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Probability of real-time detection versus probability of infection for aerosolized biowarfare agents: A model study

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Abstract

Real-time biosensors are expected to provide significant help in emergency response management should a terrorist attack with the use of biowarfare, BW, agents occur. In spite of recent and spectacular progress in the field of biosensors, several core questions still remain unaddressed. For instance, how sensitive should be a sensor? To what levels of infection would the different sensitivity limits correspond? How the probabilities of identification correspond to the probabilities of infection by an agent?

In this paper, an attempt was made to address these questions. A simple probability model was generated for the calculation of risks of infection of humans exposed to different doses of infectious agents and of the probability of their simultaneous real-time detection/identification by a model biosensor and its network. A model biosensor was defined as a single device that included an aerosol sampler and a device for identification by any known (or conceived) method. A network of biosensors was defined as a set of several single biosensors that operated in a similar way and dealt with the same amount of an agent. Neither the particular deployment of sensors within the network, nor the spacious and timely distribution of agent aerosols due to wind, ventilation, humidity, temperature, etc., was considered by the model. Three model biosensors based on PCR-, antibody/antigen-, and MS-technique were used for simulation. A wide range of their metric parameters encompassing those of commercially available and laboratory biosensors, and those of future, theoretically conceivable devices was used for several hundred simulations.

Based on the analysis of the obtained results, it is concluded that small concentrations of aerosolized agents that are still able to provide significant risks of infection especially for highly infectious agents (e.g. for small pox those risk are 1, 8, and 37 infected out of 1000 exposed, depending on the viability of the virus preparation) will remain undetected by the present, most advanced, or even future, significantly refined real-time biosensors.

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Keywords: Biosensor modeling; Simultaneous probability of detection; Infection; BW agents

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1. Introduction

Never, not even in the Cold War era, was there a threat of the usage of biowarfare (BW) agents, comparable to the one that exists today. The 2005 budget of the US Department of Homeland Security (DHS) alone, allocated to biological terrorism countermeasures, is over $350 million. Any amount of BW agents from a few milligrams to several kilograms may be released during a terrorist attack, yet it is very likely that this amount will still be much less than that expected to be released during military operations. Can the attack be prevented? Hardly, can the consequences be mitigated? Yes, in a way. Real-time biosensors, that can detect and identify airborne BW in minutes, might be one of the answers. They are expected to help in selecting the proper emergency response management (ERM) that should a bioterrorist attack occur (Graham and Sabelnikov, 2004).

These highly sophisticated and powerful sensor techniques may be roughly divided into two groups (Graham and Sabelnikov, 2004). The first group uses a specific biological recognition step that is provided by an appropriate ligand-receptor binding, such as antibody/antigen binding (Winter and Milstein, 1991; Emanuel et al., 2000), complementary binding of specific oligonucleotides to target DNAs, as in PCR-based techniques (Rapley, 2000; Schmidt, 2002), or DNA-chips (Wang, 2000; Lapa et al., 2002), etc. Further, the event of recognition/identification is revealed and reported in a certain measurable way.

In case of antibody/antigen binding/recognition, special highly sensitive devices called transducers are used for this purpose. In fact, antibodies form a layer on the "surface" of a transducer, so that the binding/recognition occurs within this layer. The event of binding triggers changes of some physical parameters, measured by the transducers, such as refractive indices of the layer [Surface Plasmon Resonance transducer, SPR (Homola et al., 1999; Nikitin et al., 1999; Naimushin et al., 2002; Su and Zhang, 2004)], the layer's weight/thickness [Quartz Crystal Microbalance transducer, QCM (O'Sullivan and Guibal, 1999; Utenhaler et al., 2001; Su and Zhang, 2004)], orientation of molecules within the layer ["Liquid Crystal" transducer (Gupta et al., 1998; Woolverton et al., 2001)], the sound velocity within the layer [Surface Acoustic Wave transducer, SAW (Grate et al., 1993,a,b; Stubbs et al., 2002)], etc.

In PCR-based recognition/detection, a DNA fragment specific to a particular microbe is first recognized by a complementar oligonucleotide probe (in this case called a "primer"), then amplified in tens of repetitive cycles by polymerase chain reaction (PCR), and finally detected and quantified with the use of fluorescence, where the amount of amplified fragment is directly proportional to the fluorescent signal. Because of this amplification, the sensitivity of the PCR-based sensors is considered one of the highest. A fluorescent label and a fluorimeter play the role of transducer in this case. These sensors, however, cannot identify biological toxins (i.e. botulinum, ricin, etc.), and an additional enzymatic step is required for RNA-containing BW agents (such as Ebola and Marburg viruses, as well as some others).

