or small molecules (nucleotides) are used commonly as second messengers, but they must rely on a complex system guiding the ion diffusion inside the cell as in the case of Ca^{2+} waves, or associating nucleotides to more complex downstream signals like calmodulin, PKA, PKC, etc., to guarantee an adequate message addressing. Small molecules and ions are signals faster than large proteins composed by catalytic and modulatory subunits. Also, microtubular transportation systems may be assumed to play inside the cell a similar role played by axons at the organic level. Gas signals (e.g. NO) are also fast signals, but in general they may exercise their actions in a broad neighborhood, unless kept inside boundaries provided by neural glomeruli or rapidly destroyed by specific enzymes if not used for communication purposes.

10. FORMAL LANGUAGES

This section is devoted to the introduction of the concept of FFLs and to discuss some interesting characteristics of these formal tools which are of interest to biology. The reader not familiar to the use of mathematics to formalize biological concepts probably will feel no difficulty in following the main reasoning stream about the application of formal language theory to describe the physiology of the signal transduction pathways if he/she understands the above discussion about cellular systems, because of the perfect equivalence of the two descriptions.

10.1. Definition

The theory of formal languages was introduced as a formalism to support the analysis both of the human language as well of those artificial languages used in computers. According to this theory, a grammar G (e.g. Chomsky, 1957; Mizumoto et al., 1973; Negoita and Ralescu, 1975; Pinker, 1994; Rocha et al., 1980; Rocha, 1992; Searls, 1992) is a structure defined as:

\[ G = \{ V_s, V_n, V_t, P, \eta \} \]  

where:

(a) \( V_s \): is a set of initial or starting symbols;
(b) \( V_n \): is a set of non-terminal symbols;
(c) \( V_t \): is a set of terminal symbols;
(d) \( \eta \): is the empty element; and:
(e) \( P \): is a set of rewriting rules defined as:

\[ p: \alpha \beta \rightarrow \gamma \delta \]  

In other words, \( p \in P \) rewrites the string \( \alpha \beta \) as the string \( \gamma \delta \). \( \alpha \) and \( \beta \) are contextual strings, i.e. \( \alpha \beta \) is rewritten into \( \gamma \delta \) in the context defined by \( \alpha \) and \( \beta \). For the sake of simplicity, let:

\[ V^+ = V_s \cup V_n \quad \text{and} \quad V^* = V_s \cup V_n \cup V_t \]  

The derivation chain \( d(s_n,s_m) \) of \( s_n \in V^* \) of G is the
ordered set of productions required to transform the initial symbol $S_0$ into $s_i$. In other words:

$$d(s_0,s_n) = s_0 \beta \rightarrow s_1 \beta \rightarrow \cdots s_{n-1} \beta \rightarrow s_n \beta. \quad (22)$$

A formal language $L$ is defined as a sub-set of the strings generated by its supporting grammar $G$. The strings generated by $G$ and accepted as belonging to $L$ are called well-formed formulas (wff) of $L$ according to $G$. A string $s_i$, produced by $G$, is a wff of $L$ if it belongs to $V_1$. In other words, the strings $s_i$ accepted by the language $L(G)$ supported by $G$ are those wff($s_0,s_n$) obtained as:

$$\text{wff}(s_0,s_n) = d(s_0,s_n) = s_0 \rightarrow s_1 \beta \rightarrow \cdots s_{n-1} \beta \rightarrow s_n \epsilon V_1. \quad (23)$$

Thus, the sentence $\alpha s_0 \beta$ is accepted as a sentence of $L$ only if there exists at least one $\text{wff}(\alpha s_0 \beta, s \alpha s_j \beta)$ to rewrite it into $s_j \beta$ belonging to $V_1$. Comparison of the definitions in Equations (5)–(9) formalizing the biological knowledge about signal transduction pathways and the basic concepts of a formal language presented in Equations (19)–(23) clearly shows the adequacy of the formal grammars to handle the knowledge about the chemical actions supporting the cell physiology. Here, ligands are initial symbols that must trigger a chain of biochemical reactions to produce one or a set of related proteins (or terminal strings) in charge of controlling a given cellular process. The adequacy of the present approach is enhanced further in the case of fuzzy formal grammars (Serapião et al., 1996; Rocha et al., 1996a; Rocha et al., 1996b) as discussed below.

The processing of any derivation chain $d(s_0,s_m)$ is a sequentially ordered set of rewriting operations, each one involving:

1. Matching: the left-hand side of a prospective rewriting rule is matched to the symbols of the string $s_i$ being processed. If this matching succeeds, then:

2. Rewriting: the matched substring of $s_i$ is then substituted by the right-hand side of the accepted rewriting rule. Finally:

3. Acceptance: the membership of the final string $s_j$ produced by the derivation chain $d(s_0,s_m)$ to $V_1$ is evaluated in the closed interval $[0,1]$.

In the same way, biochemical reactions require matching among chemicals to guarantee the atomic interactions necessary to the production of more or less stable proteins or DNA strands, which may later be tested for errors, and tagged to destruction or error correction if necessary.

Now, let the following be defined:

(a) the degree of similarity (matching) $\mu(s_i,s_j)$ of two strings $s_i,s_j$ is a measure of Cartesian space $(V_1^*)$ to the closed interval $[0,1]$, where $l$ is the length of the largest of these strings. In other words:

$$\mu(V_1^*) \rightarrow [0,1] \quad (24)$$

$$\mu(s_i,s_j) \rightarrow 1 \text{ if } s_i \text{ tends to be equal to } s_j; \mu(s_i,s_j) \rightarrow 0 \text{ otherwise;}$$

(b) the degree of acceptance $\mu(s,V_1)$ of $s_i$ as a wff of $L$ is calculated as the maximum $(\forall)$ degree of similarity $\mu(s_i,s_j)$ of $s_i$ to the strings $s_j \epsilon V_1$. In other words:

$$\mu(s,V_1) = \forall \mu(s_i,s_j)V_1. \quad (25)$$

The above defines $L$ as a fuzzy language (Mizumoto et al., 1973; Negoita and Ralescu, 1975; Serapião et al., 1996; Rocha et al., 1980, 1996b). Now, if:

(a) $\mu(s_i,s_j)$ in Equation (25) is assumed to behave as a binary function assuming a value either 1 or 0, i.e.:

$$\mu(V_1^*) \rightarrow (0,1) \quad (26)$$

$$\mu(s_i,s_j) = 1 \text{ if } s_i \text{ is equal to } s_j; \mu(s_i,s_j) = 0 \text{ otherwise;}$$

and:

(b) $\mu(s_i,V_1)$ in Equation (25) is assumed to behave like an identity function, i.e.:

$$\mu(s_i,V_1) = 1 \text{ if } s_i \epsilon V_1, \text{ otherwise } \mu(s_i,V_1) = 0 \quad (27)$$

then $L$ becomes a crisp language of the type discussed by Chomsky (1957), Searls (1992) and others. Fuzzy grammars are specially adequate to handle the ambiguity of chemical specificity in signal transduction pathways, where the same ligand may activate distinct messengers in the same or different cellular contexts. Instead of speaking about degenerated encodings because the one-to-one relation between ligand and gene response is not experimentally observed, it is better to take the ambiguity of these chemical fuzzy grammars as a key issue subserving the variability of the chemical transactions required by the explosion of life variety on Earth.

### 10.2. Ambiguity

Fuzzy languages exhibit distinctive properties concerning crisp languages, because for any $s_i \epsilon V_1^*$, many $s_i \epsilon V_1^*$ may exist for which $\mu(s_i,s_j) > 0$. This means that many derivation rules $\alpha s_i \beta \rightarrow \alpha s_j \beta$ may be allowed to rewrite $s_i$ into different $s_j \epsilon V_1^*$. Since the ambiguity of a sentence $s_0$ of $L$ depends on how many derivation strings $d(s_0,s_n)$ exist providing different $s_n \epsilon V_1$, then fuzzy languages are naturally ambiguous. A good example of such ambiguity is the well-known promiscuity among families of transmitters or ligands and their receptors. The same transmitter or ligand may bind to different receptors of the same family and the same receptor may be activated by different transmitters or ligand-sharing homology groups or chemical motifs. The processing of fuzzy languages will require concurrent operations subserving a spatial distributed process because many derivation chains will be activated by the same set of initial symbols. The same set of transmitters of ligands are known to activate concurrent chemical transactions, which results into parallel activation of different biochemical pathways.
Fuzzy language ambiguity may be kept within acceptable ranges by means of constraints on the following (Rocha et al., 1996b).

1. Derivation chain length \( l(s_{o}, s_{i}) \): the combina-
tional power of fuzzy languages may be decreased by reducing the number of allowed derivation steps of any wff of \( L \). In other words:

\[
l(s_{o}, s_{i}) < x
\]  

(28)  

the actual value \( x \) being one of the parameters determining the degree of ambiguity of \( L \).

This may imply, in the case of the cellular chemical language, to restrain the maximal number of steps of a signal transduction pathway, i.e. keeping it finite and as small as possible.

2. Cardinality of \( V_{i} \): another important parameter determining the actual value of \( a(L) \) is the number of strings in \( V_{i} \), because the possibility of any string \( s_{i} \) to become a wff of \( L \) depends on the similarity \( p(s_{i}, s_{j}) \) of \( s_{i} \) to any \( s_{j} \in V_{i} \). Thus the number \( A(L) \) of the possible wffs of \( L \) is a function of the cardinality \( C(V_{i}) \) of \( V_{i} \):

\[
A(L) = C(V_{i}).
\]  

(29)  

3. Total number \( A(s_{k}) \) of available copies of \( s_{k}\in V^{*} \): at least one copy of the string \( x s_{k} \beta \) has to be available to allow the rule \( x s_{k} \beta \rightarrow x s_{j} \beta \) to be used given that \( p(s_{i}, s_{j}) > 0 \).

4. Total number \( A(s_{j}) \) of available copies of \( s_{j}\in V^{*} \): at least one copy of a string \( s_{j}\in V^{*} \) has to be available to allow \( x s_{j} \beta \) to be rewritten into \( x s_{j} \beta \) given that \( p(s_{i}, s_{j}) > 0 \).

5. Actual number \( A(x s_{i} \beta) \) of activated copies of the sentence \( x s_{i} \beta \) to be processed: at least one copy of the string \( x s_{i} \beta \) has to be selected (activated) to be rewritten. These constraints imply that both the type of the symbol and its quantity play important roles in determining the rewriting of fuzzy sentences. This is in sharp contrast to crisp languages requiring no attention to be paid to any string copying process.

6. Matching priority: whenever enough copies of \( A(x s_{i} \beta) \) are available to trigger all possible derivation rules \( x s_{k} \beta \rightarrow x s_{j} \beta \), \( p(s_{i}, s_{j}) > 0 \), \( k = 1, \ldots, n \), then priority must be given to those rules \( x s_{k} \beta \rightarrow x s_{j} \beta \) exhibiting the greatest values of \( p(s_{i}, s_{j}) \).

Thus, the possibility \( p(d(s_{i}, s_{j})) \) of using the derivation chain \( d(s_{i}, s_{j}) \), supported by \( x s_{k} \beta \rightarrow x s_{j} \beta \), \( p(s_{i}, s_{j}) > 0 \), \( k = 1, \ldots, n \), to rewrite \( s_{i} \) must be a function (\( \Phi \)) of both \( A(s_{i}) \) and \( A(s_{j}) \), i.e.:

\[
\rho(d(s_{i}, s_{j})) = \Phi\Gamma_{k=1}^{n}[A(s_{i}), A(s_{j}), p(s_{i}, s_{j})]
\]  

(30)  

\[
\Gamma(A(s_{i}) \times A(s_{j}) \times p(s_{i}, s_{j}) \rightarrow [0;1])
\]

The number \( A(x s_{i} \beta) \) of copies of the strings \( x s_{i} \beta \) produced (activated) by \( x s_{i} \beta \) may be assumed to be dependent on \( A(x s_{j} \beta) \) and \( \rho(d(s_{i}, s_{j})) \):

\[
A(x s_{i} \beta) = \Phi(A(x s_{j} \beta), \rho(d(s_{i}, s_{j})))
\]  

(31)  

or

\[
A(x s_{i} \beta) = \Phi([0;1]A(x s_{j} \beta), \rho(d(s_{i}, s_{j})))
\]

where \( \Phi \), \( \Gamma \) and \( \beta \) are t or s-norms (Rocha, 1992; Serapião et al., 1996). A t-norm is a mathematical operation satisfying the following requisites (Rocha, 1992):

(a) boundary condition: \( t(a,1) = a, t(0,0) = 0 \);

(b) monotonicity: \( t(a,b) \leq t(c,d) \) if \( a \leq c; b \leq d \);

(c) symmetry: \( t(a,b) = t(b,a) \);

(d) associativity: \( t(a, t(b,c)) = t(t(a,b),c) \).

An s-norm is defined if:

(e) boundary condition: \( s(a,0) = a, s(1,a) = 1 \)

and the above monotonicity, symmetry and associativity conditions hold. Once again, FFL properties of are shown to correlated perfectly well to the characteristics of the biological systems, because besides the dependence of the chemical reactions to the quality of the reagents, their dynamics also depend on precise quantic relations. It is a well-established fact that efficacy of the synaptic transmission depends on the amount of transmitters stored in the presynaptic places, the amount of receptors available at the postsynaptic cell, and the chemical affinity between transmitters and receptors. In this way, Equation (30) is a measure of the signal transmission at the synopsis, which is commonly named synaptic weight. Also, the quantum theory of synaptic transmission (e.g. Edwards, 1995; Kuno, 1995) assumes that \( (1) \) the amount of transmitter \( a(t) \) released by the incoming presynaptic activity is dependent on both the activity itself but also on the available amount of transmitter; \( (2) \) the postsynaptic response \( r \) to the presynaptic input is proportional to the amount of released transmitter, i.e. \( r = k \cdot a(t) \) and \( (3) \) the actual value of \( k \) is dependent on the available postsynaptic resources.

10.3. Logic Capabilities

Let the following conditions be given:

\[
s_{z}\beta \rightarrow s_{z}\beta \text{ given } s_{z}\beta \rightarrow s_{z}\beta, \mu(s_{i}, s_{j}) > 0
\]  

(32)  

\[
s_{z}\beta \rightarrow s_{z}\beta \text{ given } s_{m}\beta \rightarrow s_{z}\beta, \mu(s_{i}, s_{m}) > 0
\]

While crisp languages are supported by monotonic reasoning, fuzzy grammars support different kinds of non-monotonic logic, such as:

(a) default logic: because matching priority supports derivation chains of the type:

\[
\mu(s_{i}, s_{m}) \rightarrow 0 \Rightarrow s_{z}\beta \rightarrow s_{z}\beta
\]

unless \( \mu(s_{i}, s_{m}) \rightarrow 1 \Rightarrow s_{z}\beta \rightarrow s_{z}\beta \)

(33)  

i.e. given \( \mu(s_{i}, s_{m}) < \mu(s_{i}, s_{j}) \), \( s_{j} \) rewrites \( s_{i} \) unless \( s_{k} \) is available to rewrite \( s_{i} \). Here, the symbol \( \Rightarrow \) means to support. This may imply that ligand if \( s_{k} \) has a binding affinity to the receptor \( s_{i} \) higher than \( s_{m} \), then the same signal transduction pathway may undergo different activations in the presence of \( s_{m} \) depending on the \( s_{k} \) availability;

(b) finite resources logic: because it may be assumed that the available \( A(s_{k}) \) copies of \( s_{k}\in V^{*} \) is decreased by an amount proportional to the amount \( a(x s_{i} \beta) \) of copied sentences \( x s_{i} \beta \) when-
ever $s_k$ rewrites $s_i$ in Equation (32) then:

$$\lambda x s_i \beta \rightarrow \lambda x s_i \beta \text{ while } A(s_k) > 0.$$  (34)

This may imply that a given signal transduction pathway may be activated while resources are available. For instance, a given synapsis remains actionable while the transmitter pool is not depleted;

(c) threshold logic: because it may assume that a sentence $\lambda x s_i \beta$ or $\lambda x s_i \beta$ is allowed to be produced only if the number of available copies $a(\lambda x s_i \beta)$ of $\lambda x s_i \beta$ in Equation (31) is above a given minimum $\theta$, i.e.:

$$a(\lambda x s_i \beta) > \theta.$$  (35)

The axonic decision making about spiking or not spiking is a classic example of a threshold controlled event;

(d) temporal logic: temporal reasoning may be supported by fuzzy languages, since it may be assumed that time restrictions may be imposed upon the availability of the $a(\lambda x s_i \beta)$ copies of the string $\lambda x s_i \beta$:

$$a(\lambda x s_i \beta) = f(t).$$  (36)

As a matter of fact, the above types of logic may be considered as special cases in a broader family of logics, called:

(e) fuzzy logic: because it may assume that a sentence $\lambda x s_i \beta$ is rewritten as:

$$Q(p(d(s_i, s_j)) \rightarrow \lambda x s_i \beta \lor \cdots \lor p(d(s_i, s_k)) \rightarrow \lambda x s_i \beta = f(p(d(s_i, s_j)) \cdots p(d(s_i, s_k))))$$

where $Q$ is a logical quantifier (e.g. the majority of the rules, $\lor$ of $n$ rules, etc.); $\lor$ and $\land$ denote $\lor$-norms and/or $\land$-norms; $p(d(s_i, s_j))$ is a function of $A(s_i), A(s_k), p(s_i, s_j)$ and $f$ may be defined as a filtering function. Therefore, the reading of Equation (37) is:

The string $\lambda x s_i \beta$ is rewritten by $Q$

$$Q(\text{relevant rules } \lambda x s_i \beta \rightarrow \lambda x s_i \beta \lor \cdots \lor p(d(s_i, s_k)))$$

into the strings $\lambda x s_i \beta$  

$$\lambda x s_i \beta = f(p(d(s_i, s_j)) \cdots p(d(s_i, s_k))))$$  (37)

Moreover, if $s_i$ is rewritten according to the rules stored in its set of genes or DNA molecules.

