Modern Aspects of Electrochemistry 53

Noam Eliaz *Editor*

# Applications of Electrochemistry and Nanotechnology in Biology and Medicine II

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# MODERN ASPECTS OF ELECTROCHEMISTRY

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Noam Eliaz
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# Applications of Electrochemistry and Nanotechnology in Biology and Medicine II

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# Preface

The emergence of nanoscience and nanotechnology has led to new developments in and applications of electrochemistry. These two volumes of Modern Aspects of Electrochemistry, entitled: "Applications of Electrochemistry and Nanotechnology in Biology and Medicine," address both fundamental and practical aspects of several emerging key technologies. All Chapters were written by internationally renowned experts who are leaders in their area.

The Chapter by A. Heiskanen and J. Emnéus provides a lucid and authoritative overview of electrochemical detection techniques for real-time monitoring of the dynamics of different cellular processes. First, biological phenomena such as the cellular redox environment, release of neurotransmitters and other signaling substances based on exocytosis, and cellular adhesion, are discussed thoroughly. Next, the capabilities of electrochemical amperometric and impedance spectroscopic techniques in monitoring cellular dynamics are highlighted, in comparison to optical and other techniques. The applications of such techniques already include biosensors and microchip-based biological systems for cell biological research, medical research and drug development. Finally, the state-of-the-art and future developments, e.g. miniaturization of planar interdigitated electrodes in order to achieve a gap/width size regime on the nanometer scale and thus considerable signal amplification, are summarized.

Electron transfer by thermally activated hopping through localized centers is an essential element for a broad variety of vital biological and technological processes. The use of electrode/self-assembled monolayer (SAM) assemblies to explore fundamental aspects of long- and short-range electron exchange between electrodes and redox active molecules, such as proteins, is reviewed comprehensively in a Chapter by D.H. Waldeck and D.E. Khoshtariya. The authors, who are pioneers in this area, nicely demonstrate that such bioelectrochemical devices with nanoscopically tunable physical properties provide a uniquely powerful system for fundamental electron transfer studies and nanotechnological applications. Studies on protein systems also reveal how the binding motif of the protein to the electrode can be changed to manipulate its behavior, thus offering many promising opportunities for creating arrays of redox active biomolecules.

A microbial fuel cell (MFC) is a bio-electrochemical transducer that converts microbial biochemical energy directly to electrical energy. In their authoritative Chapter, J. Greenman, I.A. Ieropoulos and C. Melhuish overview lucidly the principles of biofilms, biofilm electrodes, conventional fuel cells, and MFCs. Potential applications of both biofilm electrodes and MFCs are suggested, including sensing, wastewater treatment, denitrification, power packs, and robots with full energy autonomy. The symbiotic association between microbial life-forms and mechatronic systems is discussed in detail by the authors, who are internationally renowned experts in this field.

The last three chapters in Volume I deal with surface modification of implants, namely surface biofunctionalization or coating. First, R. Guslitzer-Okner and D. Mandler provide concise survey of different electrochemical processes (electrodeposition, electrophoretic deposition, microarc deposition, electropolymerization, and electrografting) to form different coatings (conducting polymers, non-conducting polymers, sol-gel inorganic-organic polymer materials, oxides, ceramics, bioglass, hydroxyapatite and other calcium phosphates) on different substrates (titanium and its alloys, stainless steels, cobalt-chrome alloys, nitinol, and magnesium alloys). The authors who are highly experienced in this field demonstrate the applicability of these coatings for medical devices such as drug eluting stents and orthopedic implants.

Different electrochemical processes to render metal implants more biofunctional and various electrochemical techniques to characterize the corrosion resistance of implants or the adsorption of biomolecules on the surface are reviewed by T. Hanawa in his authoritative Chapter. Electrodeposition of calcium phosphates or polyethylene glycol (PEG), as well as anodizing and micro-arc oxidation processes to obtain $TiO_2$ nanotube-type oxide film on Ti substrate, or electrochemical treatment to obtain nickel-free oxide layer on nitinol alloys, are described. The effects of different surfaces on phenomena such as cell adhesion, bacterial attachment and calcification are presented.