The second group of biosensor techniques is primarily represented by physical methods such as various types of mass spectrometry, MS (Van Baar, 2002; for a recent review see Noble and Prather, 2000), modern infra-red (Schuster et al., 1999; Petrich, 2001) and Raman spectroscopy (Petrich, 2001; Scully et al., 2002), etc. In order to provide real-time detection and identification of BW agents, the above methods/techniques should rely on the presence within a whole BW cell/virion of a "marker" molecule(s) specific only to the particular microbe. Since modern mass spectrometry is unsurpassed in identification of individual molecules and their mixtures not only in liquids but also in aerosols, it is considered one of the most promising techniques for the real-time identification of BW agents.

The probability of detection and identification is the key metrics of real-time biosensors. In modern biosensors, the detection of BW agents is performed within liquid samples, so the airborne BW particles should be first collected from the air and concentrated into small volumes of liquid by various kinds of samplers (Irving, 2002, Jantunen et al., 2002). While this collection/preconcentration step is absolutely required, it may significantly increase the overall time of identification. The actual time required for identification is determined by several factors, such as the airborne concentration of an agent, capability of a sampler (its air flow rate, concentration efficiency, etc.) and the biosensor itself (its sensitivity, time of identification, etc.) (Graham and Sabelnikov, 2004).

In spite of recent and spectacular progress in the field of biosensors, several core questions still remain unanswered, such as how sensitive should the sensor be? How much should it really "feel"? Recent DHS requirements for the sensitivity of future field devices capable of agent identification in aerosols indicate a rather wide range of their concentration, from 100 to 100 000 organisms/l (DHS/HSARPA, 2004). To what levels of infection would these sensor sensitivity limits correspond? In other words, how does the probability of identification correspond to the probability of infection by an agent on the same time scale? The answers to these questions would help to set proper requirements for a sampler and a sensor as a concerted detection and identification device. They would also help to optimize sensor networks, and to evaluate the level of reliability of "detection and identification" for different risks of infection.

In this paper, an attempt is made to simultaneously estimate the probability of identification and infection for various BW agents. The risks of infection of humans exposed to different doses of infectious agents and the probability of their simultaneous real-time identification by a model biosensor and/or its network were calculated within a generated, simplified probability model. The model yielded quantitative results upon the input of several incoming parameters such as an infectious dose of a microbe, parameters of a model sensor, etc. A model biosensor is defined as a single device that includes an aerosol sampler and a device for identification by any known (or conceived) method. A network of biosensors is defined as a set of several...
single biosensors that operate in a similar way and deal with the same amount of agent. Three model biosensors based on PCR-, antibody/antigen-, and MS-technique were used for simulation. Neither the particular deployment of sensors within the network, nor the spacious and timely distribution of agent aerosols due to wind, ventilation, humidity, temperature, etc. was considered by the model.

2. Rational and theory

Only infectious BW agents but not toxins will be considered by the model. Let us first formulate some important assumptions of the model, the first three of which are of general nature:

(1) There is a space that contains aerosol particles of microbes; microbes within aerosol particles and the latter within the space volume (both are discrete entities) are distributed according to Poisson distributions with parameters equal to their mean concentrations.

(2) Aerosols contain both viable and nonviable (inactivated) forms of microbes; only viable organisms are infectious; both forms, however, can be identified.

(3) Every viable pathogenic organism inhaled by the body (as aerosol) can initiate the infection process with a probability of $P$ independently of other organisms.

(4) A single model biosensor includes an aerosol sampler and an identifier, a device for identification by any known (or conceived) method.

(5) A network of biosensors consists of $m$, similar single biosensors that operate in a similar way and deal with the same amount of agent.

(6) The sampler intakes the air with a flow rate, $W$, and concentrates aerosolized particles with an efficiency, $K_e$, into a liquid collective sample of volume $V_c$.

(7) The time of sampling and the time of inhalation of infectious agent by an individual are set equal. Since the total number of organisms inhaled by the exposed individual, $D_i$, is equal to the concentration of the agent in the air multiplied by the time of exposure and the inhalation rate, $W_i$, this assumption allows to exclude from all calculations time and concentration factors. In other words, by setting a particular $D_i$ (to provide different risks of infection from 0 to 100%) the number of organisms concentrated by the sampler may be calculated from the values of flow rates, $W_i$ and $W_s$.