### 10.4. Learning

The FFLs exhibit learning capabilities, because the available amounts $A(s_i), A(s_k)$ of $s_i, s_k \in \mathbb{E}^*$ in $\lambda x s_i \beta \rightarrow \lambda x s_i \beta$ rewriting $s_i$ into $s_k$ in $d(s_i, s_k)$, as well as the $s_i, s_k$ structures, may be assumed to be dependent on the success of the rewriting rule in contributing to the processing of a wff of $L$, i.e. dependent on actual value of $\mu(s_i, V_i)$. It may be proposed that (Serapião et al., 1996; Rocha et al., 1996b):

(a) rewarding: increases $A(s_i), A(s_k)$ whenever $d(s_i, s_k)$ succeeds in activating $s_i$ to which $\mu(s_i, V_i) \rightarrow 1$. This may be assumed to be a consequence from activating copying production rules of the type:

$$\rho s_i \rightarrow s_i, \rho s_k \rightarrow s_k$$  (39)

in the rewarding context $\rho$. Rewarding is to increase both and $A(s_i)$ and $A(s_k)$ whenever $s_i$ is an acceptable solution to the problem posed by $s_i$;

(b) punishment: decreases $A(s_i), A(s_k)$ whenever $d(s_i, s_k)$ activates $s_i$ to which $\mu(s_i, V_i) \rightarrow 0$. This may be assumed to be a consequence from activating copying production rules of the type:

$$\pi s_i \rightarrow s_i, \pi s_k \rightarrow s_k$$  (40)

in the punishing context $\pi$. Here, $\pi$ is the empty symbol, and Equation (40) means the destruction (or inactivation) of $s_i, s_k$. Punishment is to decrease both and $A(s_i)$ and $A(s_k)$ whenever $s_i$ is an unacceptable solution to the problem posed by $s_i$;

(c) reconsidering: decreases $\mu(s_i, s_k)$ whenever $d(s_i, s_k)$ activates $s_i$ to which $\mu(s_i, V_i) \rightarrow 0.5, \mu(s_i, V_i) < 0.5$. This may be assumed to be a consequence from activating and copying production rules of the type:

$$\lambda s_i \rightarrow s_i, \lambda s_k \rightarrow s_k, \mu(s_i, s_k) \lor \mu(s_i, s_k) > \mu(s_i, s_k)$$  (41)

in the context $\lambda$, which changes the internal structure of the strings $s_i, s_k$ to turn them less similar strings. Reconsidering is supposed to decrease the similarity among symbols promising to contribute to an unacceptable solution of the problem posed by $s_i$;

(d) reinforcing: increases $\mu(s_i, s_k)$ whenever $d(s_i, s_k)$ activates $s_i$ to which $\mu(s_i, V_i) \rightarrow 0.5, \mu(s_i, V_i) < 0.5$. This may be assumed to be a consequence from activating and copying production rules of the type:

$$\nu s_i \rightarrow s_i, \nu s_k \rightarrow s_k, \mu(s_i, s_k) \lor \mu(s_i, s_k) \lor \mu(s_i, s_k)$$  (42)

in the context $\nu$, which changes the internal structure of the strings $s_i, s_k$ to turn them more similar strings. Reinforcing is supposed to increase the similarity among symbols promising to contribute to an acceptable solution of the problem posed by $s_i$. 


In this way, both quantitative [(a) and (b) above] and qualitative [(c) and (d) above] learning may be used to reduce the ambiguity of fuzzy languages, because reconsidering and reinforcing are associated with change in the string symbol structure, whereas rewarding and punishment are associated with changes of the number of the string available copies. All the above processes result in modifying the possibility \( \rho(d(s_0, \ldots, s_i, s_k, \ldots, s_t)) \) of firing the derivation chain \( d(s_0, \ldots, s_i, s_k, \ldots, s_t) \), and they may be used to control language ambiguity. Learning may, therefore, be a powerful tool in shaping FFL ambiguity, and this FFL property is a key component of any intelligent system, if intelligence is assumed as the capability of non-deterministic systems to solve new problems or challenge posed by a continuously changing environment.

A remarkable property of the biological systems is the G closure pointed out before: once the strings \( g \in G \) are themselves strings produced by the language specified by \( G \). In this way, the genetic code is a FFL enjoying the capability of having its own structure modified by the above learning strategies. Reconsidering and reinforcing are formal concepts which may be related to the biological concepts of mutation and recombination, and reward and punishment may be assumed as tools for implementation of natural selection. String natural selection is supported if default and finite resource logic rules privilege the copying of those most successful strings whenever resource scarcity reduces the number of available string copies. Rewarding and punishment are also key elements in all neural learning strategies, including classic and operant conditioning, since the synapsis efficacy may be set, depending on how successful the NN is in providing an adequate solution to an environmental challenge. Reinforcing and reconsidering may be thought of as resulting in selection of different isoforms of the same ligand, receptor or downstream signal due to the success (or not) of a given signal transduction pathway in contributing to the solution of a given problem.

10.5. Non-Linear Fuzzy Strings

Linearity is not a necessary requirement in the process of string matching (Serapião et al., 1996; Rocha et al., 1996b).

Let the case be considered where \( s \in V^* \) are strings of the type:

\[
s = \pi \gamma_{\ldots} \beta_{\ldots} \]

where \( \pi \gamma_{\ldots} \beta_{\ldots} \) means any string of size \( n \). A non-linear matching \( \mu(s,s) \) between \( s \in V^* \) is defined in the case:

\[
\mu(s,s) = f(\mu(s,\pi), \mu(s,\gamma), \mu(\gamma,\beta))
\]

i.e. the matching between \( s, s \) is a function of the individual matchings \( \mu(s,\pi), \mu(s,\gamma), \mu(\gamma,\beta) \), the length similarities of \( \pi \gamma_{\ldots} \) and \( \gamma_{\ldots} \beta \), and the structural similarity \( \mu(\gamma,\beta) \) of \( \gamma \) and \( \beta \).

In this context, the strings:

\[
\pi \gamma_{\ldots} \beta_{\ldots} \quad \text{and} \quad \gamma_{\ldots} \beta_{\ldots}
\]

are called the foldings \( \phi(s) \), \( F(s) \) of \( s \), respectively, because the strings \( \alpha s \beta, \alpha s \beta \) may be folded at the substrings \( \ldots \gamma_{\ldots} \), \( \ldots \beta_{\ldots} \), to become functionally similar to the linear strings \( \alpha s \beta \), \( \alpha s \beta \). The folding possibility \( \rho(\phi(s), \phi(s)) \) is defined as function of both \( \mu(k/l) \) and \( \mu(\gamma,\beta) \), i.e.:

\[
\rho(\phi(s), \phi(s)) = f'(\mu(k/l), \mu(\gamma,\beta)).
\]

In this way:

\[
\mu(s_i,s_j) = f(\mu(s_y,s_z), \mu(s_y,s_z), \mu(s_y,s_z))
\]

i.e. the matching between \( s_i, s_j \) becomes dependent on the similarities \( \mu(s_y,s_z), \mu(s_y,s_z) \) between \( s_i, s_j \) and \( s_i, s_j \) and the folding possibility \( \rho(\phi(s), \phi(s)) \).

In this condition:

(a) \( \mu(s_y,s_z) \), \( \mu(s_y,s_z) \) is assumed to support the information primary encoding in \( s_i, s_j \);
(b) \( \mu(k/l) \) is assumed to support the information secondary encoding in \( s_i, s_j \); and:
(c) \( \mu(\gamma,\beta) \) is assumed to support the information tertiary encoding in \( s_i, s_j \).

The language supported by the non-linear matching defined in Equations (43)-(47) is called the non-linear fuzzy language \( L_n \) (Serapião et al., 1996; Rocha et al., 1996b). The non-linear grammar \( G_n \), supporting any \( L_n \), has a complexity higher than a linear grammar \( G_l \) supporting a linear language \( L_l \), because it includes a specific set \( F \) of rules associated to the folding processing of the strings of \( L_n \), i.e.:

\[
G_n = \{V_s, V_n, V_l, P, F, \eta\}
\]

where \( V_s, V_n, V_l, P, \eta \) are defined as in Equations (19) and (20), and \( F \) is defined as the set folding rules such as:

(a) folding:

\[
x \gamma_{\ldots} \beta_{\ldots} \gamma_{\ldots} \beta_{\ldots} \rightarrow \pi \gamma_{\ldots} \beta_{\ldots}
\]

defines \( \gamma_{\ldots} \) as the folding of \( \alpha s \beta \), \( \alpha s \beta \), i.e. \( F(\gamma_{\ldots}, \gamma_{\ldots}) = \gamma_{\ldots} \beta_{\ldots} \);

(b) cutting:

\[
x \gamma_{\ldots} \beta_{\ldots} \beta_{\ldots} \gamma_{\ldots} \beta_{\ldots} \beta_{\ldots} \rightarrow \pi \gamma_{\ldots} \beta_{\ldots}
\]

deconcatenates \( \alpha s \beta \), \( \alpha s \beta \), \( \alpha s \beta \) and \( \gamma_{\ldots} \beta_{\ldots} \);

(c) inserting:

\[
x \gamma_{\ldots} \beta_{\ldots} \gamma_{\ldots} \beta_{\ldots} \gamma_{\ldots} \beta_{\ldots} \beta_{\ldots} \rightarrow \pi \gamma_{\ldots} \gamma_{\ldots} \gamma_{\ldots} \beta_{\ldots}
\]

inserts the string \( \gamma_{\ldots} \) into the string \( x \gamma_{\ldots} \beta_{\ldots} \);

(d) reordering:

\[
x \gamma_{\ldots} \beta_{\ldots} \gamma_{\ldots} \beta_{\ldots} \beta_{\ldots} \gamma_{\ldots} \beta_{\ldots} \beta_{\ldots} \rightarrow \pi \gamma_{\ldots} \beta_{\ldots}
\]

folding, cutting and inserting may be used to reorder the symbols of a string \( x \gamma_{\ldots} \) into \( x \gamma_{\ldots} \).

The FFL string non-linearity is well correlated to the three-dimensional properties of the chemical biological transactions, where not only the chemical composition of a given molecule is important in conferring on it defined chemical properties, but also its spatial conformation is a keystone in determining the biochemical transactions it may engage into. The DNA reading is very dependent on its actual conformation induced by promoters, inducers
Table 1. Amino Acid Code

<table>
<thead>
<tr>
<th>Code</th>
<th>Amino acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Alanine (Ala)</td>
</tr>
<tr>
<td>C</td>
<td>Cysteine (Cys)</td>
</tr>
<tr>
<td>D</td>
<td>Aspartic (Asp)</td>
</tr>
<tr>
<td>E</td>
<td>Glutamic (Glu)</td>
</tr>
<tr>
<td>F</td>
<td>Phenylalanine (Phe)</td>
</tr>
<tr>
<td>G</td>
<td>Glycine (Gly)</td>
</tr>
<tr>
<td>H</td>
<td>Histidine (Hist)</td>
</tr>
<tr>
<td>I</td>
<td>Isoleucine (Ile)</td>
</tr>
<tr>
<td>K</td>
<td>Lysine (Lys)</td>
</tr>
<tr>
<td>L</td>
<td>Leucine (Leu)</td>
</tr>
<tr>
<td>M</td>
<td>Methion (Met)</td>
</tr>
<tr>
<td>N</td>
<td>Asparagine (Asn)</td>
</tr>
<tr>
<td>O</td>
<td>Tryplophane (Try)</td>
</tr>
<tr>
<td>P</td>
<td>Proline (Pro)</td>
</tr>
<tr>
<td>Q</td>
<td>Glutamine (Gln)</td>
</tr>
<tr>
<td>R</td>
<td>Arginine (Arg)</td>
</tr>
<tr>
<td>S</td>
<td>Serine (Ser)</td>
</tr>
<tr>
<td>T</td>
<td>Threonine (Thr)</td>
</tr>
<tr>
<td>V</td>
<td>Valine (Val)</td>
</tr>
<tr>
<td>Y</td>
<td>Tyrosine (Tyr)</td>
</tr>
</tbody>
</table>

and repressors, etc. Chaperons are special molecules in charge of folding proteins in defined shapes required for some biochemical transactions. This is just to cite a few very important examples of non-linear string processing in signal transduction pathways.

10.6. Chemical Languages

The following is an example from Rocha et al. (1996a) and Serapião et al. (1996) of how to use the above concepts to begin a formal description of chemical processing supported by the knowledge about the physiology of the signal transduction pathways. Let be given the following primitive dictionaries of symbols:

(a) the complementary sets \( N^+, N^- \) of nucleotides:
\[
N^+ = \{A, T, C, G, U\}, N^- = \{a, t, c, g, u\}
\]
where: \( A, a = \text{adenine} \), \( T, t = \text{thymine} \), \( C, c = \text{cytosine} \), \( G, g = \text{guanine} \) and \( U, u = \text{uracil} \);
(b) the complementary sets \( A^-, A^- \) of amino acids:
\[
A^- = \{A, \ldots, Y\}, A^+ = \{a, \ldots, y\}
\]

where each letter is assigned to one of the 20 amino acids composing all known proteins, according to the notation in Table 1;
(c) the complementary sets \( I^+, I^- \) of chemicals such as ions, metabolic products, etc.:
\[
I^- = \{A, \ldots, Z\}, I^+ = \{a, \ldots, q\}
\]
where each underscored letter represents a different chemical.

Here, complementary sets usually will be used to represent inactivated (\(-\)) and activated (\(+\)) states of the same symbols.

