Multiplexed and Switchable Release of Distinct Fluids from Microneedle Platforms via Conducting Polymer Nanoactuators for Potential Drug Delivery

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Abstract

We report on the development of a microneedle-based multiplexed drug delivery actuator that enables the controlled delivery of multiple therapeutic agents. Two individually-addressable channels on a single microneedle array, each paired with its own reservoir and conducting polymer nanoactuator, are used to deliver various permutations of two unique chemical species. Upon application of suitable redox potentials to the selected actuator, the conducting polymer is able to undergo reversible volume changes, thereby serving to release a model chemical agent in a controlled fashion through the corresponding microneedle channels. Time-lapse videos offer direct visualization and characterization of the membrane switching capability and, along with calibration investigations, confirm the ability of the device to alternate the delivery of multiple reagents from individual microneedles of the array with higher precision and temporal resolution than conventional drug delivery actuators. Analytical modeling offers prediction of the volumetric flow rate through a single microneedle and accordingly can be used to assist in the design of subsequent microneedle arrays. The robust solid-state design and lack of mechanical components circumvent reliability issues that challenge fragile conventional microelectromechanical drug delivery devices. This proof-of-concept study demonstrates the potential of the drug delivery actuator system to aid in the rapid administration of multiple therapeutic agents and indicates the potential to counteract diverse biomedical conditions.

Keywords

Microneedle array; conducting polymer; electrochemically-switchable nanoactuator; drug delivery
1. Introduction

Conducting polymers such as polypyrrole (PPy), polyaniline (PANI), and poly(3,4-ethylenedioxythiophene) (PEDOT) have been identified as extremely attractive synthetic materials for utilization in controlled release systems [1–4] and drug delivery actuators [5–7]. The unique properties of these materials, and PPy in particular, include their reversible mechanical behavior as “artificial muscles” [8–10] and their ability to change porosity and undergo volume changes in response to applied electrochemical stimuli [11,12]. The combination of these actuators with a means to deliver medications in an effective and minimally-invasive manner would lay the groundwork for practical body-worn devices for the amelioration of disease and injury in the acute phase.

In this investigation, we present the first example of a minimally-invasive electrochemically-switchable nanoactuator microneedle platform capable of delivering multiple therapeutic agents (Fig. 1). Microneedle arrays have enjoyed recent success in the transdermal biosensing [13–15] and minimally-invasive drug delivery [16–18] domains. Advantageously, these versatile microneedle platforms can be designed and fabricated to the precise specifications demanded by the application at hand [19,20] and can assume nearly any geometry to fulfill these requirements [16,21]. Most crucially, these devices lend themselves to body-worn patch-type embodiments that are amenable to extended durations of pain-free wear. Advancements in such stimuli-responsive drug delivery systems would dramatically alter the way in which disease [22] and injury [23] are currently treated.

Whereas prior microneedle delivery devices were able to deliver a single therapy [24], the new approach enables the controlled and switchable delivery of multiple therapeutic agents. Still-frame images and real-time videos capture the alternating release of dye from different microneedles from the same tiny array platform; image analysis software (ImageJ) and ultraviolet-visible (UV-Vis) spectrophotometry are employed to demonstrate the switching accuracy and repeatability of the microneedle volumetric flow rate. These experimental results are correlated with an analytical model that assesses the fluid flow characteristics through a single microneedle and subsequently can be used to assist in the design and development of future multi-section microneedle arrays for practical body-worn devices that can deliver on demand different therapeutic agents.

Owing to the scalability of the arrayed microneedle platform, a unique drug therapy could be released at each microneedle constituent of the array, thereby enabling custom-tailored dosages of medications. In direct contrast to conventional drug delivery microsystems, this active solid-state device requires no moving parts or integrated microelectromechanical systems [25]. Thus, this simplifies low-profile device design and eliminates the need for sophisticated microfluidics-based components, which commonly complicates system architecture and increases both size and cost. Provided further insight into the biofouling effects associated with implantable devices, this minimally-invasive microneedle multi-drug delivery paradigm is well-positioned to serve as the core component in an autonomous ‘wearable nanopharmacy’ in connection to multiplexed microneedle sensor arrays.