(8) Individual samples of identical volumes, $V_s$, are taken for identification.

(9) The agent is identified in single sample with 100% probability, if and only if its amount in the sample is not less than a certain threshold value, $I$, otherwise the agent cannot be identified. For simplification, no false positives or false negatives are allowed; the value $I$ corresponds to the sensitivity of the method of identification (sensitivity of identifier).

If the general assumptions 1 and 3 are valid, the probability of infection, $P$, may be expressed as (Peto, 1953; Chermashentsev et al., 1993):

$$P = 1 - e^{-D_i D_v \ln 2 / \text{ID}_{50}}$$

where $D_i$ is a mean amount of viable and nonviable infectious organisms in the volume of air inhaled by an individual during the time of exposure, $D_v$ the fraction of viable particles, and $\text{ID}_{50}$ is an inhaled dose of an agent that causes the infection in 50% of exposed individuals.

According to assumption 9 made above, the probability of agent identification in the individual sample is equal to the probability of finding the agent in that sample in quantities not less than the threshold value, $I$. Further, according to assumption 1, the organisms are distributed in the sample volume according to Poisson distribution with a parameter, $\lambda$, equal to the mean concentration of organisms in the sample. So, the probability of identification, $P_{ID}$, of the agent in one sample with the volume $V_s$ is then:

$$P_{ID} = e^{-\lambda V_s}$$

### Table 1

Parameters of the model and the used range of their variance

<table>
<thead>
<tr>
<th>Parameters of the model</th>
<th>Values used in calculations</th>
<th>Relevant references</th>
</tr>
</thead>
<tbody>
<tr>
<td>Input general parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$D_{in}$</td>
<td>total number of inhaled organisms (microbes)</td>
<td>0.055–10000</td>
</tr>
<tr>
<td>$D_v$</td>
<td>proportion of viable organisms among total inhaled (%)</td>
<td>1, 10, 50, 90</td>
</tr>
<tr>
<td>Input parameters for sampler and sensor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$W_i$</td>
<td>flow rate (l/min)</td>
<td>4–1200</td>
</tr>
<tr>
<td>$K_e$</td>
<td>coefficient of efficacy of sampler (ratio of particles concentrated-collected to the total number of particles sampled)</td>
<td>0.2–0.8</td>
</tr>
<tr>
<td>$n$</td>
<td>number of individual samples (pcs)</td>
<td>0.001–5.0</td>
</tr>
<tr>
<td>$l$</td>
<td>minimum number of microorganism being identified (pcs)</td>
<td>1–96</td>
</tr>
<tr>
<td>Input parameters for net</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$m$</td>
<td>number of devices (pcs)</td>
<td>4</td>
</tr>
<tr>
<td>Input parameters for organism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$W_s$</td>
<td>human inhalation rate (l/min)</td>
<td>11</td>
</tr>
<tr>
<td>$\text{ID}_{50}$</td>
<td>50% infecting dose (inhaled) for organism (microbes)</td>
<td>5, 100, 1000</td>
</tr>
</tbody>
</table>
Viable and nonviable in collective and individual samples.

where \( V \) is the concentration of organisms, both viable and nonviable in collective and individual samples.

The probability of agent identification with one device, \( P_{ab} \), is equal to the probability of identification at least in one of \( n \) individual samples and is expressed as:

\[
P_{ab} = 1 - (1 - P_e)^n
\]

By analogy, the probability of agent identification with the net of \( m \) devices, \( P_{im} \), is expressed as:

\[
P_{im} = 1 - (1 - P_{id})^m
\]

For 10 min of inhalation—9.1 organisms/m³ and so on.

Since for most of BW agents the infectious doses have not yet been precisely established (Raber et al., 2001; Johnson, 2003), three assigned levels for inhaled ID50 were used for simulations: low (5 organisms), intermediate (100 organisms) and high (1000 organisms). The low level may correspond to such agents as smallpox (as suggested by Dennis et al., 2001), Q-fever (Fournier et al., 1993), plague (Iglesby et al., 1998; Johnson, 2003), and some others. The intermediate level may correspond to the Marburg virus (Chermashchetskaya et al., 1993), and some others. The high level may correspond to anthrax (Iglesby et al., 2002).

In all simulations, \( V_i \) was taken constant and equal to 10 ml for aerosolized concentrated in the fluid volume that is currently used in most advanced commercial samplers (Irving, 2002; Sceptor Industries Inc., 2004). An inhalation rate, \( W_h \), of 11 l/min for adult humans (Allan and Richardson, 1998) was used in all simulations.