Now, let the matching properties among the symbol dictionaries \( S_a, S_b \) be described by means of two-dimensional matrices \( M \) of the type:
\[
M(S, S) = \left\{ |m_{ij}|, i=1 \text{ to } k, j=1 \text{ to } k \right\}
\]

where \( m_{ij} \) is the degree of matching between the symbol \( s_is_j \) and \( s_is_j \) measured in the closed interval \([0,1]\), such that \( m_{ij} \) tends to 1 if \( s_i \) tends to perfectly match \( s_j \) otherwise \( m_{ij} \) tends to 0. The matrix \( M(N) \) for \( N \) in Equation (53) may be the crisp ideal matrix:
\[
\begin{bmatrix}
A & T & C & G & U \\
A & 0 & 1 & 0 & 0 \\
T & 1 & 0 & 0 & 0 \\
C & 0 & 0 & 1 & 0 \\
G & 0 & 0 & 0 & 1 \\
U & 0 & 0 & 0 & 0
\end{bmatrix}
\]
meaning that adenine (thymine) perfectly matches (couples or translate into) thymine (adenine), cytosine (guanine or uracil) perfectly matches guanine or uracil (cytosine), or it may be a fuzzy (real) matrix:
\[
\begin{bmatrix}
A & T & C & G & U \\
A & m_{1,1} & m_{1,2} & m_{1,3} & m_{1,4} & m_{1,5} \\
T & m_{2,1} & m_{2,2} & m_{2,3} & m_{2,4} & m_{2,5} \\
C & m_{3,1} & m_{3,2} & m_{3,3} & m_{3,4} & m_{3,5} \\
G & m_{4,1} & m_{4,2} & m_{4,3} & m_{4,4} & m_{4,5} \\
U & m_{5,1} & m_{5,2} & m_{5,3} & m_{5,4} & m_{5,5}
\end{bmatrix}
\]

In the same way, the matrix \( M(A) \) of amino acid matchings required to describe protein interactions may be characterized. The correlations among amino acids and nucleotides are to be described by means of two different matrices \( M(N,A) \) and \( M(A,N) \), related to the genetic encoding of proteins and control of gene reading, respectively.

The set \( G \) of genes is assumed to be a set of strings composed by nucleotides \( n \in N = N^+ \cup N^- \), and each \( g \in G \) is composed by two substrings:

(a) the code string \( g^c \): each nucleotide triplet encodes a specific amino acid of a given protein or stop signal marking the end of the string, and:
(b) the control string \( g^c \): composed by nucleotides of size \( t \) of nucleotides describing the conditions to enable the gene reading and to control such a reading.
Thus:
\[
g_i = \{(n_i \cdots n_{i+t})_{1 \cdots n}\} \in \{(n_k \cdots n_{k+t})_{1 \cdots n}\}
\]

or:
\[
g_i = g^c \oplus g^c = g_i = \{(n_i \cdots n_{i+t})_{1 \cdots n} \oplus \{(n_k \cdots n_{k+t})_{1 \cdots n}\}
\]

where \( \oplus \) is a concatenation operator. Also, \( g_i \) may exhibit one of two states:

(a) activated gene, \( g_i \): whenever the symbols \( n_i \) composing \( g_i \) belong to \( N^+ \), i.e. \( n \in N^+ \); or:
(b) inactivated gene, \( g_i \): whenever the symbols \( n_i \) composing \( g_i \) belong to \( N^- \), i.e. \( n \notin N^+ \).

The actual state of the strings \( g_i \) and \( g^c \) is dependent on the relation between the actual environment conditions and the control conditions...
encoded by $g'$. Whenever promoters and inducers predominate over repressors, the gene is activated, otherwise it will be considered an inactivated gene. As a matter of fact, both the control and encoding strings may be considered to be composed of other substrings. In the case of $g'$, these substrings are:

(a) $g''$: the promoter strings which are composed mainly by thymine and adenine (TATA box), which must be activated in order to enable the gene reading;
(b) $g^i$: the inducer or enhancer strings, a set of strings whose activation speeds up the gene reading, i.e. augments the degree of $g^i$ activation; and:
(c) $g^r$: the repressor strings, a set of strings whose activation inhibits the gene reading, i.e. decreases the degree of $g^i$ activation.

Thus:

$$g'_i = g''_i \oplus g^i_1 \oplus g^r_1$$

and the gene activation becomes a three step process:

(a) first, an outside protein called promoter $p$, must attach ($\ominus$) to the promoter string $g''$ to enable it:

$$p \ominus g''_i \ominus g^i_1 \ominus g^r_1 \rightarrow g''_i \ominus g^i_1 \ominus g^r_1$$

(b) in the sequence, other chemical signals $i$, called inducers or enhancers, must bind to the inducer strings to activate $g^i$:

$$i \ominus g''_i \ominus g^i_1 \ominus g^r_1 \rightarrow g''_i \ominus g^i_1 \ominus g^r_1 \rightarrow g^i_1$$

(c) and, finally, repressor chemical signals $r$ must couple to the repressor string $g^r$ to inactivate $g^i$:

$$r \ominus g''_i \ominus g^i_1 \ominus g^r_1 \rightarrow g''_i \ominus g^i_1 \ominus g^r_1 \rightarrow g^r_1$$

In this way, the degree $\mu(g'_i)$ activation of $g'_i$ becomes a function $f$ of the activated strings $g''_i$ and $g^i_1$, and an inverse $f^{-1}$ function of the activated repressor strings $g^r_1$, i.e.:

$$\mu(g'_i) = f(g''_i, g^i_1, \ldots) \cdot f^{-1}(g^r_1, \ldots)$$

where $\cdot$ is a t-norm. The encoding $g''$ substring is a string of the type:

$$s_i[\cdots \gamma \cdots]s_j \rightarrow s_i = [1 \cdots 1]_p.$$ 

Any protein $p_\alpha P = P\cup p_\alpha P_\alpha$ in (5), is a string of size $p$ of symbols $a_i A = A^* \cup A^*$ equivalent to its gene encoding exon substring $[t_1 \cdots t_j]_p$, i.e.:

$$p_\alpha = [a_1 \cdots a_k]_p \equiv [t_1 \cdots t_j]_p$$

which is produced or available in an inactivated state at some specific cellular sites, to exercise an action at the same or different address, whenever activated by some incoming signal represented by another chemical string supported by the dictionaries in Equations (54) and/or (55). Now, given the dictionary $D = A \cup I$ and a genetic $G$, the following sets of proteins may be defined:

$$G : (D)^m \rightarrow T$$  

$$G : (D)^n \rightarrow R$$  

$$G : (D)^p \rightarrow M$$

where $m$, $n$ and $p$ are, respectively, the size of the strings the sets of molecular transmitters ($T$), membrane receptors or carriers ($R$), and secondary messengers or controllers ($M$). The set $D^+ = A^* \cup I^*$ will be considered as the set of activated chemicals and the set $D^- = A^* \cup I^*$ will be the set of inactivated chemicals. For example, ABCDEF may be considered an inactivate receptor $rER$, abc may be declared an activated transmitter $tET$ and DEFMPR may be assumed to be an inactive controller $mM$. Transmitters $t_i$ (primary messengers) are assumed to bind membrane receptors $r_j$ to activate secondary messengers $m_k$:

$$t_i \ominus r_j \rightarrow m_k$$

whose main action is to serve as trigger signal controlling the activation of other chemical chains. Some of these messengers will control metabolic chains involving both cyclic ATP, GMP, etc. Some other controllers may be directed to the nucleus to act as gene promoters, inducers or repressors. In this way, transmitters $t_i$ may be considered as initial symbols of a chemical grammar, using messengers $m_k$ as non-terminal strings to control the production of end-products encoded by a genetic $G$. In other words:

$$s_i[\cdots \gamma \cdots]s_j \rightarrow s_i = [t_1 \cdots t_j]_p.$$ 

For example, the binding of the activated transmitter $abc$ to the complementary site $ABC$ of the receptor $ABCDEF$ may be assumed to activate its site $DEF$, which may, in turn, couple to the controller $DEFMPR$ in order to activate and release the messenger string $MPR$. In other words:

$$abc \otimes ABCDEF \rightarrow ABCdef \otimes DEFMPR \rightarrow mpr.$$  

The released string $mpr$ may be directed to the nucleus to activate a gene $g_i$ in charge of specifying the production of the protein $KKLOP$:
mpr \otimes XYW \ldots vwww \ldots WYX
\rightarrow xyw \ldots vwww \ldots WYX \rightarrow \{t_1 \ldots t_j\} \rightarrow KKLOP
(76)

where \ldots vwww \ldots is the activated promoter substring, WYX is the inactivated repressor string, XYW and xyw are the inactive and active inducer substring controlled by mpr, and \{t_1 \ldots t_j\} is the exon string of the gene g, encoding the protein KKLOP. Now, the binding of an activated transmitter fgh to the complementary site FGH of another receptor FGHKLM may be assumed to activate its site KLM, which may, in turn, couple to the controller KLMNOP in order to activate and release the string NOP, which is a repressor the above gene g. In this way, the synthesis of KKLOP may be stopped. In other words:

fgh \otimes FGHKLM \rightarrow FGHklm \otimes klmNOP
\rightarrow nop \otimes xyw \ldots vwww \ldots WYX
\rightarrow xyw \ldots vwww \ldots wyx \rightarrow \eta
(77)

where \eta is the null symbol. Now, the FFL supporting the synaptic chemical language (SCL) may be defined as:

SCL = \{T, R \cup M, S, G, P\}
(78)

where:

(a) G is the set of genes defined in Equations (5) and (60);
(b) T is the set of initial symbols;
(c) R \cup M is the set of non-terminal symbols;
(d) S is the set of terminal messages produced as the result of the synaptic activation; and:
(e) P is the set of derivation chains of the type defined by Equations (73)-(77) associated to a set of signal transduction pathways.

10.7. An Example Genetic Network

Rocha et al. (1996a) used the above concepts to simulate the λ phage of the Escherichia coli genetic network responsible for decision-making about phage replication or incorporation into the host genome (McAdams and Shapiro, 1995). The rationality under this genetic decision is very similar to many other genetic decisions taking place in the nervous systems responsible for cellular differentiation, transmitter switching, etc. There are two main methods for describing the simulation of λ phage genetic network here. First, the composition and the behavior of this net is relatively well known, and the simulation results published by McAdams and Shapiro (1995) provide the adequate background to which the capability of FFL may be compared. Second, there is no equivalent body of knowledge in the literature concerning neural genetic networks, besides those discussed by Duclet and Changeux (1995) about the development of the neuromuscular junction. However, these authors pointed out the incompleteness of the knowledge concerning the genetic decision taking place at the different muscle cell nuclei about locally producing (or not) Ach receptors. For the sake of simplicity, the matching among amino acids is described here by means of the similarity between capital and small letters, although in stricter notation both strings must be encoded by different letters, and the corresponding matching matrix in Equation (56) must be defined. For example, if the transmitter abc is assumed to perfectly match the receptor MNOKLO if the following matching matrix is assumed:

\ldots K L \ldots O \ldots
\begin{array}{c}
a \\
b \\
c \end{array}
(79)

for the sake of simplicity, the same receptor will be denoted as MNOABC, assuming that ABC describes the same amino acid sequence originally described by KLO. In the same line of reasoning, the following is a very useful gene notation:

REP.PRO.IND.MPOST \ldots
(80)

where:

(a) the activated protein rep is the repressor to bind at the gene location REP composed by corresponding the complementary nucleotides to the amino acids r, e and p;
(b) the activated protein pro is the promoter to bind at the gene location PRO composed by corresponding the complementary nucleotides to the amino acids p, r and o;
(c) the activated protein ind is the enhancer to bind at the gene location IND composed by corresponding the complementary nucleotides to the amino acids i, n and d; and:
(d) the inactivated protein MPOST \ldots is encoded by the encoding substring:

g^e = MPOST \ldots
(81)

Finally, some amino acids, or combinations of them, are known to operate over other proteins, in order to fold or to cut them, to insert a new element into them, or to reorder their elements, etc. These are the operations defined in F of Equation (48), in the case of non-linear fuzzy grammars. In other words, the following operations may be assigned to a protein, according to their amino acid composition:

(a) folding:

abc!fgh! + ABC\ldots FGH \rightarrow ABCFGH + \{\ldots\}
(82)

i.e. the activated protein abc!fgh! folds the protein ABC\ldots FGH between ABC and FGH, independent of the actual composition of the string \{\ldots\}. An alternative semantic of the folding operator ! is:

abc???? + ABC\ldots FGH
\rightarrow ABCFGH + \{\ldots\} + abc????
(83)

i.e. the activated protein abc! does a fold of four amino acids in size in the protein ABC\ldots FGH after the site ABC, independent of the actual composition of the string \{\ldots\};
The Brain as a Symbol-processing Machine

(b) exchanging:

\[ abc\$DEF + ABC\_KLM_ \rightarrow ABC\_DEF_ + abc\$KLM \]  

\[ (84) \]

i.e. the activated protein abc\$DEF binds to the site ABC of ABC\_KLM_ and exchanges KLM for DEF. The operator $ is useful to change the state of activation of a site:

\[ abc\$def + ABC\_DEF_ \rightarrow ABC\_DEF_ + abc\$DEF \]  

\[ (85) \]

(c) deleting:

\[ %abc\$def + ABC\_DEF_ \rightarrowABC\_def_ \]  

\[ (86) \]

i.e. the rewritten string %abc\$DEF is destroyed after %abc\$def exercised its exchanging action;

(d) copying and appending:

\[ abc@ + ABC\_DEF_ \rightarrow ABC\_DEF + abc\$DEF \]  

\[ (87) \]

i.e. the activated protein abc@ copies the string DEF and appends it to itself;

(f) copying and releasing:

\[ abc\| + ABC\_DEF_ \rightarrow ABC\_DEF + abc\| + DEF \]  

\[ (88) \]

i.e. the activated protein abc@ copies the string DEF and releases it in the environment;

(g) merging:

\[ abc&def + ABC + DEF \rightarrow ABCDEF + abc&def \]  

\[ (89) \]

i.e. the activated protein abc&def combines the chemicals ABC and DEF into a new molecule ABCDEF.

Also, let the following connectives be defined:

(a) AND (\(\land\)) to denote that a string conjunction is required in any of the above operations. For example:

\[ \%mno + abc\$def + MNO \land ABC\_DEF_ \rightarrow MNO \land ABC\_def_; \]  

\[ (90) \]

(b) OR (\(\lor\)) to denote that a string disjunction supports any of the above operations. For example:

\[ \%mno\$def + MNO \lor ABC\_DEF_ \rightarrow MNO \lor ABC\_def_; \]  

\[ (91) \]

\[ \%abc\$def + MNO \lor ABC\_DEF \rightarrow MNO \lor ABC\_def_; \]  

\[ (92) \]

Any other string operation may be defined in a similar way, but it must be kept in mind that the above string transactions are dependent on the amount of available strings and on the degree of activations of some of the strings, as stated by Equations (30) and

(31). Also, any protein is composed by the matching (e.g. %abc, abc, etc.) and operator (e.g. $def, $DEF, @, etc.) strings. In this way: (a) proteins encode the rewriting rules of a fuzzy chemical language; and (b) any gene is composed by strings associated by means of stop signals or connectives and describes a fuzzy rewritten rule. Now, the following gene string may be defined to simulate the \(\lambda\) phage of \textit{E. coli}'s decision-making genetic network (Fig. 18), preserving the notation used by McAdams and Shapiro (1995):

(a) the PL gene: its promoter gpl is activated initially at the moment of the infection, and it determines the production of the proteins N, CIII, XIS and INT. Two gates control the velocity of gene reading by poly nu clease (POL), one of them between the N and CIII encoding strings, and the other between the CIII and XIS encoding strings. The gene is repressed by either the activated cro* or ci* proteins. PL is described by the following string:

\[ \text{CRO}^*_{\_gpl} \_\text{CI}^*_\_\text{POL}_{N} \_\text{CTN}_{gate1} \_\text{POL}_{C}; \]  

III.\_\text{CTN}_{gate2} \_\text{XIS}_{\_\text{POL}_{\_\text{INT} \_\text{AttP}_{;}}} \]  

\[ (93) \]

(b) the PR gene: its promoter gpr is activated initially at the moment of the infection, and it determines the production of the proteins CRO, CII, O, P and Q. Two gates control the velocity of poly nu clease (POL) reading, one of them between the CRO and CII strings, and the other between the P and Q encoding strings. The gene is repressed by either the activated cro* or ci* proteins. The PR gene is described by the following string:

\[ \text{CRO}^*_{\_gpr} \_\text{CI}^*_\_\text{POL}_{\_\text{CRO}_{\_\text{CTN}_{gate2}}} \_\text{POL}_{\_\text{C}} \]  

III.\_\text{POL}_{O} \_\text{POL}_{C} \_\text{CTN}_{gate3} \_\text{POL}_{Q_;} \]  

\[ (94) \]

(c) the PRE/PRM gene: its promoters GPRE and GPRM are inactivated initially at the moment of the infection, and it determines the production of the non-sense protein "CRO and protein CI. The GPRE is activated by cii*, and GPRM is activated by ci* and inactivated by cro*. The gene is repressed by either the activated protein cro* or ci*. Here, PR/RPM is described by the following string:

\[ \text{CII}^*_\_\text{GPRE}_{\_\text{POL}_{\_\text{CRO}_{\_\text{CTN}_{gate3}}} \_\text{POL}_{\_\text{C}}} \]  

III.\_\text{POL}_{O} \_\text{POL}_{C} \_\text{CTN}_{gate2} \_\text{POL}_{Q_;} \]  

\[ (95) \]

(d) the PAQ gene: its promoter GPAQ is inactivated initially and it is turned on by cii*, and it encodes the production of the anti-sense protein "q:

\[ \text{GPAQ}_{\_\text{CII}^*_{\_\text{POL}_{\_\text{Q}_{;}}} \_\text{POL}_{C}} \]  

\[ (96) \]

(e) the PI gene: its promoter GPI is inactivated initially and it is turned on by ci*, and it encodes
Fig. 18. After infecting host *Escherichia coli* cells, phage M either propagates as a prophage integrated into the host DNA (lysogeny) or becomes an actively replicating virus (lysis) in the non-prophage state. See text for further details. From Rocha *et al.* (1996a).