2. Experimental

2.1. Reagent and supplies

Sodium dodecylbenzenesulfonate (NaDBS), methylene green (MG), chresol red (CR), potassium phosphate monobasic (KH$_2$PO$_4$), and potassium phosphate dibasic (K$_2$HPO$_4$) were obtained from Sigma Aldrich (St. Louis, MO) and were used without further purification or modification. Pyrrole (Sigma Aldrich) was distilled daily under vacuum and stored at 4 °C prior to electropolymerization. All reagents were prepared in a 0.1 M solution.
phosphate buffer solution (pH 7.00). Ultrapure water (18.2 MΩ·cm) was employed in all of the investigations.

Polydimethylsiloxane (PDMS) was purchased from Dow Corning Corp. (Midland, MI) and mixed by hand in a 10:1 polymer: fixing agent ratio. The suspension was then poured into a custom mold and degassed in a vacuum desiccator. Subsequently, the PDMS suspension was baked at 110 °C for 15 min. The resultant structures were exposed to UVO ozone (Jetline Co., Irvine, CA) at a gas flow rate of 3 sccm for 5 minutes. 25 mm-diameter black polycarbonate (PC) track etch membrane filters were procured from SPI Supplies (West Chester, Pennsylvania); these filters possessed a pore diameter of 600 nm.

2.2. Instrumentation

A CH Instruments (Austin, TX) model 1232A electrochemical analyzer was employed for all of the electrochemical measurements. An Ag/AgCl wire reference electrode and a platinum wire counter electrode were used to establish a three-electrode electrochemical system. A Shimadzu (Kyoto, Japan) UV-2450 UV–VIS spectrophotometer was used for all of the optical measurements. A commercially-available consumer digital video camera / camcorder was employed to capture the still-frame images and videos. A Philips XL30 field emission scanning electron microscope (Amsterdam, the Netherlands) was employed to investigate the surface morphology of the microneedle array. The arrays were coated with a gold film (~ 15 nm) using an Emitech (East Sussex, UK) K575X sputtering instrument prior to scanning electron microscopy imaging. The resultant electron micrograph is shown in Fig. 2. The PC membranes were sputtered with a gold thin film (~ 75 nm) using an Emitech K575X sputtering instrument prior to the deposition of the NaDBS-doped PPy conducting polymer.

2.3. Fabrication of hollow microneedle arrays

The hollow microneedle arrays were fabricated at the UNC/NCSU Department of Biomedical Engineering. The microneedle designs were originally prepared using Solidworks (Dassault Systemes S.A., Velizy, France). Substrate support structures were subsequently created with Magics RP 13 (Materialise NV, Leuven, Belgium). The hollow needles were pyramidal in shape with a triangular base. The dimensions of each hollow microneedle were as follows: an edge length of 1174 ± 13 µm, a height of 1366 ± 15 µm, and a vertical cylindrical bore of 342 ± 5 µm diameter on one of the faces of the pyramid structure. The hollow needles were arranged into 3 × 3 square arrays with 2 mm periodicity. Substrates for the microneedle arrays were 10 mm × 10 mm in extent and possessed thickness values of 500 µm. Details regarding the fabrication of these microneedle arrays have been previously published [13–15].

2.4. Preparation of PC/Au/PPy/DBS membranes

The technique for the creation of the electrically-actuatable nanoporous membrane was adapted from the experimental protocol presented in [11]. Briefly, gold-sputtered PC membranes (PC/Au) (Cyclopore – Whatman International, pore diameter ~ 600 nm, porosity ~ 0.2) were attached at the periphery to a copper wire using silver conductive epoxy. A solution of 0.1 M NaDBS was purged with nitrogen for 40 min after which the pyrrole monomer was added to achieve a final concentration of 0.25 M. Subsequently, the PC/Au membrane was immersed in the solution and served as the working electrode in an electrochemical cell while 0.6 V vs Ag/AgCl was applied for 10 min. The application of this potential for the given amount of time resulted in optimal deposition of the polypyrrole polymer on the PC/Au membrane, thereby minimizing the leaching of the solution through the membrane under the ‘closed’ state while enabling the solution to flow at appreciable rates under the ‘open’ state. Following electropolymerization of polypyrrole/DBS (PPy/
DBS), the PC/Au/PPy/DBS membranes were rinsed with deionized water and stabilized by cycling between −1.1 V and 0.5 V vs Ag/AgCl for ten iterations in the buffer solution. This fabrication process enabled the membrane to swell in the reduced state (−1.1 V) and contract in the oxidized state (0.5 V) in a reversible manner - switching potentials that are similar to those established by Jeon et. al [11]. When not in use, the membranes were stored in the buffer solution at room temperature.