3. Results

Several hundred Excel simulations simultaneously provided the probabilities of detection and infection for all three model biosensors. It turned out that an overwhelming amount of simulation data yielded extremely low values of probability of detection for doses less than 500 microbes, so in this paper only the simulation results obtained with the best existing or conceivable metric characteristics for a particular model sensor are presented. Evidently, these metric parameters provided the most beneficial conditions for detection, rarely achievable in real life with equipment currently used in the field or in laboratories. The dependence of the probability of infection (risk of infection) with BW agents of all three ID50 levels on the inhaled dose within the range of 1–100 organisms is shown in Fig. 1. \( D_i \) (fraction of viable organisms) were taken as 0.1 for all pathogens. Evidently, pathogens with lower ID50 levels (more infectious or virulent) exhibit steeper curves. The inserted table shows the exact values of infection risks for high level ID50 organisms (anthrax), ID50 = 1000 and Marburg virus, ID50 = 100 at doses 1, 5, 10, and higher.

The inhalation doses providing various probabilities/risks of infection may be easily converted to the concentration of an agent in the air (C, microbes/l) and vice versa, provided the time of exposure (t, min) is indicated and the inhalation rate, \( W_h \) (l/min) is known, according to a simple formula:

\[
C = D_i/W_h
\]

or

\[
D_i = rW_hC
\]

For instance, a dose of 1 organism \((D_i = 1)\) accumulated during 1 min of exposure (breathing rate, \( W_h \), of 11 l/min) would correspond to an agent concentration of 91 organisms (both viable and nonviable) per cubic meter of air \((1/111) = 0.009\, l / 1000 = 0.009\). For 10 min of inhalation—9.1 organisms/m³ and so on.

3.1. PCR-based sensor

Fig. 2 shows the results of a simulation for a model, PCR-based sensor with the best combined metrics of some currently available commercial devices (Idaho Technology Inc., 2004; Smiths Detection, 2004; BDS/In Vitrogen, 2004; Cepheid, 2004; Sceptor Industries Inc., 2004, etc.). This sensor would be able to analyze 16 identical samples of an agent \((n = 16)\) of volume, \( V_i = 12.5\, \mu l / sample \), with the sensitivity, \( I \), of 15 organisms. It would be attached to a sampler with \( W_h = 1000\, l / min \) and \( K_i = 0.8 \). Since biosensors do not usually discriminate between viable and nonviable organisms, the viability parameter, \( D_v \), has no effect on the probability of detection and identification. In contrast, it is very important in determining the probability (risk) of infection.

As follows from the results presented in Fig. 2, this PCR-based model sensor can identify 100 and more microbes with the probability of more than 50%, reaching 100% with doses of...
of 130 and higher. Situation is a little bit better with the network of 4 sensors: 100 microbes are detected with almost 100% probability. For all other doses, the probability of identification even with a net of 4 identifiers gradually drops to a 50% level at about 70 microbial counts, and 0 at around 50 microbial counts. However, those smaller undetected doses can still provide pretty high risks of infection (see Fig. 1) even for the high level ID50 organisms, such as Bacillus anthracis (4 infected for 1000 at a dose of 50 microbial units, and 7 out of 10 000 for a dose of 10 organisms, Fig. 1, inset table, second column, the third and the last row) not mentioning lower level ID50 organisms, such as Marburg (34 infected for 1000 exposed at a dose of 50 microbial units, Fig. 1, inset table) and small pox (500 infected for 1000 exposed, Fig. 1) For aerosols containing highly viable microbes (with $D_v > 0.1$) of intermediate and high levels of infectivity/virulence (intermediate and low ID50 level organisms) and especially of those with high contagious potential, such as small pox, that would have catastrophic epidemiological consequences.

So, quite unexpectedly, a PCR-based model sensor with metric parameters hardly achievable in the field at present, either alone, or in a net of 4 devices, failed to identify organisms (of all infectivity levels) in doses that could still provide high and very high risks of infection.

3.2. Antibody/antigen-based sensor

The results of simulations for an antibody/antigen-based model sensor (such as that used by, e.g. Naimushin et al., 2002; Larichia-Robbio and Revoltella, 2004; Utenhaler et al., 2001, etc.) presented in Fig. 3, showed that with the best available (and combined) metrics ($W_s = 1000$; $K_e = 0.8$; $V_s = 1$; $n = 4$; $I = 1$) it outperformed the best PCR-based model sensor discussed above. A single unit could detect with 50% probability the dose of 6 microbial units and with 100% probability the dose of 10 microbial units (Fig. 3). As expected, the performance of a network of four sensors is even better: 6 microbial units could be detected with 50% probability and that of 130 units could be detected with 100% probability (Fig. 4). However, as well as the other model sensors, it still failed to provide identification of lower infection risks either alone, or in a network of 4.