The production of the protein int:

\[
\text{GPI} \cdot \text{CII} \cdot \text{POL} \cdot \text{INT}; (97)
\]

(f) the PR' gene: its promoter GPR' is activated, and it encodes the production of many proteins required by a replicating virus. This production is governed by a gate controlled by the amount of the activated protein q:

\[
gpr'. \text{CTQgate} \cdot \text{POL} \cdot \text{S}.
\] (98)

The actual gene activation is considered to be a function of both the inducer and repressor activities (see Gene Activation Function in Fig. 19). For example, the repressor effects of the proteins ci* and cro* (see Fig. 18) upon the genes PR and PL are encoded by the following type of productions:

\[
%\text{croSGP}? + \text{CRO} \cdot \text{gpl} \ldots \rightarrow \text{CRO} \cdot \text{GPL} \ldots
\]

\[
%\text{croSGP}? + \text{CRO} \cdot \text{gpr} \ldots \rightarrow \text{CRO} \cdot \text{GPR} \ldots
\]

\[
%\text{ciSGP}? + \text{CI} \cdot \text{gpl} \ldots \rightarrow \text{CI} \cdot \text{GPL} \ldots
\]

\[
%\text{ciSGP}? + \text{CI} \cdot \text{gpr} \ldots \rightarrow \text{CI} \cdot \text{GPR} \ldots
\]

\[
%\text{ciSGP}? + \text{CI} \cdot \text{gpaq} \ldots \rightarrow \text{CI} \cdot \text{GPAQ} \ldots
\]

\[
\text{here } ? \text{ denotes a 'do not care' symbol. The production of ci and cro are specified by the gene PRE/RM and the protein cro is described in the gene PR. he repressor string } %\text{ciSGP}? \text{ is assumed to be delivered at CI* site2 to block the PL gene reading whenever its mRNA is read in the PRE/PRM gene. The}
\]

produced repressor strings are assumed to be distributed over different places, according to specific time/quantity cost delivering functions (see Protein Distribution Function in Fig. 19), describing the degree of difficulty in delivering the string at the required place. The repressor string %\text{croSGP}? is assumed to be available at CRO* site2, depending on the production ratio of the protein cro and the antisense protein cro, evaluated at the interaction site CRO2 (see Protein Activity Function in Fig. 19). The degree of repression of %\text{croSGP}? over PL and PR is assumed to be a function (see Gene Activation Function in Fig. 19) of the amount of available repressor string at the interaction sites CI or CRO and delivered at the sites 1 (PL) and 2 (PR) (see Fig. 18). The available amount of ci* at the interaction site UV is controlled by the amount of ultra-violet light (UV) in the environment, as proposed by McAdams and Shapiro (1995). The gene reading augmentation produced by the proteins ci* and cii* is encoded by the following types of production:

\[
%\text{ciSGp}? + \text{CI} \cdot \text{gprm} \ldots \rightarrow \text{CII} \cdot \text{gprm} \ldots
\]

\[
%\text{ciSGp}? + \text{CI} \cdot \text{gpre} \ldots \rightarrow \text{CII} \cdot \text{gpre} \ldots
\]

\[
%\text{ciSGp}? + \text{CI} \cdot \text{gpi} \ldots \rightarrow \text{CII} \cdot \text{gpi} \ldots
\]

\[
%\text{ciSGp}? + \text{CII} \cdot \text{gpaq} \ldots \rightarrow \text{CII} \cdot \text{gpaq} \ldots
\]

\[
\text{here } ? \text{ denotes a 'do not care' symbol. The production of ci and cro are specified by the gene PRE/RM and the protein cro is described in the gene PR. The repressor string } %\text{ciSGP}? \text{ is assumed to be delivered at CI* site2 to block the PL gene reading whenever its mRNA is read in the PRE/PRM gene. The}
\]
GENE ACTIVATION = mRNA

PROTEIN PRODUCTION

PROTEIN ACTIVITY

Protein distribution

The Brain as a Symbol-processing Machine

The inducer string %ci*$gp? is assumed to be delivered at C1*_site1 to activate the promoter PRM whenever its mRNA is read in the PRE/PRM gene. The inducer string %cii*$gp? is assumed to be available to activate the promoters PRE (site 1), PL (site 2) and PAQ (site 3), depending on the production ratio of the proteins cii and ciii evaluated at the interaction site CII*. The production of these proteins is controlled by the genes PR and PL, to be distributed over different places, according to specific cost-delivering functions. The degree of induction of each gene is assumed to be a function of the amount of available enhancer string at each delivering site. The promoter PRM is inhibited by the string %cro$gp? available at site CRO2_3. The gate control exercised by the protein N is encoded by the following type of production:

%ctn!????...! + POL......CTN_gateA~POL......

The polynomial DNA reading of an activated gene is encoded by the following type of production:

_gp?_ + GP?[poll---+pol[ + GP?lpol[

POL_cro_ + poll-----+poll + cro

POL_cii_ + poll--+pol[ + cii

e tc. (103)
where: \( g_p \) is the corresponding promoter of the genes \( PL, PR, PRE, PRM, PI, \) or \( PAQ \). The available amount of the string \( pol \) at the protein encoding site \( CRO, CI, CII, \) etc. is assumed to be dependent on the degree of promoter activation, time and the gate control state. For example, the string \( pol \) is assumed (see Fig. 18) (a) to be released whenever the promoter string \( GPR[pol] \) is activated; (b) to be available first at the encoding site \( CRO \) depending on the degree of activation of the promoter \( gpr \); (c) to act sequentially at the encoding sites \( CI, O \) and \( P \), depending on the degree of activation of the promoter \( gpr \) and the state of the control gate \( N_3 \); and (d) finally, to activate the reading at the encoding site \( Q \), depending also on the state of the control gate \( N_4 \). The state of the control gates \( N_3 \) and \( N_4 \) are set accordingly to the available amount of the \( n \) string at the sites \( N_3, N_4 \), respectively. For sake of simplicity, the production of any protein is encoded by the following type of rule:

\[
\text{PROD}_1 + \text{PROD}_2 + \%\text{prod}_1 & \%\text{prod}_2 \\
\rightarrow \text{PROD}_1\text{PROD}_2 = \text{protein} \quad (104a)
\]

where (a) each of the mRNA encoding one of the proteins cro, ciii, etc. is assumed to be a string of the type \( \%\text{prod}_1 & \%\text{prod}_2 \) (e.g. \( \%\text{cro1} & \%\text{cro2}, \%\text{ciii1} & \%\text{ciii2} \), etc.), describing the products \( \text{prod}_1 \) and \( \text{prod}_2 \) required to produce the corresponding proteins; and (b) the amount of copies \( a(P) \) of the protein \( P \) is assumed to be dependent on the available amount \( a(mRNA) \) of its mRNA and of the amounts \( a(\text{PROD}_1), a(\text{PROD}_2) \) of the raw components \( \text{PROD}_1, \text{PROD}_2 \), according to the function:

\[
a(P) = \min\{a(\text{PROD}_1), a(\text{PROD}_2)\} \times \]

\[
a(mRNA) \times \text{Max}_P \quad (104b)
\]

where \( \text{Max}_P \) is the maximum possible \( P \) production. Different protein production functions are defined for each product supporting the \( \lambda \) phage decision-making, depending on the degree of infection \( DI \) of the host by the \( \lambda \) phage as proposed by McAdams and Shapiro (1995). For example, high MOI induces a 10-fold increase on \( CI \) production and a two-fold augmentation on \( CRO \) compared to low MOI. Any of the above string manipulations involved the following steps: (1) to obtain the right side strings; (2) to execute the string operations; (3) to calculate the amount of produced strings; and (4) to distribute the produced strings to defined sites. These tasks are assigned to specific agents (e.g. promoter, ribosome, interaction site, gate, etc.), whose computational structure was composed by (a) an input interface: in charge of obtaining data from other agents or from specific sites in a blackboard; (b) a processing unit: in charge of handling the string operations and numeric calculations; and (c) an output interface: in charge of distributing production to specific places of the blackboard or delivering messages to specific agents. The agents perform the operations describe by a specific gene, were organized into defined nets and, according to the relations shared by them and by the ordered sequence, they are requested to perform their jobs. Two special agents (DI and RecA) inform the other agents about the degree of infection and the amount of UV in the environment. The order of activation of the different genetic networks is: \( PL, PR, PRE/PRM, PI, PAQ \) and \( PR' \). After the nets are processed, the phage actual state is calculated according to the rules proposed by McAdams and Shapiro (1995). The actual state of promoter activation, gate closure and string production are updated continuously and displayed by setting adequately their corresponding gauges in the output screen (Fig. 18), such that the user can follow the simulation being processed. A graphic display summarizes the results of the simulations. Figure 20 shows that the \( \lambda \) phage decision is for lysogeny in the presence of high DI, while low DI favors lysis. These results obtained by Rocha et al. (1996a) are similar to those published by McAdams and Shapiro (1995) using a modified version of the theory of electrical circuits as an adequate tool to the analysis and simulation of complex genetic networks. However, genetic networks are mainly symbolic computational devices because, although the amount of chemicals plays a central role in determining the output of many chemical reactions, quality is the key issue in determining which chemicals interact with which chemicals. The behavior of electrical circuits is dependent mainly on intensity of currents, although Boolean gates are largely responsible for the computational capacity of computers. Molecular encoding and processing are three-dimensional processes, while the theory of electrical circuits supports two-dimensional representations and calculations. Also, a 'fuzzy logic' capability is claimed to be an important issue in genetic networks (McAdams and Shapiro, 1995) in contrast to the 'crisp logic' of these computational gates. But fuzziness handling is what FFL is designed for. From this, Rocha et al. (1996a) concluded that FFL, rather than the theory of electrical circuits, provides a theoretical framework for genetic network modeling.

11. DISTRIBUTED INTELLIGENT PROCESSING SYSTEMS

The central subject of DIPS theory is the study of intelligent communities which comprise collections of interacting, coordinated and specialized agents. Agents specialize in data collecting (sensors), problem solving (experts), data communication (channels), acting upon the surrounding environment (effectors), etc. Intelligence is approached in terms of a society of communication of specialized experts (Chandrasekaran, 1981; Hewitt and Inman, 1991; Gasser, 1991, etc.). The brain and human societies are natural examples of DIPS (Dennet, 1991; Edelman, 1987; Luck, 1995; MacLeod and Laurent, 1996; Maunsell, 1995; Ornstein, 1991; Rocha, 1992; Sakurai, 1996; Singer, 1995; Stoerig and Cowey, 1995; Ungerleider, 1995). Microtheories are the way of formalizing knowledge in DIPS. A microtheory is defined to be a derivative calculus together with a prespecified operation that can check the correctness of any indi-
Fig. 20. Simulation results in presence of High (left) and Low (right) MOI. Evolution of gene activation is displayed for 11 consecutive simulation steps at the bottom of the figure. The concomitant variation of the produced amounts of the control proteins is shown at the middle graphics. The resultant produced end products are presented at the top functions. As described by McAdams and Shapiro, 1995; high MOI resulted into a quick lock-on of PRM and shut-off of PL and PR, because of (a) the PL/PR inhibition promoted by high levels of CRO and CI*; (b) PRM/PRE activation due to an enhanced production of CI* and CI*; (c) the early high production of Int PL and Int PI due to high levels of CI*. On the contrary, low MOI was associated to the maintenance of PL and PI activation, because of a low CRO production. The simulation step at which the lock-on is established depends mainly on the assigned production distribution functions. As difficulty increases, later is the lock-on. From Rocha et al. (1996a).

Asynchrony enables each participant to operate as quickly as possible given local circumstances (Hewitt and Inman, 1991), but it also favors conflict, because new information can generate new commitments conflicting with pre-existing not yet updated local commitments. Local authority enables participants to react immediately to changing circumstances (Hewitt, 1977; Hewitt and Inman, 1991), but they may have to consult (or be consulted by) more central decision makers when conflicts arise. Synchronous activity enforces agents to import and export data at more or less defined epochs to reduce any possible measure disagreement in a changing environment, or to keep pace with rhythmic events. Rhythmic activity in the brain is both a local subject...
Division and specialization of labor and multiple authorities can increase pluralism, diversity and robustness. However, these capabilities can produce conflict when the specialized commitments of multiple authorities are incompatible and come into conflict (Hewitt and Inman, 1991). There are numerous ways in which this can happen. It may have conflict over resources, one agent may unknowingly undo the results of another, the same actions may be carried out redundantly, etc. In general terms, the collection of agents may somehow fail to act as well-coordinated, purposeful team (Davis and Smith, 1983). This problem is due to the fundamental difficulty of obtaining coordinate behavior when each agent has only a limited, local view of the problem to be solved. Coordination could, of course, be guaranteed if every agent 'knew everything', i.e. it had complete knowledge. Complete information is at least impractical, whereas incomplete knowledge leads to inconsistency, conflict, etc. Any distribution of the problem-solving effort appears to imply incomplete, local knowledge, and therefore, conflict. Any central coordination certainly reduces the computational capacity of the distributed system proportionally to the computational capacity of the central scheduler. Self-reliance is the agent's capability to act using the resources available locally, whereas interdependence refers to its capacity to obtain resources elsewhere in order to act (Hewitt and Inman, 1991). The balance between self-reliance and interdependence is the key issue of any DIPS, to keep conflict within acceptable boundaries and to allow intelligence to emerge from the coherent activity of a team of agents. The DIPS is a partially opened (closed) system, because it is concerned with the trade-off between self-reliance (closure) and interdependence (openness). Knowledge in a closed system always means something locally situated, but some sort of generalization is what makes knowledge useful and what, ultimately, makes knowledge.

While the locality of action and information means that distributed problem solving is feasible, the necessity of incomplete knowledge means that guaranteeing coordinated activity is difficult. One general answer is to provide something that extends across the network of agents, something that can be used as a foundation for cooperation and organization: negotiation (Davis and Smith, 1983; Hewitt and Inman, 1991). Negotiation has four important components: (a) a common language shared by all involved agents; (b) a two-way exchange of information; (c) each party to the negotiation evaluates the information from its own perspective; and (d) final agreement, achieved by mutual selection. Negotiation is creative, it results in commitments among different agents in a joint course of action in problem solving. To enable distribution of tasks, there must be a way for experts with tasks to be executed to find idle experts capable of executing those tasks. This is called the 'commitment problem' (Davis and Smith, 1983). Participants with tasks to be executed negotiate with idle agents over the appropriate matching of tasks and agents. This negotiation may result in establishing commitments among these agents and the degree of commitment in the problem solution varies among agents. The success of any negotiation depends upon agents willing to reach a consensus, but it also depends upon the expressive power of the language used to negotiate. Negotiation is the main issue during the embryogeny, when apoptosis, cell replication and specialization shape the main nuclei and functional neural systems. Negotiation is also the main issue during learning, when local controllers and neuromodulators model synaptic transaction specifying the quality and quantity of ligands, receptors and downstream signals.