2.5. Construction of the drug delivery actuator

The PC/Au/PPy/DBS membranes were cut into slivers possessing dimensions of approximately 12 mm × 4 mm. These slivers were subsequently affixed to the reverse side of the 3 × 3 microneedle array using adhesive epoxy such that one sliver completely covered a column of three microneedles. The center column of the array was obstructed using modeling clay, enabling formation of two individually-addressable electrically-actuatable channels. A component-level view is illustrated in Fig. 1A. Electrical leads were attached using silver epoxy to each of the two PC/Au/PPy/DBS membranes to facilitate ohmic contact with each actuator. The PDMS dual-channel reservoir was subsequently aligned over the membranes and affixed using adhesive epoxy. As shown in Fig. 1B, the reservoirs were finally loaded with ~ 20 µL of the model chemical agent(s).

3. Results

3.1. Investigation of switching operation and time

Initial experimental efforts were aimed at validating and visualizing the switching capability of the PC/Au/PPy/DBS membrane and the dual-channel operation. Both reservoirs in the assembled multiplexed drug delivery actuator, reservoir 1 (R1) and reservoir 2 (R2), were initially loaded with 12 mM of methylene green (MG) dye and immersed in a buffer solution along with the counter and reference electrodes. Continuous agitation at a constant speed (140 rpm) was applied with a magnetic stirring bar. The DBS-doped PPy membrane entered the reduced state and engorged upon biasing with −1.1 V vs Ag/AgCl, thereby obstructing the flow of the solution through the porous material. Ejection of MG at either channel was not observed at this potential (represented as being in the ‘OFF’ state), as shown in Fig. 3A. Subsequently, the R2 membrane nanoactuator was maintained at the reduced state (−1.1 V vs Ag/AgCl, ‘OFF’) and the membrane at R1 was switched to the oxidized state (‘ON’) by applying a potential of 0.5 V vs Ag/AgCl. This “ON” state caused the DBS-doped PPy membrane to become oxidized and contract, thereby facilitating the flow of the solution through the nanoporous membrane and subsequently through the microneedles. As can be observed from Fig. 3B, the emission of MG from R1 is visible whereas R2 remained closed and did not permit the release of the dye. Following this operation, R1 was kept at the oxidized state (0.5 V vs. Ag/AgCl, ‘ON’) while R2 was switched to the oxidized state (0.5 V vs. Ag/AgCl, ‘ON’), thus releasing MG from both reservoirs (Fig. 3C). Subsequently, R1 was switched to the reduced state “OFF” and R2 was kept at the oxidized state “ON”, as shown in Fig. 3D. This controlled and alternating release of MG from the individual reservoirs by switching potentials on the nanoporous membranes is illustrated in a real-time manner in Video 1 (see Supporting Information).

The execution of repeated ‘ON-OFF’ cycles demonstrates that the drug delivery array maintains its ability to open and close in a cyclic fashion, even following 10 iterations. Furthermore, the temporal duration (~ 30 s) required to observe the release of MG at the tenth cycle was identical to that of the first cycle. The time duration for complete flow shutoff was approximately 35 s following the application of the “OFF” potential. Based on the above results, R1 was loaded with CR and R2 was loaded with MG. All four “ON / OFF” permutations were applied; the video of the device with this arrangement is shown in...
3.2. Temporal evolution of the drug release

Image analysis and UV-Vis spectrophotometry techniques were used to analyze the drug delivery capability of the microneedle array by experimentally quantifying the flow rate of the MG dye from a single microneedle channel. Fig. 4 illustrates the release of MG from a single microneedle into a quiescent buffer solution at fixed time intervals of 30 s. A potential of 0.5 V (vs Ag/AgCl) was applied to open the nanoporous membrane and release the dye during the experiments. After 30 s of applying this potential, the dye began to emerge from the microneedle aperture; a small column of dye was clearly observed at 60 s. A well-defined column of dye possessing a height of approximately 0.5 cm was observed after 120 s. Afterwards, the estimated experimental flow rate of the released dye was calculated by measuring its column height \( h \) with image processing software (i.e., ImageJ) in conjunction with the flow rate equation (Eq. 1):

\[
Q = \frac{\Pi d^2 h}{4(t - t_o)} \quad (1)
\]

where \( d \) is the microneedle channel diameter and \( h \) is the column height associated with a particular point at time \( t \).