3.3. Mass spectrometry (MS)-based sensor

As evidenced by the results of a simulation for a model MS-based biosensor (such as that used by, e.g. Doroshenko et al., 2002; Madonna et al., 2003; Warscheid and Fenselau, 2003) presented in Fig. 4, this sensor with regard to identification capability occupies the intermediate position between PCR- and antibody/antigen-based sensors. The imaginary operational concept for that sensor was as follows: aliquots of 0.001 ml ($V_s$) were withdrawn from 10 ml concentrated collected sample ($V_c$) and applied onto a target plate. They were then evaporated, ionized with a laser beam and analyzed. Accordingly, $n$ was set as 1, and $I$ as 1. All other parameter values were the same as in other simulations (see above). When operating on its own, the sensor could identify with probability slightly higher than 50%, doses of 100 microbial units Fig. 4. However, 100% probability is reached only with more than 500 microbial units. The situation is much better with a net of 4 units: the dose of 23 microbial units (against 79 in PCR-based network) could be detected with 50% probability and that of 130 units could be detected with a 100% probability (Fig. 4). However, as well as the other model sensors, it still failed to provide identification of lower infection risks either alone, or in a network of 4.
3.4. Undetectable “critical doses”

So, none of the model sensors analyzed (Figs. 3–5) could identify the quantities of agents corresponding to inhalation doses equal to or less than Di = 5 microbes. Meanwhile, as shown in Fig. 1, these doses were still able to provide significant risks of infection especially for highly infectious agents. So, it is reasonable to introduce here the concept of “critical dose” of infection. The critical dose may be defined as the dose of microbes that cannot be reliably (with the probability of more than 0.5) detected by any existing real-time biosensors, but still can provide a significant probability/risk of infection. So, the critical doses in our case (see Fig. 1) correspond to Di values of around 5 and lower.

Further analysis focused on whether it was possible to achieve the identification of those critical doses by varying some crucial parameters of the sensors (such as the number of organisms in the sample, the volume and number of samples to be analyzed, n, and the sensitivity of identifier, I).

As an example, the dependence of probability of detection on the sensitivity and the volume of samples for PCR-based identifiers (for a critical dose of Di = 0.55 microbes) is shown in Fig. 5. Curves correspond to different values of n (in: (1) 1000; (2) 1.25; (3) 0.25; (4) 0.105; (5) 1; (6) 0.200; (7) 0.300).

Fig. 5. (A) and (B) Probability of identification (Pd) of an agent vs. sensitivity (I) and the sample volume (V) for a model PCR-based identifier. The following parameters were used in plotting: Di = 0.55 microbes, W = 1000 l/min, Kc = 0.8. (A) n = 16 samples; (B) n = 96 samples. Curves correspond to different values of n (in: (1) 1000; (2) 0.125; (3) 0.25; (4) 0.105; (5) 1; (6) 0.200; (7) 0.300).

For lower doses (Di = 0.5) the probability of identification over 50% can be achieved only starting with the sample volumes of no less than 32 and 100 μl.

Similar analysis of a model antibody-based sensor, described above, showed that the detection probability of over 50% for the critical doses of 1.5 and more microbes may be reached starting with sensitivities of 14 and lower. For smaller critical doses (Di = 0.5), the probability over 50% may be achieved by increasing either the sample volumes, V, or the sensitivity, or both (e.g. to 2.5 ml at sensitivity, I, of 14 microbes; to 4 ml at sensitivity of 20, or the same 1 ml with I increased to 7 and less). The practical use of bigger volumes (2.5 and 4 ml) does not seem feasible even with the best currently available samplers (flow rate, W = 1000; Ke = 0.8; Vc = 10), unless two samplers are used in parallel. A significant increase in sensitivity (to I = 7) seems very unlikely, at least in the nearest future. Furthermore, due to physical characteristics of transducers, such as SPR-based, SAW-based, etc., it is reasonable to expect much lower sensitivity of these devices towards virus agents compared to bacteria (Dorozhkin et al., 2004).