The last Chapter in Volume I, by T. Kokubo and S. Yamaguchi, lucidly summarizes the pioneering work and inventions of these authors in the field of bone-bonding bioactive metals for orthopedic and dental implants. The metals include titanium, zirconium, niobium, tantalum and their alloys. The main surface modification technique presented in this chapter is chemical, followed by heat treatment, although other techniques such as ion implantation, micro-arc treatment, hydrothermal treatment and sputtering are also described. The bone-bonding ability of metals with modified surfaces is attributable to the formation of apatite on their surface in the body environment, which can be interpreted in terms of the electrostatic interaction of the metal surface with the calcium or phosphate ions in a body fluid. These findings open numerous opportunities for future work.

Volume II begins with a Chapter by P.S. Singh, E.D. Goluch, H.A. Heering and S.G. Lemay which provides a lucid overview of the fundamentals and applications of nanoelectrochemistry in biology and medicine. First, some key concepts related to the double layer, mass transport and electrode kinetics and their dependence on the dimension and geometry of the electrode are discussed. Next, various fabrication schemes utilized in making nano-sized electrodes are reviewed, along with the inherent challenges in characterizing them accurately. Then, the “mesoscopic” regime is discussed, with emphasis on what happens when the Debye length becomes comparable to the size of the electrode and the diffusion region. Quantum-dot electrodes and charging and finite-size effects seen in such systems are also described. Then, recent advances in the electrochemistry of freely-diffusing single molecules as well as electrochemical scanning probe techniques used in the investigations of immobilized biomolecules are presented by the authors, who have pioneered several of the developments in this area. Finally, a brief survey of the applications of nanoelectrodes in biosensors and biological systems is provided.

During the last decade, nanowire-based electronic devices emerged as a powerful and universal platform for ultra-sensitive, rapid, direct electrical detection and quantification of biological and chemical species in solution. In their authoritative Chapter, M. Kwiat and F. Patolsky describe examples where these novel electrical devices can be used for sensing of proteins, DNA, viruses and cells, down to the ultimate level of a single molecule. Additionally, nanowire-based field-effect sensor devices are discussed as promising building blocks for nanoscale bioelectronic interfaces with living cells and tissues, since they have the potential to form strongly coupled interfaces with cell membranes. The examples described in this chapter demonstrate nicely the potential of these novel devices to significantly impact disease diagnosis, drug discovery and neurosciences, as well as to serve as powerful new tools for research in many areas of biology and medicine.

The Human Genome Project has altered the mindset and approach in biomedical research and medicine. Currently, a wide selection of DNA microarrays offers researchers a high throughput method for simultaneously evaluating large numbers of genes. Electrochemical detection-based DNA arrays are anticipated to provide many advantages over radioisotope- or fluorophore-based detection systems. Due to the high spatial resolution of the scanning electrochemical microscope (SECM), this technology has been suggested as a readout method for locally immobilized, micrometer-sized biological recognition elements, including a variety of DNA arrays with different formats and detection modes. In his concise review, K. Nakano explains the underlying electrochemistry facets of SECM and examines how it can facilitate DNA array analysis. Some recent achievements of Nakano and his colleagues in SECM imaging of DNA microdots that respond toward the target DNA through hybridization are presented.