Stable alliances or systems of commitments even produce the demarcation and ongoing existence of individual complex agents, called here institutional agents, as units of knowledge and interactions. In other words, successful agents in solving a given class of problem may strengthen their commitments and may eventually start to act as a specialized team, such that they will always enrol together to solve the task they are specialized for. The elements of an institutional agent are organized into three general categories: (a) input agents: in charge of receiving messages to be processed; (b) associative agents: in charge of reasoning with the incoming messages; and (c) output agents: in charge of delivering messages according to the computations done by the associative agents.

11.1. Decision Making by DIPS

Physical indeterminacy, deductive indecision in circumscription, knowledge incompleteness, etc. have been pointed as some of the reasons that classic logic inference is inadequate to support reasoning in DIPS (Davis and Smith, 1983; Hewitt and Inman, 1991). The problem of physical indeterminacy may be illustrated by the example discussed by Hewitt and Inman (1991), of an intelligent automatic teller machine deciding which of two concomitant money withdrawal requests to honor if there were not enough funds available for both. No amount of knowledge of the physical circumstances in which the withdraw requests are made determines the outcome. Thus, the outcome cannot be decided deductively, even from complete knowledge of all circumstances. This is the deductive indecision problem. It may be solved by extra-logic arguments like priority, ranking of customers according to some criteria based either on a qualitative decision, e.g. good customers provide big profits, or statistical considerations, e.g. most frequent transactions are to be honored.

Self-reliance implies that no agent can describe fully its assumptions to another, yet they must mutually take some things for granted (default) to act jointly without conflict. This is called, by Gasser (1991), the joint qualification problem. However, when there has been some disparity at some level between two agents with different knowledge about the same situation, the conflict leads to a failure of action. So, how are they to determine where the cause of the failure lies? This problem is called the failure indeterminacy problem. According to Gasser
certainly well-distributed reasoners rely on agreement on many experiments and on many participants supporting a given decision, as well as on the weakness of opponent participants trying to discredit the same decision (Hewitt and Immn, 1991; Rocha, 1992). Again, the solution of the problem requires extra-

logic tools based on issues like relevance, frequency, credibility, consensu~s, etc. Approximate reasoning implies the need to make a decision in this uncertainty space as reliable as possible when supported by the minimal possible amount of knowledge.

11.2. Message Organization

The SCL discussed in the previous section provides the brain with a formal language to generate messages its neurons have to exchange among them. Thus, SCL may be said to be the language spoken by the neural DIPS agents and the messages it generates may be of two different types, as follows.

1. Reasoning messages: messages which are basic pieces of information for the problem solving. These messages speak about numeric or linguistic and dependent or independent variables of the problem domain. They are provided by sensory agents responsible for getting information from the external world, by associative agents in charge of combining information to support decision making, and by output agents generating the action intended to solve the problem. In the brain, this type of message is carried mainly by electrical codewords and FRTs.

2. Control messages: messages which basically are used to organize DIPS reasoning message exchange. In the brain, these messages are those transmitted by the modulators involved in learning and the controllers (e.g. differentiation factors, neuromodulators) involved in negotiation between pre- and postsynaptic cells. Controllers are local messages exchanged by neighboring agents to organize their transactions and possibly to associate them as a specialized team in solving specific tasks. The following is an example of how control messages may be processed at a given synopsis (Fig. 19):

(a) a controller Cc released by a neighboring neuron n« may modify, at the transition (synapsis) Pc, the action of the controller c2 in charge of specifying the available transmitter at the presynaptic place T: the action of the controller c1, activated at the transition S1, may be that of acting as a receptor ABC at the transition P1C. If no message is assigned to the place Cc, the transmitter cdf may be specified to be produced at the place T1. On the other hand, if the controller CDGabc is stored at the place Cc as the result of the activation of a neighboring neuron nC, or even nI itself, then another transmitter cdg may be selected to be stored at the place T1, as a result of the concatenation between the controller strings ABC and CDGabc:

(b) the same or another controller Cc may modify, at the transition (synapsis) PC, the action of the controller c3 in charge of specifying the available receptor at the postsynaptic place R: the action of the controller c3, activated at the transition S3, may be that of acting as a receptor MPR at the transition P3C. If no string is assigned to the place Cc, the receptor CDF may be specified to be produced at the place R, On the contrary, if the controller CEGmpr is stored at the place Cc as the result of the activation of a neighboring neuron nC, or even nI itself, then another receptor CEG may be selected to be stored at the place R, as the result of the concatenation between the controller strings MPR and CEGmpr.

The same neuron may produce precursor molecules P for different transmitters, and the synthesis of a specific transmitter t1 at a defined axonic terminal branch may be put dependent on a postsynaptic cell message Cc (Rocha, 1980a,b, 1992). The consequence is that different transmitters may be allocated to distinct terminal branches contacting different postsynaptic cells. Also, the same postsynaptic cell may produce different receptors R to combine with different presynaptic transmitters t1, depending on messages received from its presynaptic neurons. Each specific coupling between presynaptic transmitter and postsynaptic receptor activates different types of controllers, some of them to be used to specify the adequate receptor to be produced by the post...
A. F. Rocha

synaptic cell. Hence, the controller \( c_c \) plays an important role in the competition and cooperation between the different presynaptic cells for the control of the postsynaptic cell. These mechanisms are used to select the subset \( SCL_i \) of productions of \( SCL \) to be used by a neighboring collection \( N_i \) of agents of a DIPS. In this way, \( SCL_i \) may be said to be the SCL dialect spoken by \( N_i \). Control messages are, then, used to select the \( SCL_i \) used by \( N_i \) to produce its reasoning messages; also:

(c) a controller \( c_c \) released by a neighboring neuron \( n_i \) may, like modulators, modify both the transmitter releasing at the transition \( P_i \) and/or the filtering function \( f_i \) at the transition \( P_i \) (Fig. 21). In this way, controllers may modify locally both the relevance and confidence associated to reasoning message exchange, and may be used to adjust the semantics of \( SCL_i \) to describe the task being processed.

An institutional agent is, therefore, a set of neighboring elements speaking the same dialect \( SCL_i \), and committed in solving a defined task. Since messages are transmitted by both mail and broadcast systems, the notion of neighborhood may be either geographic or functional. In the case of brain, geography defines nuclei and functionality defines systems. In other words, a nucleus is a geographic institutional agent which may be involved in different systems specialized to solve distinct tasks. Modulators are global messages released by central managers in charge to evaluate goals, to act as moderators in case of complex negotiations, to elaborate global plans, etc. In this way, modulators guarantee coherence among the dialects \( SCL \), spoken at the different DIPS neighborhoods, and the embodiment of global directives into the \( SCL \) semantics. Each \( SCL_i \) dialect spoken by an institutional agent is supported by the signal transduction pathways activated at each of its elementary agents (neurons).

11.3. Organizing Knowledge

The use of concepts to abstract models from reality is an ancient strategy in our culture going back to the Greek ages (Sowa, 1984) and supported by extensive psychological research (Jackendoff, 1995; Ornstein, 1991; Pinker, 1994). Reasoning through concepts is a recursive process by means of which the modeling complexity is increased by using higher-order concepts derived either as abstraction or composition of lower-level concepts. For instance, a visual scene analysis is performed in the brain (Crick and Koch, 1990; Crick, 1995; Kandel, 1992; Rocha, 1992; Serapião et al., 1996; Sowa, 1984): (a) by, first, the processing of elementary features extracted by low-level neural circuits such as line detectors, angles processors, etc.; and then (b) the recognition of the full scene as a set of relations learned to hold among these elementary features. Sowa (1984) called precepts these elementary features extracted by low-level neural circuits (or primitive agents) and proposed concrete concepts to be supported by sets of learned relations among precepts. Abstract concepts are, then, built as a set of learned relations among concepts. Here, the word concept will be used in a general sense meaning either precept, or concrete or abstract concept, unless stated otherwise.

Let \( C \) be a set of concepts, \( R \) a set of possible relations to be established among these concepts and \( F \) a set of facts about the universe \( U \). A theory or model \( T \) about \( U \) is:

\[
T \supset C \times R \leftarrow F \tag{105}
\]

where \( \supset \) means contained and \( \leftarrow \) denotes supported. Thus, \( T \) is a set \( R \) of relations among concepts \( C \) learned or proved to hold in \( U \), because it is supported by a set \( F \) of facts extracted from \( U \). A high-order concept is a theory in a preceding low level of analysis. The following shows how Equation (105) is implemented in neural DIPS.

Let \( X \) be a variable to be defined as the restriction \( R \) over the universe of discourse \( U \) (Zadeh, 1975):

\[
R : X \times U \rightarrow [0,1] \tag{106}
\]

\[
x = u : R(u), u \in U, x \in X.
\]

Given a set \( T \) of linguistic terms (transmitters) \( t_i \), a linguistic variable \( X \) is defined by a family of \( n \) restrictions \( R_i \) over the universe of discourse \( U \) each one defining the semantics \( m_i \) of \( t_i \); \( M \) is a semantic rule associating each \( t_i \) to its semantics \( m_i \) (Zadeh, 1975):

\[
R_i : X \times U \rightarrow [0,1] \tag{107}
\]

\[
x = \{ t \in T | M(t) \equiv R_i(u), u \in U, x \in X \}_{i=1,n}.
\]

This means that the actual value of \( x \) is evaluated as the degree of memberships of \( u \in U \) to the fuzzy sets \( R_i(u) \) associated with each term \( t \in T \) (Zadeh, 1975). The following is an example of linguistic variable about temperature:

Fig. 21. Chemical control of the synaptic transactions. The synapses shared by neurons \( n_i, n_j, n_k \) constitute a complex structure that may be formally considered to be composed by places (e.g. \( T_1, R_1, M_1, C_1 \)) where strings (e.g. CDGabc, MPR, CDFmpr) are stored and transitions (e.g. \( M_2, S_1, P_1, P_2, P_3 \)) where the strings (messages) are processed. Arches join places to transitions. Messages from input places are moved to transitions to be processed, and strings produced at the transition are moved to the output places. See text for further details.
X = (-10°C, 60°C), T = (low, medium, high)  \hspace{1cm} (108)

M = \{u < 0°C, 0°C < u < 30°C, u > 30°C\}  \hspace{1cm} (109)

x = \{\mu_l(u)/low, \mu_m(u)/medium, \mu_h(u)/high\}

where \(\mu_l(t), \mu_m(t)\) and \(\mu_h(u)\) are the memberships of the actual value of the temperature to the fuzzy sets LOW (\(u < 0°C\)), MEDIUM (\(0°C < u < 30°C\)) and HIGH (\(u > 30°C\)), supporting the semantics of these same terms.

A sensory neuron \(n_i\) is defined if \(q\) by Equation (1) is assumed to be a measurement in the universe of discourse \(U\) and the filtering function \(f\) in Equation (1) is taken as the restriction \(R\) defining \(X\). In other words:

\[ q = u \]  \hspace{1cm} (110)

\[ v_j = f(q). \]  \hspace{1cm} (111)

The neuron defined by Equation (110) will be called here the fuzzy sensory neuron, and that defined by Equation (111) will be called the fuzzy linguistic sensory neuron. As a matter of fact, the fuzzy sensory neuron is a special case of the linguistic sensory neuron, when just one term (string) \(t_i\) is defined in \(T\). Both the set of terms \(T\) and the semantic set \(M\) may be assumed to be specified by controllers released by other neurons, which means that sensory neurons may be specified to make specific readings of \(U\) according to the reasoning involved in the decision making.

Let \(P\) be a set of readings performed by a neural DIPS about a family \(\{X^k\}_{k=1}^n\) of variables in \(U\), i.e.:

\[ P = \{x_i \in X^k\}_{i=1}^n, \text{ with } x_i \in \Omega_{1 \ldots n} \]  \hspace{1cm} (112)

The role of any primitive institutional sensory agent \(S_i\) of a neural DIPS is to recode \(P\) into a string \(p\) of symbols \(\{tm_1, \ldots, tp_P\}\), according to the relation \(R\) shared by points \(x_i \in \Omega_{1 \ldots n}\) in the sensory \(X^k\). Both \(R\) and \(T\) specialize \(S_i\), which in turn depends on the specialization of each elementary agent of \(S_i\) as well as on the commitments established among (relations shared by) these elementary agents. In this way, concrete concepts about \(U\) may be learned, both by specializing primary agents and by strengthening successful relations (commitments) among these agents. However, now, higher-order institutional agents \(H_i\) may create complex models or theories \(T_i\) about \(U\) support by facts \(F \subset \{T_i^{-1}\}_{i=1}^n\) to \(u\) using a set of concrete and abstract concepts C. In other words:

\[ T_i \subset C \times R \iff F \subset \{T_i^{-1}\}_{i=1}^n. \]  \hspace{1cm} (115)

This means that a theory \(T_i\) at the hierarchical level \(I\) is supported by facts provided by theories \(T_i^{-1}\) constructed at level \(I-1\). \(H_i\) is called reasoning agent.

The bottom-up process described by Equations (112)-(115) may now be reverted if \(T_i\) is supposed to be used to control a set of effector agents \(E_i\) in charge of acting upon \(U\). In other words, models of action \(M_i^{-1}\) may now be supported by a set of high-order theories \(\{T_i^{-1}\}_{i=1}^n\), such that:

\[ M_i^{-1} \subset C \times R \iff F \subset \{M_i^{-1}\}_{i=1}^n. \]  \hspace{1cm} (116)

\[ A \subset C \times R \iff F \subset \{M_i^{-1}\}_{i=1}^n \]  \hspace{1cm} (117)

where \(A\) is the desired action to be exercised upon \(U\). In general, this action \(A\) is supposed to modify some variables \(\{X^k\}\) defined over \(U\). This is because (103) may, in some conditions, be rewritten as:

\[ D(P) \subset C \times R \iff F \subset \{M_i^{-1}\}_{i=1}^n \]  \hspace{1cm} (120)

In this way, the neural DIPS is able to act over the same observed universe \(U\). This re-entrant action over \(U\) reduces the strength of the hierarchy described by Equations (112)-(120).

A high-order theory \(L^1\) may now be learned by some specialized institutional agents \(S_i, A_i, H_i^1\) and \(E_i\) to act upon \(P, P\) such that:

\[ P_1 \equiv L^1. \]  \hspace{1cm} (121)

In other words, \(P_1\) becomes a projection of \(L^1\) in \(U\). In this way, abstract concepts may be introduced in \(U\) by the complex agent \(L^1\):

\[ L^1 = \{S_i, A_i, H_i^1, E_i\}. \]  \hspace{1cm} (122)

In this condition, \(L^1\) may introduce in \(U\) at least some of the \(T_i\) learned by the DIPS it belongs to.
Hence, it may speak about the DIPS' concepts. If different DIPSs share the same theory $L^I$, they may also learn to share common theories $L^I$. This high-order theory $L^I$ is called the language spoken by these DIPSs, and its complexity is defined by the actual value of $I$.

The knowledge hierarchy introduced by Equations (112)-(115) provides another mechanism to cope with conflict, since knowledge at the $l$th level may be used to solve dispute at the $I-l$th level (Damasio, 1990; Rocha, 1982b).

### 12. VISUAL SYSTEMS

Research over the last three decades has yielded a wealth of information about the neural mechanisms underlying vision. Dozens of cortical visual areas, characterized over the occipital, temporal, parietal and frontal lobes, have been shown to have a very complex network of bilateral connections (Fig. 22), and are proposed to specialize (at least partially) in the analysis of distinct characteristics of the visual input (e.g. Albright, 1995; Bullier et al., 1996; Crick, 1995; Hilgetag et al., 1996; Levitt et al., 1996; Maunsell, 1995; Miyashita, 1995; Nakamura and Kubota, 1996; Steriog and Cowey, 1995; Ungerleider, 1995; Walsh and Butler, 1996a; Schiller, 1996; Van Essen and Felleman, 1996). Owing to this, visual processing is now considered to be the task for a distributed system composed by numerous of neurons, which specialize in analyzing of a large number of features of the visual input and the relations shared by these primary features to characterize complex objects and scenes.