Any further enhancement of the probability of identification with MS-based model sensors is possible only with the significant increase of the number of cells/virions on the target plate. In terms of the present model sensor (see its operational description earlier in the text), to provide a 50% probability of detection of critical doses, the volume of sample, V, that is applied to the target plate should be increased to no less than 20 μl (instead of 1 μl) for the dose of 5 microbes and to over 180 μl for that of 0.5 microbes.

So, concluding this section, it should be emphasized that currently, even the sensors with the best possible metrics will not be able to detect in real-time critical doses—small doses of BWA that still have a significant infection potential. In the future, only a modest progress in identification may be expected for doses of, or around Di = 1. In case of lower doses, the prognosis is even bleaker.

4. Discussion

The model presented above allows to calculate simultaneously the probability of infection (risk of infection) of an exposed individual with any infectious agent of known, or alleged ID50 and other characteristics, and the probability of its identification by any existing or conceivable biosensor. The model helps to
inhaled by an individual of 1100 microbes/min (i.e. 1100 microbes/l of air required by DHS for current and future detection ability. For instance, the minimal detection level of \( D_{90} \) for the L. pneumophila aerosol is 10 microbes. This dose would correspond to the very high risks of infection regardless of the ID50 levels and the viability of the agent. For instance, 317 individuals out 1000 exposed to \( B. anthracis \) will be infected at 50% viability of the agent, and 782 will be infected by small pox aerosol with only 1% of viable virions. According to the results presented in Figs. 2–4, two of the tested model sensors (with the best possible metrics) alone or in a net of four would be able to identify the above risks with a 100% probability. For agents without epidemiologic potential, such as \( B. anthracis \), the aforementioned timely identification might seem sufficient. However, for agents with high epidemiologic potential, such as small pox virus, identification of much lower quantities of the agent is required. In this respect, none of the model sensors analyzed could identify the quantities of agents corresponding to inhalation doses of 5 microbes or less, and called here critical doses. However, it is conceivable that such small doses might originate from the terrorist act itself, when very small amounts of a BW agent are intentionally released. They could also be an immediate aftermath of a more extensive terrorist attack when the original “cloud” is gone and for some reason (gusts of wind, etc.) cannot be detected. Finally, tiny concentrations of a BW agent may also arise as remnants left after decontamination of sites of a terrorist attack. Apparently, the real-time efficient biosensors are not required for the latter case. The concept of critical dose formulated in this paper may be of help in defining the requirements for sensitivity of real-time biosensors designated for identification of a particular agent. It should be emphasized, however, that real-time identification, no matter how quick and sensitive, cannot prevent infection. It can only mitigate the consequences and help with a proper emergency management. Additionally, in most cases it should be expected that real-time identification, if it indeed takes place, will estimate at best only the lowest possible doses inhaled by the exposed individual, since this individual keeps on breathing during the identification time. Therefore, the fastest identification will be extremely beneficial. In this respect, MS-based sensors capable of identification within minutes are the most promising. Antibody-based sensors occupy the second position, and PCR-based—the last. Finally, as predicted by the model for PCR-, antibody-, and MS-based sensors, the reliable identification of critical doses equal to or less than single microbes could be achieved either by the increase of the identifier sensitivity or the concentration of the agent in the sample. Therefore, it is very likely that small concentrations of aerosolized agents, that are still able to provide significant risks of infection will remain undetected by any real-time biosensors. Further experimentation in this field should prove whether these predictions are right or wrong.

5. Conclusions

Simple probability model is presented that allows simultaneous calculation of probabilities of infection (risks of infection) of an exposed individual with any infectious agent of known, or alleged \( D_{90} \) and other characteristics, and the probabilities of its identification by any existing or conceivable biosensor. The model yielded quantitative results upon the input of 11 variable, incoming parameters such as an infectious dose of a microbe, parameters of a model sensor, etc.

Three model biosensors based on PCR-, antibody/antigen-, and MS-technique were tested by the model with regard to their detection/identification ability. A wide range of their metric parameters encompassing those of commercially available and laboratory biosensors, and those of future, theoretically conceivable devices was used for several hundred simulations.

The results of simulations indicate that small doses of aerosolized agents (less than 5 microbes) that are still able to provide significant risks of infection especially for highly infectious agents (e.g. for small pox those risk are 1, 8, and 37 infected out of 1000 exposed, depending on the viability of the virus preparation) will remain undetected by the present, most advanced, or even future, significantly refined real-time biosensors.

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References


A. Sahelikin et al. / Biosensors and Bioelectronics 21 (2006) 2070–2077