Biological membranes are the most important electrified interfaces in living systems. They consist of a lipid bilayer incorporating integral proteins. In view of the complexity and diversity of the functions performed by the different integral proteins, it has been found convenient to incorporate single integral proteins or smaller lipophilic biomolecules into experimental models of biological membranes (i.e. biomimetic membranes), so as to isolate and investigate their functions. Biomimetic membranes are common in pharmaceuticals, as well as for the investigation of phase stability, protein-membrane interactions, and membrane-membrane processes. They are also relevant to the design of membrane-based biosensors and devices, and to analytical platforms for assaying membrane-based processes. The last two chapters in Volume II are dedicated to these systems. In their thorough Chapter, R. Guidelli and L. Becucci overview the principles and types of biomimetic membranes, the advantages and disadvantages of these systems, their applications, their fabrication methodologies, and their investigation by electrochemical techniques – mainly electrochemical impedance spectroscopy (EIS). This authoritative Chapter was written by two authors who are among the leaders in the field of bioelectrochemistry worldwide.

Ion channels represent a class of membrane spanning protein pores that mediate the flux of ions in a variety of cell types. They reside virtually in all the cell membranes in mammals, insects and fungi, and are essential for life, serving as key components in inter- and intracellular communication. The last Chapter in Volume II, by E.K. Schmitt and C. Steinem, provides a lucid overview of the potential of pore-suspending membranes for electrical monitoring of ion channel and transporter activities. The authors, who are internationally acclaimed experts in this area, have developed two different methods to prepare pore-suspending membranes, which both exhibit a high long-term stability, while they are accessible from both aqueous sides. The first system, nowadays known as nano black lipid membrane (nano-BLM), allows for ion channel recordings on the single channel level. The second system – pore-suspending membranes obtained from fusing unilamellar vesicles on a functionalized porous alumina substrate – enables to generate membranes with high protein content. The electrochemical analysis of these systems is described thoroughly in this chapter, and is largely based on EIS.

I believe that the two volumes will be of interest to electrochemists, chemists, materials, biomedical and electrochemical engineers, surface scientists, biologists and medical doctors. I hope that they become reference source for scientists, engineers, graduate students, college and university professors, and research professionals working both in academia and industry.

I wish to thank Professor Eliezer Gileadi who was the driving force making me edit these two volumes. I dedicate this project to my wife Billie, our two daughters – Ofri and Shahaf, and our newborn – Shalev, for their infinite love and support.

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# Professor Noam Eliaz

Noam Eliaz is an Associate Professor at Tel-Aviv University, Israel, where he serves as the Head of The Biomaterials and Corrosion Laboratory and as the first Head of the multi-faculty Materials and Nanotechnologies Program. He also serves as a Chief Editor of the journal *Corrosion Reviews* (jointly with Professor Ron Latanision). He received his B.Sc. and Ph.D. (direct track) in Materials Engineering, both *cum laude*, from Ben-Gurion University. After completing his doctorate, he became the first ever materials scientist to receive, simultaneously, a Fulbright postdoctoral award and a Rothschild postdoctoral fellowship. He then worked for two years in the H.H. Uhlig Corrosion Laboratory at M.I.T. To-date, he has contributed more than 220 journal and conference publications, including 28 invited talks, as well as 4 book chapters. He is currently editing a book on *Degradation of Implant Materials*, to be published by Springer during 2011. He has garnered numerous accolades, including the T.P. Hoar Award for the best paper published in *Corrosion Science* during 2001 (with co-authors), the 2010 Herbert H. Uhlig Award granted by NACE International in recognition of outstanding effectiveness in postsecondary corrosion education, and the 2012 NACE Fellow award. His main research interests include corrosion, electrodeposition, biomaterials and bio-ferrography.

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### 1

# Nanoelectrochemistry: Fundamentals and Applications in Biology and Medicine

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## I. INTRODUCTION

The compound word nanoelectrochemistry comprises the prefix *nano* and the noun *electrochemistry*. Both these components by themselves encompass a vast variety of meanings and envelop enormously diverse areas of scientific inquiry. For example, it can be argued that all of molecular electrochemistry occurs on a scale much smaller than nano—i.e., the molecular scale. The most basic aspects of a simple heterogeneous electron transfer reaction, from the description of the electrical double layer in the vicinity of the electrode to the theories for electron transfer and finally the reactants and products of such a reaction are all microscopic entities.