The experimental flow rate of released dye was determined to be 6.3 ± 0.4 µL / hour \( (n = 10) \) through analysis of multiple time-lapse video still-frames (Fig. 4).

In an effort to validate the flow rate obtained via image analysis, UV-Vis spectrophotometry was employed to quantify the amount of released dye and subsequently assess the microneedle flow rate as well as the repeatability of the release. The absorbance spectra for the MG released from a single microneedle was recorded sequentially, every 2 minutes, as shown in Fig. 5. The inset in Fig. 5 (bottom right) substantiates the reproducibility of the MG release from the drug-delivery nanoactuator over the same release time. The maximum deviation among these ten repetitions was 5.5 % from the original absorbance, which was measured at the maximum wavelength. Linear regression analysis was performed on the absorbance vs time plot, yielding a slope of 3.5 mOD min\(^{-1}\) with a high coefficient of determination \( (R^2 = 0.993) \) and low relative standard deviation \( (RSD = 2.74 \%, n = 3) \); this result indicated a constant release of dye from the microneedle. From these experiments, the fluid flow rate was calculated to be 5.5 ± 0.2 µL / hour, which is in good agreement with the image analysis data collected from the time-lapse video still-frames. The fabricated membranes were highly reproducible; exhibited calculated flow rates deviated by less than 10 % under identical electropolymerization conditions.

3.3. Fluid mechanics modeling of the drug flow rate and correlation with experimental results

The understanding of the fluid flow characteristics of the microneedle array is crucial for delivering the precise amount of drug to subcutaneous tissue during transdermal drug delivery. To augment this understanding and to analytically estimate the drug delivery capability, the fluid flow characteristics of a single microneedle was modeled via the Modified Bernoulli Equation (Eq. 2):

\[
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\]
where $P_1$ and $P_2$ are the atmospheric and microneedle outlet pressure, $V_1$ and $V_2$ are the average fluid velocities, $z_1$ and $z_2$ are the heights at the top of the reservoir and microneedle outlet respectively, $f$ is the friction factor, $\rho$ is the fluid density, $L$ is the channel or pore length, and $D$ is the hydraulic diameter (Fig. 6) [26,27]. The second term in Eq. 2 refers to the friction losses through the actuating nanopores, polycarbonate membrane, and microneedle channel as shown in expanded form (Eq. 3).

$$\sum f \frac{L}{D} = \frac{f_{\text{pores}}}{\varepsilon_{\text{pores}}} \frac{L_{\text{membrana}}}{\varepsilon_{\text{membrana}}} + \frac{f_{\text{microneedle}}}{\varepsilon_{\text{microneedle}}}$$ (3)

where $\tau$ and $\varepsilon$ represent the tortuosity and porosity of the nanopores and polycarbonate membranes, respectively [11] and $D$ is the diameter of a single microchannel (342 µm). The porosity of the PC membrane is 0.1 (see Experimental Section) and the porosity of the actuating nanopores is 0.4 due to the pore narrowing created by the Au/PPy/DBS functionalization. An approximate tortuosity values of 1.5 was assigned to the PC membrane and the actuating nanopores to take into account the increased channel curvature created by the nanopores. The respective friction factors were calculated according to Stokes flow theory for water flow in microchannels [28–30], where the product of the friction factor and Reynolds number ($Re = 64$) utilized for macroscale laminar flow in circular channels is employed [31]. The friction factors for each flow section can be obtained by the Reynolds numbers obtained for fluid flow in each of the 3 flow sections of the microneedle channel (Table 1).

The values presented in Table 1 are calculated according to the following considerations. $A_c$ is the cross sectional area of the microneedle $[\pi (D_{\text{microneedle}})^2/4]$. The Reynolds number ($Re = \Omega D / \mu$) was calculated using the density ($\rho = 1000$ kg/m$^3$) and viscosity ($\mu = 1.000$ N s/m$^2$) of water at room temperature [32]. The velocity used to estimate the Reynolds number for fluid exiting the microneedle channel was determined a priori by averaging the experimental velocities obtained by image analysis and UV-Vis spectrophotometry. Furthermore, the a priori velocities for the polycarbonate membrane and the nanoporous membrane were obtained by utilizing Conservation of Mass for incompressible fluids ($V_1 A_1 = V_2 A_2$) in conjunction with the average experimental velocity to calculate the corresponding Reynolds numbers.