Also, the different visual systems are assumed to be organized under some hierarchy, whose strength is reduced by the many information re-entries from high-order areas into low stages of processing. This recursive processing of the visual input is claimed to be important for support of a state-dependent interpretation of the incoming visual image (e.g. Maunsell, 1995; Ungerleider, 1995).

#### 12.1. Central Organization of the Visual System

Visual data collected at the retina are proposed to reach the primary visual cortex ($V_1$) by means of three distinct geniculate channels: (a) the magnocellular ($M$) system that is proposed to be in charge of transmitting information about temporal (motion) and broad spatial relations; (b) the parvocellular ($P$) system that is believed to be involved deeply in providing information about fine spatial relations and luminance; and (c) the intralaminar ($I$) system — the main channel for color information transmission. The majority of $P$ neurons project to the layer $4C_\beta$ of cortical area $V_1$ (Fig. 16), and a smaller population projects to layer $4A$ in a cytochrome oxidase (CO)-rich lattice (Levitt et al., 1996). Most $M$ axons have terminal fields that provide synapses to at least the lower two-thirds, if not the entire depth, of layer $4C_\beta$, and nearly all $M$ axons provide collaterals to layer 6. The $I$ axons target the layer 2/3 CO blobs as well as layer 1. Visual area $V_1$ is shown to retain a retinotopic organization and to be specialized in extracting very primary visual features like edges, lines, etc. of particular orientation (simple cells), or covering all orientations (complex cells) in the visual field (Crick, 1995; Gochin, 1996).

A patient with lesions involving $V_1$ but sparing the other visual areas can detect stationary and moving stimuli, discriminate their orientation, motion direction and wavelength. The patients show reflexive responses, but in addition they can voluntarily initiate responses to visual stimulation and, under ideal conditions, their performance can be up to 100% correct. Nevertheless, when asked what...
they perceive, they insist that they do not see anything at all. At best, they say they feel something, which happens preferentially when stimuli are large or fast-moving (Crick, 1995; Dennett, 1991; Stoerig and Cowey, 1995). These patients lack the phenomenal experience of seeing, or the visual qualia. Once the lesion is beyond the primary visual cortex and destroys a portion of the secondary, extrastriate cortex, deficits such as achromatopsia, stereo-blindness, and motion blindness are observed, depending which of the specialized extrastriate cortical areas are damaged (Crick, 1995; Farah, 1996; Horel, 1996; King et al., 1996; Stoerig and Cowey, 1995).

Whereas neurons in V1 are interested primarily in simple features of the visual input (e.g. edges), those at later stages of processing represent increasingly complex aspects (e.g. face recognition) of the retinal image. Neurons in later states of the visual cortex can be extremely selective, responding only to specific complex forms or patterns of motion. Although V1 is the source of information to the other cortical areas, they also receive visual input directly from subcortical areas, and the activity of neurons in V1 is modified by re-entrant information from these high-order areas. This is because hierarchy among visual areas cannot be strong and some researchers (e.g. Schiller, 1996) criticize the dominant theory, proposing that complex pattern recognition by high-order areas is dependent on relations previously learned holding onto low features processed by low-order visual systems. Specialization of agents to recognize complex patterns is an useful strategy in creating both concrete and abstract concepts, but it has to be kept between boundaries, otherwise grandmother cells have to be created to recognize every trivial visual scene the animal is to supposed to register during his life. This means specializing a huge, although finite, number of agents so as to memorize these scenes. The intelligent solution in the case of visual systems must be similar to that found for natural language processing: (a) phonetic features are extracted at early processing stations and phonemes are recognized by subcortical neurons; (b) words may have individualized cortical representation at both Wernicke and Broca's areas; but (c) phrases are to be recognized by obeying the set of rules defining a grammar. In the same line of reasoning: (a) elementary features on the visual are recognized by specialized columns of early cortical visual areas; (b) simple images (e.g. squares, triangles, etc.) and complex ones (e.g. faces, car shapes, tree patterns, etc.) may have cortical representation at high-order visual areas depending on their relevance to the animal; but (c) scenes must be recognized by obeying a visual grammar, e.g. the rules of perspective, etc. The visual cortex areas are proposed to be organized into two functionally specialized processing pathways, each having the primary visual cortex V1 as its source and each being composed of multiple areas beyond V1. The occipitotemporal pathway, or ventral stream, is crucial for the identification of objects, whereas the occipitoparietal pathway or dorsal stream is crucial for the appreciation of the spatial relations among objects, as well as the visual guidance of movements toward objects in space (e.g. Battaglini et al., 1996; Farah, 1996; Gochin, 1996; Horel, 1996; Humphrey et al., 1996; King et al., 1996; Ungerleider, 1995; Walsh and Butler, 1996b; Tanaka, 1996; Yoshioka et al., 1996; Yoshioka and Dow, 1996). Ungerleider (1995) proposed that a simple way in which to conceptualize the function of the two streams is 'what' (temporal) vs 'where' (occipital) (see Fig. 22).

Creating representations of the retinal image is, however, just one component of vision. Vision is an active process that selects a limited part of the visual image for concentrated attention. Although non-selected portions of the image are not lost to perception, at any moment we can give full attention only to a severely limited amount of visual information (Maunsell, 1995). Once this subset of signals has been selected, it must then be interpreted. Thus, the events leading to visual awareness include a substantial editing process that de-emphasizes irrelevant information and adds interpretations and inferences about the meaning of the targeted information (Bressler, 1996; Chelazzi, 1995; Connor et al., 1996; Desimone et al., 1995; Luck, 1995; Orban et al., 1996; Ringo, 1996). State-dependent modulations uncouple the representations in the visual cortex from the retinal stimulus. A shift in attention can alter the pattern of activity throughout large regions of visual cortex without any change in the activity in the retina or other early levels in the visual pathway. By filtering out irrelevant signals and adding information about objects whose presence is remembered or inferred, the cortex creates an edited representation of the visual world that is modified dynamically to suit the immediate goals of the viewer (Maunsell, 1995). The human data, like those from monkeys, suggest that when we see a visual stimulus, visual cortical areas become active, and then afterward, when we hold the memory of that stimulus in 'mind', the prefrontal cortex becomes activated as well, presumably because its feedback projections are necessary for reactivating the representation of the stimulus in visual cortical areas (Ishai and Sagi, 1995; Miyashita, 1995; Ungerleider, 1995). If prefrontal cells are involved in activating object representation in visual areas during working memory, they may have an analogous role during the retrieval of information from memory.

12.2. Sensor: An Artificial Visual System

Sensor (Serapiao et al., 1996) is a distributed intelligent sensory system hierarchically organized in such a way that low-order agents are created to recognize elementary features of the incoming sensory input, and high-order agents are in charge of recognizing progressively more complex patterns associated to concrete concepts. The concepts are, in turn, assumed as the elementary components defining the set of symbols to be handled by a sensory grammar. In this condition, high-order abstract concepts arise as well-formed formulas (wff) of this grammar. The following is a brief formal description of Sensor.

Let Z be a set of pairwise observations:

$$Z = \{v_i, y_i\}_{i=1}^k$$

(123)

of the trajectory of a point p in the sensory XY
space. Specific features (border, shape, closure, etc.) of this trajectory \( P \) may be disclosed by the analysis of the relations (e.g. relative consecutive or alternate point positions, direction changes, etc.) shared by the points \( p \in P \). A couple \( c_i, v_i \) of associated \( c_i \) and \( v_i \) cells may be tailored to recode \( P \) into a description \( (s_i, v_i) \), furnishing both the string \( s_i \) describing the characteristics of a particular feature of \( P \), and its associated vectorial \( v_i \) location in the \( XY \) space. A family:

\[
\mathcal{D}(P) = \{(s_1, v_1), (s_2, v_2), \ldots, (s_n, v_n)\}
\]

of such descriptions may be used to classify \( P \) according to some specific prototypic patterns \( p \in P \). A multicellular system \( MCS \) may be organized to perform such a task. The example in Fig. 23 shows a cellular network tailored to process symbolic pattern recognition of shapes contained in scanned images \( P \), e.g. like the car bitmap depicted in the same figure.

The first step in this process is to obtain the description of the borders of the figure \( P \). This is the job of the cells \( B_{ori,j} \) using information provided by the cells \( L_{umi,j} \) and \( C_{onti,j} \) about luminance and contrast. Given the dictionary:

\[
d_1 = \{b = \text{black}, w = \text{white}\},
\]

the cell \( L_{umi,j} \) rewrites the scanned bitmap into the string \( s_1 \) composed by symbols of \( d_1 \) recoding the actual luminance in the linguistic variables black and white. The luminance is calculated taking into consideration the degree \( r \) of redness, \( g \) of greenness and \( b \) of blueness:

\[
luminance = 0.3r + 0.59g + 0.1lb
\]

such that:

- black if luminance < \( \alpha \), otherwise white.

The cell \( C_{onti,j} \) is in charge to rewrite the string \( s_1 \) into the string \( s_2 \) defined upon the following dictionary and rewriting rules:

\[
d_2 = [n, f]
\]

and the cell \( B_{ori,j} \) rewrites the string \( s_2 \) into the string \( s_3 \) defined upon the following dictionary and rewriting rules:

\[
d_3 = [g, h]
\]

Now, the cells \( D_{dirij} \) combines the above strings \( s_2, s_3 \) into another string \( s_4 \) of symbols from the following dictionary:

\[
\]

associated with the allowed directions in the \( XY \) space (see diagram in Fig. 23). The following grammar \( G_1 \) supports this processing:

\[
G_1 = \{V_{s1}, V_{n1}, V_{t1}, P, \eta\}
\]

where * means ‘don’t care’, to produce strings of the type:

\[
s_4 = \{DBC \ldots JGFHH\}
\]

Now, given that:

\[
Dx = x_i - x_j, Dy = y_j - y_i
\]

as the coordinate variation in \( v_1 \) of the neighboring cells signaling \( g \) in \( s_1 \), the cells \( P_{dir_{xi,j}} \) and \( P_{dir_{yi,j}} \) at the location \( Dir \) (Fig. 23) produce the strings \( s_3 \) and \( s_4 \) defined upon the dictionary:

\[
\{p = \text{positive}, n = \text{negative}, z = \text{zero}, a = \text{null}, b = \text{small}, c = \text{medium}, d = \text{big}, e = \text{huge}\}
\]

such that:

- negative \( \rightarrow \) \( Ax \) or \( Ay < 0 \)
- positive \( \rightarrow \) \( Ax \) or \( Ay > 0 \)
- zero \( \rightarrow \) \( Ax = 0 \)
- null \( \rightarrow \) \( Ay/Ax < \alpha_1 \)
- small \( \rightarrow \) \( \alpha_1 < Ay/Ax < \alpha_2 \)
- medium \( \rightarrow \) \( \alpha_2 < Ay/Ax < \alpha_3 \)
- big \( \rightarrow \) \( \alpha_3 < Ay/Ax < \alpha_4 \)
- huge \( \rightarrow \) \( Ay/Ax \geq \alpha_4 \)

Now, the cells \( D_{dir_{ij}} \) combines the above strings \( s_2, s_3 \) into another string \( s_4 \) of symbols from the following dictionary:

\[
\]

describing the directions shared by consecutive points composing the figure border. The following
string was generated in the location Dir$_1$ in the case of the car bitmap in Fig. 23:

\[
\text{HDDCCPCPPPPCCCCCPPPPPPPPPPPPM}
\]

\[
\text{CMLLKKHEEEHHHHHHHHHHHHH}
\]

\[
\text{KKKEEHHHH}
\]

\[
\text{D}
\]

(136)

The location DIR in the artificial system Sensor is supposed to correlate to the primary cortical area V$_1$.

In the sequence, the cells C.Dir$_{ij}$ at the location C.Dir rewrite the string $s_4$ into the string $s_5$ composed by symbols from the dictionary:

\[
\begin{align*}
z &= \text{no change}, & c &= \text{clockwise change}, \\
\text{d} &= \text{counterclockwise change}
\end{align*}
\]

(137)

describing the changes of directions between the bitmap cells associated with two consecutive symbols of $s_4$. Thus, $s_5$ describes the changes of direction in the figure border. The cells Psig$_{ij}$ at the location Psig search for the position of the following substrings: zcc, ddc, zdd, cdd, czc, zdz, zcc, zdd, and zdz, in $s_5$ to generate the vector $v_6$ containing the $xy$ coordinates where the above patterns of direction change occur. This vector describes the border points $p_{sign}$ (significant points) where an important change of direction occurs. Cells C.Dir$_{ij}$ and Psig$_{ij}$ use the following grammar $G_2$ to do such calculations:

\[
G_2 = \{V_{w}, V_{n}, V_{t}, P_2, \eta\}
\]

\[
V_{w} = \{s_4, v_4\}
\]

\[
V_{n} = \{z, c, d\}
\]

\[
V_{t} = \{S, N\}
\]

\[
P_2 = \begin{cases} 
zcc \rightarrow S & ddc \rightarrow S & zdd \rightarrow S & cdd \rightarrow S \\
zc \rightarrow S & zdz \rightarrow S & zcc \rightarrow S & zzd \rightarrow S \\
zc \rightarrow S & zdz \rightarrow S & \\
\text{otherwise} \rightarrow N
\end{cases}
\]

(138)

producing strings of the type:

\[
s_6 = [SNN, \ldots, S]
\]

(139)

associated with the vector $v_6$. The following is the vector generated for the example of the Fig. 23:
in the format x/y/z.

Now, another set of cells \( \text{Dir}_j \) at the location \( \text{Dir}_r \) (Fig. 23) recodes \( s_6 \) into the string \( s_7 \) describing the main directions among the \( P_\text{Sig} \) points of the P border. The following is the string produced in the case of the example of Fig. 23:

\[
s_7 = \{\text{HDDBBPCCPPMMCMMLKKEHHJKFFHD}\}. \tag{140}
\]

It must be noted that the number of cells in \( \text{Dir}_2 \) is smaller than the number of cells in \( \text{Dir}_1 \), such that the sensory fields of the former are bigger than those of the latter cells (compare \( L_2 \) to \( L_1 \) in Fig. 23).

The string \( s_7 \) is matched by the cells of Class (Fig. 23) to the strings \( p_1-p_n \) learned by corresponding cells in \( P_1-P_n \) to represent prototypical shapes of figures to be recognized as different types of cars, houses, ships, etc. If \( s_7 \) and \( p_1-p_n \) are considered to be non-linear strings, noisy characters may be skipped by means of string folding. The locations \( C_\text{DIR}, P_\text{SIG}, \text{Dir}_r, P_1-P_n \) and Class in the artificial system Sensor are supposed to correlate to non-striate cortical areas distributed over the occipitotemporal pathway. Cells in \( P_1 \) are assumed to encode complex patterns either of special cases (e.g. the shape of a particular car) or general classes or prototypical cases (types of cars, trucks, etc.). In this way, these cells correlate to those very complex cells in natural systems encoding, e.g. faces. In the first case, \( P_1 \) encodes a memory, in the latter it learns a pattern or concept; the cells of Class are in charge of discovering ‘what’ does exist in the visual input.

Alternatively, the vector \( v_r \) is matched by the cells of Perc to the vectors \( r_{x1}-r_{yn} \) learned by the corresponding cells in \( P_1-P_n \) to represent prototypical figures to be recognized. This approach was used by Alegre et al. (1993a,b) and Rocha et al. (1996b) to implement an automated pattern recognition for control purposes, and by Rocha and Rocha (1996) to classify different types of leaves. The choice of using \( s_7 \) or \( v_r \) for pattern recognition processing depends on the necessity (or not) of taking into consideration spatial position invariance.

The learning of the prototypical strings \( p_1-p_n \) is accomplished by discovering the common symbols shared by a set of \( s_7 \) strings describing a set \( E \) of examples (e.g. the bitmaps in Fig. 24) of the shapes to be recognized. It must be stressed that the set of examples contains figures of the same shape but different sizes, as well as distorted shapes. There exist many different strategies to learn these common characters. For example, any of the current learning methods in NNs (e.g. in the case of Perc) and genetic algorithm theories may apply for such a purpose. However, Serapião et al. (1996) used a process taking one initial string \( c_i \) of \( E \) as template and changing its structure depending on its similarity to the other strings of \( E \). These authors called this strategy the template learning algorithm.

Since any string is an ordered set of characters, the following must be considered in calculating the fuzzy matching of \( s_j-s_k \) if these strings are defined by a non-linear grammar:

(a) a fuzzy neighborhood \( N_{c_i} \) must be defined to each \( s_j \) character \( c_i \) of order \( c \), as an index interval \( (l_i, l_i) \), such that any \( s_j \) character \( c_i \) of order \( l_i < c < l_i \) is eligible to be matched to \( c_i \);
(b) the ordered set \( M_{c_j} \) of matching characters \( c_{im} \) assumed to be equivalent to \( c_j \) must be provided;
(c) the actual matching degree \( \mu(c_i,c_j) \) must be calculated as:

\[
\mu(c_i,c_j) = \max(\mu(c_{im},c_j))^s(f(c_i)) \tag{142}
\]

where \( f(c_i) \) is the membership function defining \( N_{c_i} \);
(d) the actual matching degree \( \mu(s_j,s_k) \) between the strings \( s_j,s_k \) is to be calculated as:

\[
\mu(s_j,s_k) = \Sigma\mu^s(c_i,c_{im})/n \tag{143}
\]

that is to say, as the average of the matching degree calculated for all \( n \) \( s_j \) characters.

A partial fuzzy matching is defined if some \( s_j \) character \( c_i \) are allowed to be missing in \( s_k \). In this case, \( \mu(s_j,s_k) \) is to be calculated as the average of the \( m \) \( s_j \) characters \( c_i \) for which \( \mu(c_i,c_{im}) > 0 \), and the partial matching is signaled by assigning a negative value to \( \mu(s_k,s_j) \).

To learn a prototypical pattern string \( p_i \) is to learn not only its significant characters but also the associated set \( M_{c_j} \) and neighborhood \( N_{c_j} \). The template learning algorithm is implemented as follows:

(a) the dictionary:

\[
D = \{c_1 \cdots c_n\} \tag{144}
\]

of characters composing the example strings to be alphabetically ordered, such that \( c_i \) precedes \( c_j \) if \( i < j \);
(b) provide a maximal index interval \( (l_n,l_n) \) to constrain the learning of \( N_{c_i} \), such that its learned index interval \( (l_n,l_n) \) is restricted to \( l_i \geq l_n \) and \( l_n < l_i \);
(c) provide a maximal index interval \( (l_n,l_n) \) to constrain the learning of \( M_{c_j} \), such that the characters \( c_{im} \) learned to match \( c_j \) are constrained to \( l_i < c - m < l_i \). In this way, each learned \( M_{c_j} \) is composed by the symbols in the interval \( (m, m) \);
(d) take the first two strings of \( E \) as the template string \( s_j \) and the modifying string \( s_m \);
(e) find for each \( s_j \) character \( c_i \) the best matching \( s_m \) character \( c_{im} \) constrained by \( b \) and \( c \) above; and:
Fig. 24. The set of examples used to train Sensor to recognize cars. The figure shows some of the bitmaps used to train Sensor to recognize a type of car. Cars of different sizes and shapes were used to train the system to generalize concepts having distinct degrees of abstraction. Modified from Serapião et al. (1996).

(f) given that it actually matched \( c_c \) at the position \( p \), then adjust the limits of the actual \( (l_i, l_s) \) and \( (m_i, m_s) \) according to:

\[
\begin{align*}
  l_i &= \min(\max(p, l_a)) \\
  l_s &= \max(\min(p, l_b)) \\
  m_i &= \min(\max(m, l_d)) \\
  m_s &= \max(\min(m, l_u));
\end{align*}
\]

(g) replace \( s_i \) by the string composed by all \( s_i \) characters \( c_c \) to which \( \mu(c_c, c_c) > 0 \);

(h) take the next string in \( E \) as the new \( s_m \) and repeat the steps f, g and h; and:

Table 2. CAR Pattern Recognition

<table>
<thead>
<tr>
<th>Example</th>
<th>Training</th>
<th>Matching</th>
<th>Matching</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.00*</td>
<td>0.96</td>
<td>-0.30</td>
</tr>
<tr>
<td>2</td>
<td>-0.71</td>
<td>-0.80</td>
<td>-0.47</td>
</tr>
<tr>
<td>3</td>
<td>0.96*</td>
<td>1.00</td>
<td>-0.36</td>
</tr>
<tr>
<td>4</td>
<td>-0.73*</td>
<td>-0.76</td>
<td>-0.30</td>
</tr>
<tr>
<td>5</td>
<td>-0.33</td>
<td>-0.80</td>
<td>-0.50</td>
</tr>
<tr>
<td>6</td>
<td>-0.78*</td>
<td>-0.73</td>
<td>-0.57</td>
</tr>
<tr>
<td>7</td>
<td>-0.36</td>
<td>-0.83</td>
<td>-0.50</td>
</tr>
<tr>
<td>8</td>
<td>-0.53</td>
<td>-0.86</td>
<td>-0.43</td>
</tr>
<tr>
<td>9</td>
<td>-0.80*</td>
<td>-0.86</td>
<td>-0.57</td>
</tr>
<tr>
<td>10</td>
<td>-0.37</td>
<td>-0.50</td>
<td>-0.47</td>
</tr>
<tr>
<td>11</td>
<td>-0.45</td>
<td>-0.80</td>
<td>-0.30</td>
</tr>
<tr>
<td>12</td>
<td>-0.64</td>
<td>1.00</td>
<td>-0.30</td>
</tr>
<tr>
<td>13</td>
<td>-0.34</td>
<td>-0.50</td>
<td>-0.47</td>
</tr>
<tr>
<td>14</td>
<td>-0.52</td>
<td>-0.80</td>
<td>-0.50</td>
</tr>
<tr>
<td>15</td>
<td>-0.74*</td>
<td>-0.66</td>
<td>-0.57</td>
</tr>
<tr>
<td>16</td>
<td>-0.56</td>
<td>-0.76</td>
<td>-0.50</td>
</tr>
</tbody>
</table>

Prototypical string:
\[
\text{DEC/5,0}&\text{PAO/6,0}&\text{BCA/6,1}&\text{PAO/5,2}&\text{MNL/7,0}&\text{KLI/5,1}&\text{HIG/5,1}&\text{KLI/6,0}&\text{HIG/3,0}&\text{DEC/5,2};
\]

*(Reproduced by permission from Serapião et al. (1996).
Fig. 25. Scene analysis. Scene recognition is a complex process requiring identification of its main objects (foreground); selection of one (or a set) of them as the focus of attention, and analysis of the spatial relations shared by these objects, according to a given G encoding a knowledge of possible (or frequent) object composition in the sensed environment. This grammar may encode general type of knowledge like the rules of perspective, or it may describe specific object relations learned to hold in defined specialized environments like hospitals, offices, home, etc.

Broca's aphasia is markedly characterized by an important (if not total) reduction of the human capability to produce grammatically correct phrases (minor lesions) or any verbal sound at all (severe aphasia), whereas lesions in the Wernicke's area is associated with a grammatically fluent, but almost meaningless, speech. Broca's area is adjacent to the part of the motor-control strip dedicated to the jaws, lip and tongue, and it was thought to be involved in the production of language, but now it is proposed that its main job is to process the grammar of the language being used. Wernicke's patients have consistent difficulty naming objects; in general, they come up with related words or distortions of the sound of the correct one. The striking symptom of Wernicke's aphasia is that the patients show few signs of comprehending the speech around them. In a third kind of aphasia, the connection between the Broca's and Wernicke's areas (the arcuate faciculus) is damaged, and these patients are unable to repeat sentences. Finally, if the above verbal system is preserved but isolated from other cortical areas, patients are able to repeat the sentence they hear without understanding it or ever speaking spontaneously. Because of this, Wernicke's area is proposed to have the role in looking up words and funneling them to other areas, notably the Broca's area. Language processing remains a left hemisphere job in the majority of the right-handed people and in the minority of the left-handed people (e.g. Iaccino, 1993; Jackendoff, 1995; Penfield and Roberts, 1959; Pinker, 1994; Rocha, 1990). Remarkably, similar deficits are observed in American Sign Language 'speaking' patients having lesions of Broca's and Wernicke's area (e.g. Jackendoff, 1995; Pinker, 1994). This stresses the fact that the function of these areas is not exclusively dependent on verbal sound processing, but is mainly devoted to verbal symbol recognition and grammar processing.

Speech perception is the result of a progressive oriented process. (1) It begins with a phonological, visual, etc. analysis taking place at subcortical and primary sensory areas to identify the primary verbal symbols (words). (2) Then, high-order cortical areas are recruited to recognize or to produce phrases supported by a given grammar. (3) Finally, these phrases are combined into a meaningful dialog or
theory about a set of events (e.g. Greco and Rocha, 1988; Jackendoff, 1995; Pinker, 1994; Rocha and Rocha, 1985; Rocha, 1990). The EEG activity evoked by verbal stimuli is considered to be a complex pattern composed by distinct components, believed to correlate with these different and sequential stages of message processing. Early components in the evoked response were assumed to reflect the analysis of the primary verbal symbols (phonemes or morphemes and words) at the initial stages of neural processing, whereas latter components are considered to be associated with more complex processing of task relevance, uncertainty, attention, motivation, etc. (McCallum et al., 1983; Neville et al., 1982; Ritter et al., 1979; Rocha, 1990).

A clear evoked activity is recorded at both right and left sides of the brain during language understanding of a text, and the analysis of this activity reveals a complex interaction of the two hemispheres in speech perception. The amplitude of the EEG waves recorded at the left side is greater than the activity registered at right locations, and the individual performance in recalling the listened text is a linear function of the left dominance. But it also increases as synchronization of the right hemisphere activity augments (Rocha, 1990). Experiment results support the idea that verbal analysis is an expectancy-controlled process, in which the expectancy is built up during the word, phrase and text recognition as the verbal and semantic models of the input are developed. In this way, the verb recognition may prompt the brain to look for its complement, the decision making about the theme (central subject) of the text or dialog may guide the focus of attention over specific phrases to compose a model of what is said about the theme, etc. (Pinker, 1994; Rocha, 1990). This guided analysis may attain important conclusions and decisions even before the word and/or phrase is ended, dismissing a full analysis for word and phrase recognition. Once established hypotheses are confirmed by early pieces of information, the remaining portion of the verbal message is considered redundant and may be dismissed from further analysis.

13.1. JARGON

JARGON© is a intelligent tool to help the user to analyze the contents of a natural language data base (F) using a formal grammar G to encode the queries he/she is interested to have answers for. The purpose of this analysis is to extract from each data base F, a set of significant words associated with a set of primitive concepts, to be used to disclose complex concepts or theories, described by phrases or sets of phrases. These phrases are well-formed formulas according to a given grammar G describing the possible relations among concepts about the universe U. In this way, the user may encode his/her queries into a set of possible relations described by a defined grammar G, which will be used by JARGON© to disclose those phrases or set of phrases of F obeying the rules of this G. The wffs of L supported by F are then assumed to be the answers to the proposed queries. The grammar G may be the ordinary syntax of a given natural language, or may be of any other formal language used to encode the specific knowledge of any area of human expertise, that is to say, to encode the jargon used in this area of expertise.

JARGON© is a neural system composed by three sets (areas or nuclei) of nets (Fig. 25, devoted to learn the most frequent words, phrases and phrase combinations existing in F, written in a natural language. The knowledge registered in F is acquired by means of the following iterative procedure:

1. First, the system reads the F to build a DICTIONARY composed by its most significant words. This is accomplished by creating different neural modules (columns) to represent the different words existing in F. Each of these modules is composed by an indexing (or start symbol) sub-module called germ, and many other complementary sub-modules (or non-terminal symbols) called haloes (see Fig. 26). Combinations of a given germ and its haloes represent those words (terminal symbols) sharing the same indexing property, like the different tenses of a verb.

2. In the sequence, JARGON© allows the user to modify the learned dictionary, to eliminate words which are meaningless to the purpose of the intended analysis of F, and to specify synonym relations among words. This modified dictionary must contain its words grouped according to the primitive concepts supporting the intended analysis of F. Here it will be called the Primitive Concept Dictionary (PCD).

3. Once the PCD is built, the user must define the grammar G supporting phrase recognition. This grammar must encode the relations among the primitive concepts the user is interested in studying in F.

4. In the next step, the user associates classes of this grammar with the PCD words to build the Word Dictionary (WD) to be used to search for phrases or Complex Concepts in F.

5. JARGON© uses WD to learn the word combinations in F satisfying the defined grammar G, and to construct a Phrase Dictionary (PD) containing the phrases which may be of interest to the user.

6. The recursive repetition of steps 1–5 allows the user to search for phrase combinations in F which may describe concepts of high order of complexity in which he/she may be interested. The recursion is allowed by using only PD phrases to rewrite F. This rewriting process recodes the data base, by substituting each PD phrase found in F by the corresponding internal code of the neural module representing the phrase. The recoded F is a synthesis of the original data base, since it contains only those wffs of L supported by the facts registered in F.

13.2. Finding Words

JARGON© reads the data base to create neural modules (cortical columns) to represent its words (Fig. 27). Each word module is composed by two
sub-modules, called germ (or starting module $s_g$) and halo (non-terminal module $s_h$), respectively. The germ contains the word-indexing substring, and the haloes are those substrings added to the germ to reconstruct the indexed words. JARGON© tries to match each word it reads in $F$ to all previously learned germs. If the matching succeeds, the amount of transmitters/receptors in the corresponding module is increased by a fixed amount. If necessary, a new halo is created to represent the actual word fully. If the matching does not succeed, the system creates a new word module to represent the actual word. This is done by assigning an input neuron to each ASCII character composing the word (e.g. manager), and joining these input cells to an output neuron (Figs 26 and 27). This type of word module is called simple module. Whenever a new word (e.g. management) is found to share an indexing substring with a simple module, the module undergoes a structural change [Fig. 27(a)–(b)], because associative neurons are created to represent the selected germ (start symbol) and halo (non-terminal symbols) sub-modules. Also, new output neurons (terminal symbols) are created to represent the indexed words [Fig. 27(b)].

The JARGON© word-learning algorithm was developed to select those words having the highest entropy in $F$, since both very frequent and rare words are, in general, meaningless for any purpose of analysis. The relevance of a word for any analysis of $F$ is, then, related to its entropy in the data base. The entropy $h(w)$ of the words $w$ in $F$ is the entropy of their associated germs, and it is calculated as:

$$h(w) = -p \log p, \quad p = \frac{N_p}{N_t}$$  \hspace{1cm} (147)$$

where the germ's probability $p$ in $F$ is calculated as the quotient of the number $N_p$ of its instances in $F$ by the total number $N_t$ of instances of all germs in $F$. The relevant words $w$ of $F$ are those phrases exhibiting an entropy greater than a defined threshold $\theta$:

$$h(w) > \theta.$$  \hspace{1cm} (148)$$

The words JARGON© learned to be relevant in $F$ were used to create the WDs associated with each query proposed by the user. The words saved in these dictionaries are those associated with the Primitive Concepts which are relevant to the purpose of the intended analyses.

### 13.3. The Phrase Structure

The possible theories, which the user may be interested to disclose in $F$, are those relations among these primitive concepts supported by a given or grammar $G$, encoding either a common sense knowledge as in the case of the natural grammars, or some kind of specific knowledge in the case of a jargon. The Complex Concepts supported by $F$ are described by the wff of the language $L$ obeying the
The Brain as a Symbol-processing Machine

M~( N A~G E OR P 1 P2

output neuro~  ~ ~iJ rrn e n t ==~' associative ~ ~ ~ ~ ~

MANAGER

germ haloes

A

B

Fig. 27. The word module structure. Each word module is composed by two subnets: the germ (or indexing module) and the halo (or complementary module). Neurons in the first layer are set to represent each letter of the word read from the data base $F$. The germ is assumed to be the minimum set of neurons representing the radical of a set of words that differ among themselves by the different suffixes added to the radical. See text for further details. Modified from Rocha et al. (1996b).

grammar $G$ associating Primitive Concepts taken as Key Words (starting symbols $s_0$) and Complementary Words (non-terminal symbols $s_n$), into Complex Concepts described by phrases (terminal symbols $s_n$) of $L$.