The last term ($\Sigma K$) in Equation (2) represents the sum of minor losses due to the inlet, exit, and hydrodynamic development length, which is shown in expanded form below: (Eq. 4)

$$\Sigma K = K_{\text{inlet}} + K_{\text{outlet}}$$ (4)

where $K_{\text{inlet}}$ and $K_{\text{outlet}}$ are loss coefficient factors for a square edge inlet (0.5) and for an exit (1) typically associated with hollow microneedles [26,27].

Finally, an expression (Eq. 5) for the theoretical flow rate of the fluid exiting the microneedle channel can be formed by assuming quiescent flow at the top of the reservoirs ($V_1 = 0$), and negligible pressure gradients throughout the flow network ($\Delta P = P_1 - P_2 = 0$).

$$Q_2 = A_c \sqrt{\frac{2g(z_1 - z_2)}{\Sigma f \frac{L}{D} + \Sigma K}}$$ (5)
4. Discussion

The ability to transdermally release multiple drugs is profoundly important for the autonomous treatment of a metabolic syndrome (a combination of hypertriglyceridemia, hypertension, and insulin dependent diabetes mellitus), human immunodeficiency virus, and other chronic medical conditions. In this work, we have presented a self-contained multiplexed drug delivery system that utilizes arrays of microneedles coupled with conducting polymer nanoactuators for the controlled release of fluidic agents. The ability of the PPy/DBS conducting polymer to undergo volumetric changes with applied electrical potentials permits the release of fluid in a controlled and switchable fashion without the need for moving parts or integrated microelectromechanical systems. These nanopore-actuated microneedle arrays are well suited for integration into wearable drug delivery devices, in which cost and power constraints must be minimized.

In an effort to elucidate the drug delivery capacity of the microneedle array, the fluid flow characteristics were analyzed both experimentally and analytically. Image analysis software and UV-Vis spectrophotometry were used to empirically determine the flow rate of the fluid exiting the microneedle channel while the Modified Bernoulli Equation was employed to analytically determine the flow rate. The resultant flow rates obtained through image analysis (6.3 ± 0.4 µl/hr), UV-Vis spectrophotometry (5.5 ± 0.2 µl/hr), and analytical modeling (6.4 µl/hr) were in good agreement, hence validating the accuracy of the developed model. Furthermore, the low standard deviation obtained from the experimental flow rate measurements is indicative of the high repeatability of the volumetric flow rate exiting the microneedle channel. This coupling of theoretical modeling and experimental results provides much-needed insight into the transport of fluids through distinct multi-diameter flow sections of microneedle arrays. Thus this experimentally-corroborated analytical model provides a foundational backbone for subsequent microneedle designs, in which the model results can be used to predict fluid flow characteristics in untested microneedle configurations. The detailed understanding of the fluid flow characteristics as well as the repeatable, precise release of fluid is of critical importance for drug delivery applications.

When compared with conventional drug delivery systems, the presented methodology obviates the need for sophisticated microfluidic and/or microelectromechanical systems such as micropumps in order to actuate the delivery of the target therapeutic agent. As is evident, flow rates are somewhat lower using this ‘passive’ approach, however the proposed technology embodies unique advantages including minimized overall system complexity, substantially increased robustness due to its purely solid-state nature, and the ability to be sustained by a given power source for extended periods of use. Although the approach possesses these noteworthy advantages, a limitation of the approach must be considered: the relative difficulty encountered in actuating the release of highly viscous fluid formulations from the microneedle array device. Thus, in future work the construction of this drug delivery system, including the individual microneedle diameters, should be adjusted and optimized to assure the appropriate flux rate through the membrane nanopores for fluids of different viscosities and molecular weights.
4. Conclusions

In summary, the presented nanoporous membrane-actuated microneedle array establishes the foundation for practical body-worn devices that can deliver different therapeutic agents in an on demand manner. This microneedle array could potentially deliver multiple drugs with higher precision and temporal resolution than conventional macroneedle delivery techniques while reducing the pain, patient anxiety, and risk of infection commonly associated with conventional drug delivery platforms. Moreover, the new multiple-drug delivery microsystem can be integrated with a microneedle sensor array, hence coupling multiplexed analyte detection with the corresponding therapeutic intervention. Such a closed-loop sensing / drug delivery microneedle paradigm is well-positioned to precisely deliver multiple therapeutic agents in an on-demand basis. This type of autonomous “Sense-Act-Treat” system may not only provide an avenue for responding to biomarker fluctuations with a targeted therapy, but may also herald the development of self-regulating drug delivery microdevices that can adjust patient dosage based on the severity of the injury or the disease process. The development of such responsive multiplexed drug-delivering systems is expected to dramatically transform outpatient, home-based civilian medical treatments as well as military medical care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Biographies