The symbols in the sets $V_o$, $V_n$ and $V_t$ defining $L$ are associated with strings assigned to JARGON's neurons, and the production rules supported by $G$ are encoded into transmitter/receptor/controller concatenation rules. In this way, the wff of $L$ are those derivation chains supported by the adequate string concatenations, which, in turn, define the connectivity of the neurons in the Phrase area. The following is an example from Rocha et al. (1996b).

Let the derivation chain:

$$VVV \rightarrow vvvPLA \rightarrow vvvplaTIM \rightarrow vvvplatim$$

(149)
define a wff of $L$, requiring information about place to be incorporated to the phrase specified by a given verb $VVV$, but before information about time is checked to be part of the sentence. Now, let the strings $vvpvPLA$, plaTIM and tim to be assigned as the transmitters of the word neurons $N_1$, $N_2$ and $N_3$ in Fig. 28. Whenever the neuron $N_1$ representing the verb in the Word Area (or Nucleus) is activated, it releases the transmitter $vvpvPLA$ to couple the receptor $VPP$ assigned to the post-synaptic neurons $I_1$ in the Phrase Area. This coupling rewrites the $I_1$'s receptor to $vvpvPLA$, prompting it to be activated by neuron $N_2$. In this way, whenever a word speaking about place is found in the sentence, $N_2$ releases the transmitter plaTIM to couple the receptor $vvpvPLA$ to the output neuron $T_1$. This coupling transfers the token TIM to the output neuron $T_1$. Now, if a word speaking about time is found in the sentence, $N_3$ releases the transmitter tim to couple the receptor TIM assigned to $T_1$. This coupling fires $T_1$, indicating that the actual sentence is a wff of $L$, because it represents the following token concatenation:

$$VVV \oplus vvpvPLA \oplus vvvplaTIM \oplus vvvplatim \ .$$

(150)

A different type of syntax is implemented if the strings are assigned to the neurons as in Fig. 28(b). In this case, the token $vvvPLATIM$ is assigned as the transmitter of the verb neuron $N_1$, while the strings pla and tim are considered to be the transmitters of the complement neurons $N_2$ and $N_3$, respectively. Now, whenever $N_1$ is activated, it releases $vvvPLATIM$ to concatenate to $VVV$ at the output neuron $T_1$. This coupling rewrites:

$$VVV \rightarrow vvpvPLATIM \ .$$

(151)

Now, if neuron $N_2$ or $N_3$ is activated either by a word speaking about time or place, the coupling:

$$VVV \oplus vvpvPLATIM \oplus vvvPLATim \ .$$

(152)
or:

$$VVV \oplus vvpvPLATIM \oplus vvpvplaTIM$$

take place at $T_1$. Also, the firing of both $N_2$ and $N_3$ supports:

$$VVV \oplus vvpvPLATIM \oplus vvpvplatim \ .$$

(153)

In this condition, the following rewriting rules are implemented:

$$VVV \rightarrow vvpvPLATIM \rightarrow vvpvPLAtim \ (154a)$$

$$VVV \rightarrow vvpvPLATIM \rightarrow vvpvplaTIM \ (154b)$$

$$VVV \rightarrow vvpvPLATIM \rightarrow vvpvplatim \ .$$

(154c)

On the one hand, if the threshold of neuron $T_1$ is set adequately at a value of 1, $T_1$'s firing will be triggered by any of the above T/R couplings. On the other hand, however, if the threshold is set at a value of 1, $T_1$ fires only in condition (154c).
The following is the description of one of the grammars used by Rocha et al. (1996b) to query a data base named EROSION, containing the English abstracts of more than 600 scientific papers concerning Soil Erosion, Fertilizer Use and Tillage Systems, contained in the CAB ABSTRACTS on CD-ROM of SilverPlatter Information, in the years 1993/1994.

The synaptic strings:

\[ \text{ERO&} \rightarrow \text{KEY WORD} \]

\[ \text{REMer} \rightarrow \text{NON - TERMINAL SYMBOL} \]

\[ \text{re} \rightarrow \text{TERMINAL SYMBOL} \]

supporting string concatenations where the terminal symbol rem binds to the initial symbol ERO& only if the non-terminal symbol REMero& is previously found in \( F \):

\[ \text{ERO&} \rightarrow \text{REMer} \rightarrow \text{rem} \text{ero}, \]

were assigned to the words of the corresponding Word Dictionary (see Table 3) to encode the query:

\[ \text{SOIL DESTRUCTION: What is the relation between erosion and soil destruction?} \]

because derivations of the type:

\[ \text{EROSION} \rightarrow \text{REMOVING} \rightarrow \text{TOPSOIL or NITROGEN or NPK} \]

are answers to the question, showing that Erosion removes Nitrogen or NPK or Topsoil. This derivation is supported by the phrases of \( F \) like those shown in Fig. 29(a). Figure 29(b) shows the abstract containing the first phrase shown in Fig. 29(a).
Table 3. The World Dictionaries Associated to the Queries

<table>
<thead>
<tr>
<th>Primitive concepts</th>
<th>Words</th>
<th>Frequency</th>
<th>Strings</th>
</tr>
</thead>
<tbody>
<tr>
<td>QUERY1.DIC</td>
<td>EROSI_ERODED_EROSION_-</td>
<td>1013</td>
<td>USEero&amp;</td>
</tr>
<tr>
<td></td>
<td>TILLAGE</td>
<td>250</td>
<td>SYS&amp;NOT&amp;</td>
</tr>
<tr>
<td></td>
<td>TILLAGE</td>
<td>250</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CONTROL</td>
<td>392</td>
<td>ERO&amp;NOT&amp;</td>
</tr>
<tr>
<td></td>
<td>CONTROLLIN_MANAGEMENT</td>
<td>392</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SYSTEM</td>
<td>385</td>
<td>USEsys&amp;</td>
</tr>
<tr>
<td></td>
<td>SYSTEM_MODEL_METHOD_</td>
<td>385</td>
<td></td>
</tr>
<tr>
<td></td>
<td>USE</td>
<td>453</td>
<td>use&amp;</td>
</tr>
<tr>
<td></td>
<td>NOT USE</td>
<td>139</td>
<td>not&amp;</td>
</tr>
<tr>
<td></td>
<td>USE</td>
<td>453</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SOIL</td>
<td>1307</td>
<td>USEsoil&amp;</td>
</tr>
<tr>
<td></td>
<td>SOIL</td>
<td>1307</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CONSERVATION</td>
<td>148</td>
<td>SOI&amp;NOT&amp;</td>
</tr>
<tr>
<td></td>
<td>CONSERVATION</td>
<td>148</td>
<td></td>
</tr>
<tr>
<td>QUERY2.DIC</td>
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<td>1307</td>
<td>COSsoil&amp;</td>
</tr>
<tr>
<td></td>
<td>EROSI_ERODED_EROSION_-</td>
<td>1013</td>
<td>COSero&amp;</td>
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<td>INCREASE</td>
<td>604</td>
<td>adj&amp;</td>
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<tr>
<td></td>
<td>TILLAGE</td>
<td>250</td>
<td>SYS&amp;</td>
</tr>
<tr>
<td></td>
<td>CONTROL</td>
<td>392</td>
<td>ERO&amp;</td>
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<tr>
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<td></td>
<td>SYSTEM</td>
<td>385</td>
<td>CO Sys&amp;</td>
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<td>CONSERVATION</td>
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<td></td>
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<td>REDUCTION</td>
<td>315</td>
<td>adj&amp;</td>
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<td>REDUC_DECREASE_-</td>
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</tr>
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<td></td>
<td>LOW</td>
<td>61</td>
<td>adj&amp;</td>
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<tr>
<td></td>
<td>LOW</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>QUERY3.DIC</td>
<td>EROSI_ERODED_EROSION_-</td>
<td>1013</td>
<td>ERO&amp;</td>
</tr>
<tr>
<td></td>
<td>TOPSOIL</td>
<td>79</td>
<td>rem&amp;</td>
</tr>
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<td></td>
<td>TOPSOIL</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NITROGEN</td>
<td>29</td>
<td>rem&amp;</td>
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<tr>
<td></td>
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<td>29</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NPK</td>
<td>11</td>
<td>rem&amp;</td>
</tr>
<tr>
<td></td>
<td>NPK</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td></td>
<td>REMOVE</td>
<td>65</td>
<td>REMero&amp;</td>
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<td>65</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FERTILIZER</td>
<td>128</td>
<td>rem&amp;</td>
</tr>
<tr>
<td></td>
<td>FERTILIZER</td>
<td>128</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 29. An example of query. The rule in (A) encodes the query “Soil destruction: what is the relation between erosion and soil destruction?” Answers to this question are phrases shown in (A) and (B). Reproduced from Rocha et al. (1996b).
The synaptic strings:

SYS\&\ NOT\&//KEY WORD1
ERO\&\ NOT\&//KEY WORD2
SOI\&\ NOT\&//KEY WORD3
USEsys\&//NON – TERMINAL SYMBOL associated to KEY WORD1
USEero\&//NON – TERMINAL SYMBOL associated to KEY WORD2
USEsoi\&//NON – TERMINAL SYMBOL associated to KEY WORD3
USE&//TERMINAL SYMBOL
not\&//TERMINAL SYMBOL (156a)

support the following derivations:

not\& \leftrightarrow SYS\&\ NOT\& \rightarrow USEsys\&
not\& \leftrightarrow ERO\&\ NOT\& \rightarrow USEero\& \rightarrow use&
not\& \leftrightarrow SOI\&\ NOT\& \rightarrow USEsoi& (156b)

and they were designed to support the query (see Table 3):
CONTROL: Are soil conservation; erosion control and tillage techniques currently used by farmers?
because derivations of the type:

TILLAGE \rightarrow SYSTEM
CONTROL \rightarrow EROSION \rightarrow COST/PRICES \rightarrow CONSERVATION \rightarrow SOIL
\rightarrow INCREASE/REDUCTION/HIGH/LOW
(157c)

are answers to the question.

13.5. Answering the Queries

JARGON used the previous grammars and the dictionary shown in Table 3 to find the possible answers in F to the queries posed by the user. The result of this search is encoded in three different ways:

1. Conceptual description: the learned phrases are encoded as the wff of L supported by facts in F.
2. Specific meaning: the learned phrases are encoded as the string of the words of F which supported the above wffs.
3. Data base indexing: the corresponding data base addresses of the abstracts containing each CCD item are saved, to provide access to all information about the selected abstracts.

Figure 30 shows JARGON’s output for concepts associated with Query 2: What are the relations
between crop prices and soil conservation, erosion control and tillage system costs?

In the first example, high crop prices are associated with soil conservation. This derivation, represented by the token concatenation soi&adj&cos, was supported by the phrase *High relative prices for hay also lead to more soil conservation*, in the abstract of the paper by J. A. Miranowski, 1989, located in folder 11, slot DD, cabinet EROS (Fig. 31). When the word conservation was recognized in the above phrase by its neural module in the Word nuclei, the initial symbol SOI& was transferred to the Key Word neuron of a neural module in the Phrase area, prompting it to bind the Word module activated by the word soil. The coupling of the string COSSoi& released by this latter module, to the string SOI&, enabled the first complement neuron of the Phrase module to concatenate ADJcos& released by the Word module activated by the word *prices*. In the sequence, the string ADJ was transferred to the output neuron, and allowed the binding of the string adj released by the Word module recognizing the word *high*. This string concatenation produced the terminal string soi&adj&cos& and activated the output neuron to classify the incoming phrase as a wff of the language L supported by the grammar in (49).

In the second example, erosion is associated to reduced yields, increased cost, and reduced management efficiency, or erosion control is associated to reduced cost and increased yields. These derivations, represented by the string concatenation ero&adj&cos, were supported by phrases from four different abstracts, one of them (Colacicco et al., 1989) is shown in Fig. 31.

Finally, in the third example, tillage is associated to soil loss costs or increased yields. These derivations, represented by the string concatenation sys&adj&cos, were supported by two different abstracts, one of them (by R. M. Klemme) shown in Fig. 31.

These results demonstrate JARGON©s capability in finding a few adequate papers concerning the subject in which the user is interested, in a large set of abstracts initially selected by the conventional key word system.

14. CONCLUSION

Our understanding of brain physiology will change dramatically in the years ahead, as a consequence of the increasing body of knowledge being acquired on the neurochemical transactions involved with the processing of information both encoded by genes as well as provided by actual data collected from the surrounding environment. The complexity of the brain's processing will be increased largely by our comprehension of the glial and neuro-glial interactions. It is sure that the near future will demand new conceptions about the computational capacity of the brain and powerful mathematical tools to help us to formalize these new conceptions into empirically testable models. The FFL theory was discussed here as one of these possible tools. Ambiguity and non-linearity were stressed as the most praised properties of these languages to...
describe adequately the capacity of the brain to adapt to novel environmental conditions and to cope with high computationally demanding problems.

Fuzzy grammars may be used as the adequate formalism to describe cerebral processing, both at the cellular level supported by a set of signal transduction pathways, as well as at the macroscopic level where primitive concepts are encoded by specialized neurons or columns and their connectivity constrains the possible production rules involved with complex pattern recognition or theory processing. This latter approach may be used, e.g. to develop an alternative modeling of the visual processing that may be closer to the real brain, which may reconcile findings showing that (a) some neurons (grandmother cells) or columns specialize to recognize useful visual patterns or features; with (b) data pointing to conclusion that complex scenes are to be uniquely recognized through a distributed representation inside the brain. Chemical grammars may be an interesting alternative to explain some complex cerebral processings, like language understanding and production. The possibility of encoding the natural language grammar by means of an adequate set of transmitters, receptors and second messengers was demonstrated theoretically here. This opens the field to some interesting empirical investigations to test whether or not the (unique?) human language mastery rests upon the capability of some neurons (in the left temporal lobe?) to produce an adequate family of chemicals.

Recent experimental findings about the neural events related to the sensory consciousness are very encouraging and point to the involvement of energetic transactions governed by specific signal transduction pathways involving the glutamate-receptor system either at the level of neurons or neuro-glial transactions. The complexity of such processing, which ultimately has to result in our unified perception of both the external and internal environments, is expected to require new computational capabilities, which may be provided by the ambiguity and non-linearity of the fuzzy neurochemical grammar. Consciousness at the primitive level of qualia may be thought to be supported by unstable energetic states triggered by reproducible and specific activation of defined signal pathways. However, a high number of distinct unstable but reproducible energetic states are required to explain the variety of the conscious experiences triggered by the different sensory stimuli. This set of qualia provides the set of initial symbols upon which the augmentation of the complexity of consciousness supported by evolution has to be explained, by means of new computational capabilities acquired by neural systems of increasing
symbol processing capabilities. Other chemicals, like Ach, 5-HT, HA, NE, etc. are supposed to modulate the actual set of qualia available for conscious processing. The activity of the mesencephalic cholinergic system is the main determinant of the available code for neural processing. On the one hand, burst rhythmical firing is associated with unconsciousness, perhaps because it does not induce the LTP required to unlock the NMDA channel, and favors LPT to support a conscious sensory processing. The role played by NA, HA, 5-HT, etc. may be that of tuning the semantics of the neural codewords being processed by determining the basal level of activity in the single-spike firing mode and consequently adjusting the basal degree of activation of the NMDA system. In this way, both the set of symbols and the set of rewriting rules available for conscious or unconscious processing are specified, depending upon the degree of activation of specialized neural systems. Consciousness is temporally, but not spatially, constrained and life is mainly, if not exclusively, supported by a huge set of concurrent and specific temporal energetic transactions. The FFL concurrent processing capability may be of much help in trying to understand and formalize these phenomena.

REFERENCES