Gabriela Valdés Ramírez received her B.S. and Ph.D degrees in Chemistry Since from Universidad Autónoma Metropolitana-Iztapalapa (Mexico) 2005 and 2008, respectively; a joint Ph.D. degree at Agrochemistry Université de Perpignan Via Domitia (France) 2008. She did Postdoctoral research at Professor Joseph Wang group in NanoEngineering at University of California San Diego (USCD), USA 2010–2011. Her scientific interests are areas of sensors, biosensors and materials with biomedical and environmental applications.

Joshua Ray Windmiller received the B.Sc., M.Sc., and C.Phil. in Electrical Engineering in 2007, 2009, and 2011, respectively, from the University of California, San Diego. He was awarded with the Charles Lee Powell Foundation fellowship and bonus award and is a Gordon Scholar and Fellow in engineering leadership. He is currently pursuing the Ph.D. degree in Electrical Engineering at UCSD where his research focuses on the development of advanced sensor and actuator devices for the detection and treatment of trauma. He has published over 30 manuscripts in peer-reviewed journals and conference proceedings and has one issued and four patents pending.

Jonathan C. Claussen received his BS in Mechanical Engineering and BA in Spanish and Portuguese Studies at the University of Minnesota in 2006, his MS in Mechanical Engineering and PhD in Biological Engineering from Purdue University in 2008 and 2011 respectively, and is currently working as a postdoctoral scholar at the University of California San Diego under Prof. Joseph Wang. He has co-authored over 15 journal articles,

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received awards for top presenter at the Institute of Biological Engineering and Materials Research Society annual meetings, and received the coveted outstanding Ph.D. Graduate Student Award from the Department of Agricultural & Biological Engineering at Purdue University.

**Alexandra G. Martinez** is pursuing her B.S. in Biotechnology : Bioengineering in the Department of Bioengineering in the Jacobs School of Engineering at the University of California San Diego. Currently she is working with Dr. Wang’s laboratory for nano-bioelectronics on projects varying from microneedles to self-powered bio-fuel cells. Her research interests include nanotechnology and biosensors for biomedical applications to promote human health.

**Filiz Kuralay** received her PhD in analytical chemistry from Hacettepe University Department of Chemistry (Turkey) in 2009. Since April 2011 she works as an Assistant Professor at the Chemistry Department of Ordu University. Currently she is working as a Postdoctoral Scholar in the research group of Prof. J. Wang at the Department of Nanoengineering in UCSD, USA. Her research areas include electrochemical DNA biosensors, chemically modified electrodes and conducting polymers.

**Ming Zhou** received his B.S. (2004) and M.S. degrees (2007) from Northeast Normal University, China. In 2007, he joined Prof. Shaojun Dong’s group at Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, and received his Ph.D. degree in 2010. He is currently a Postdoctoral Research Associate in Prof. Joseph Wang’s group in the Department of NanoEngineering at University of California, San Diego. His major research focuses on biosensors, biofuel cells, biocomputing systems, and nanomotors.

**Nandi Zhou** received his B.Sc. and Ph.D degree in biochemistry and molecular biology from Nanjing University, China in 1996 and 2007. From 2010 to 2011, he worked as a visiting scholar in Prof. Joseph Wang’s lab at University of California, San Diego. He is now an associate professor in School of Biotechnology, Jiangnan University, China. His research interests include biosensors, biomolecular electron transfer and interaction, and nano-scale structures and devices.

**Ronen Polsky** received his M.Sc. From Bar-Ilan University in 1998 and his PhD in 2004 from New Mexico State University under the supervision of Prof. Joseph Wang. Following a one year postdoctoral fellowship at the Hebrew University in the laboratory of Ilamar Willner he joined Sandia National Laboratories in 2006 where he currently holds a position as a senior member of technical staff in the department of Biosensors and Nanomaterials. His current research interests include electroanalytical chemistry, biosensors, and photopatterned 3D nanostructures.

**Philip R. Miller** received his B.S. from North Carolina State University in 2008 in Mechanical Engineering. He is currently a Ph.D. student at the Joint Department of Biomedical Engineering between the University of North Carolina and North Carolina State University under the guidance of Roger Narayan and Ronen Polsky. His research includes microneedle sensors, two photo polymerization, tissue scaffolds, and drug delivery.

**Roger Narayan** is a Professor in the Joint Department of Biomedical Engineering at the University of North Carolina and North Carolina State University. He received a Ph.D. in Materials Science & Engineering from North Carolina State University and an M.D. from Wake Forest University. Dr. Narayan is an author of over one hundred publications as well.
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Joseph Wang received Ph.D. from Israel Institute of Technology in 1978. From 1978 to 1980 he served as a research associate at the University of Wisconsin, and joined New Mexico State University (NMSU) at 1980. In 2001–2004, he held a Regents Professorship and a Manasse Chair positions at NMSU, and served as the director of Center for Bioelectronics and Biosensors of Arizona State University. Currently, he is Professor in Department of Nanoengineering at University of California, San Diego, he has published more than 800 papers and he holds 12 patents. He became the most cited electrochemist in the world and received the 4th place in the ISI's list of ‘Most Cited Researchers in Chemistry’ in 1996–2006. He is the Editor-in-Chief of Electroanalysis. His scientific interests are concentrated in the areas of biosensors, bioelectronics, bionanotechnology and electroanalytical chemistry.

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Fig. 1. (A) Schematic illustration of the microneedle-based multiplexed drug delivery actuator detailing the (i) hollow microneedle array, (ii) gold-sputtered polycarbonate membrane functionalized with sodium dodecylbenzenesulfonate-doped polypyrrole (PC/Au/PPy/DBS), and (iii) polydimethylsiloxane (PDMS) reservoir. (B) Schematic illustration of the assembled dual-channel drug delivery system outlining the reservoirs for (iv) drug 1 and (v) drug 2.
Fig. 2.
(A) Scanning electron micrograph detailing the surface morphology of the hollow microneedle array. (B) Single needle with well-defined cylindrical lumen.
Fig. 3.
Triggered release of methylene green (MG) from the individually-addressable reservoirs: (A) reservoirs R1 and R2 OFF, (B) reservoir R1 OFF, reservoir R2 ON, (C) reservoir R1 ON, reservoir R2 ON, (D) reservoir R1 ON, reservoir R2 OFF.
Fig. 4.
Time-lapse still frame images of the release of methylene green (MG) from a single microneedle at distinct time intervals of (A) 30 s, (B) 60 s, (C) 90 s, and (D) 120 s.
Fig. 5.
UV-Vis spectrum illustrating the absorbance for the release of methylene green (MG) from a single microneedle at a 2 minutes release interval over a 20 minute period. The upper inset displays the UV-Vis spectra and the lower inset displays absorbance of 10 distinct experiments over a constant time release.
Fig. 6.
Schematic of a single microneedle during drug delivery. Microneedle components include the following: (i) reservoir, (ii) lumen (342 μm diameter), (iii) hollow microneedle (iv) Au/PPY/DBS nanoporous membrane, (v) PC membrane, and (vi) the released drug.
Table 1

Dimensions and flow characteristics of a single microneedle channel.

<table>
<thead>
<tr>
<th>Flow Section</th>
<th>Length (µm)</th>
<th>Total Cross Sectional Area</th>
<th>Re</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microneedle Channel</td>
<td>1366</td>
<td>$A_c$</td>
<td>$6 \times 10^{-1}$</td>
</tr>
<tr>
<td>Polycarbonate Membrane</td>
<td>7 (0.2) $A_c$</td>
<td></td>
<td>$5 \times 10^{-4}$</td>
</tr>
<tr>
<td>Nanoporous Membrane</td>
<td>0.75 (0.4) $A_c$</td>
<td></td>
<td>$9 \times 10^{-5}$</td>
</tr>
</tbody>
</table>
Table 2
Comparison of calculated theoretical and experimental microneedle flow rates.

<table>
<thead>
<tr>
<th>Method</th>
<th>Flow Rate ($Q_2$) (µl/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theoretical Model</td>
<td>6.4</td>
</tr>
<tr>
<td>Image Analysis</td>
<td>6.3 ± 0.4</td>
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<tr>
<td>UV-Vis Spectrophotometry</td>
<td>5.5 ± 0.2</td>
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</tbody>
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