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Here, our primary focus will be on the fundamental and practical consequences of working with electrode systems with lateral dimensions that are below 100 nm. In some instances we will also consider nano-gap electrodes, where although the electrodes themselves are micrometer scale, they are separated from another electrode by distances < 100 nm. We will only deal with systems that involve some manner of *electron transfer* between molecules in solution and an electrode.

Therefore, although they may, in a sense, be considered *electrochemical*, we will refrain from considering advances in areas such as nanowires[1-3] and other low-dimensional nanomaterials[4-6] and nanopores[7]—areas which have witnessed great fundamental advances in the last decade and hold tremendous potential for analytical, biological, bio-medical and energy-related applications. We will also refrain from addressing the areas of solid-state electrochemistry as applicable in battery and fuel-cell research. The progress in using nanostructured materials as electrodes in these areas holds great promise, but again lies outside the scope of this chapter.[8-12] Finally, also omitted for purposes of brevity are electrodes based on arrays of nanoparticles or carbon nanotubes. In the last two decades carbon nanotubes as electrode materials of nanoscale dimensions and as components of sensing systems (for example, field-effect transistors (FETs) etc.) have received considerable attention, perhaps more than any other material. The accumulated body of literature is hence enormous and the interested reader is again referred to more specialized reviews.[13-16]

The underlying motivation for many researchers exploring nanoelectrochemistry is that shrinking the dimensions of electrodes is rife with many unexplored and potentially exciting fundamental phenomena that are, in principle, inaccessible to electrochemistry done on the macro-scale. Therefore, we attempt to provide a general appraisal of the promises inherent in nanoelectrochemistry, the progress made towards the realization of some of these goals, and finally the challenges that lie ahead.

The efforts to shrink dimensions of electrodes down to the nanoscale regime can be considered the logical denouement of a process than began nearly three decades ago with the introduction of microelectrodes and ultramicroelectrodes (UMEs). The expectation is that the key advantages of enhanced mass-transport and relatively easy access to the steady-state regime (on account of the diffusion length being much larger than the dimension of the electrode) that came with the advent of UMEs will be further amplified as the electrode is made smaller still. While this is undoubtedly true, it is merely one among many other interesting possibilities that result from nanoscale electrodes.

Besides the critical dimension of the electrode itself, two other crucial scales are the double-layer thickness (or Debye length (*vide infra*)) and the number of molecules being probed at the electrode. An interesting question is what happens when the size of the electrode is of the same order or smaller than the Debye length. For a typical 0.1 M, 1:1 electrolyte at 25°C, the Debye length is about 1 nm. It is thus readily apparent that in order for the scale of the electrode to approach that of the double layer thickness, at least one dimension of the electrode will have to be on the order of 1 nm! This points to the fundamental difficulty in approaching truly nanoscale phenomena via the means of electrochemistry. Another interesting scale that opens up for investigation, particularly in the context of nano-gap electrodes, is the number of molecules being probed. As electrode dimensions shrink, it becomes possible to utilize them to electrochemically detect molecules in and across confined spaces such as membranes and cells. Thus, when dealing with a small, finite number of molecules, one enters a regime where the discreteness of individual molecules cannot always be ignored. The culmination of this scale is the single-molecule limit where individual molecules are probed, and interesting dynamical properties masked by ensemble averages can be revealed.

The present chapter is structurally organized on the basis of these disparate scales. Although in all instances our focus will be on nano-sized electrodes, we start off with the *classical* regime, wherein the Debye length is still shorter than the dimension of the electrode and ensemble averages of molecules are being probed. We briefly introduce some key concepts related to the double layer, mass transport and electrode kinetics and their dependence on the dimension and geometry of the electrode. We review various fabrication schemes utilized in making nano-sized electrodes, and discuss the inherent challenges in characterizing them accurately. We then move to discuss the *mesoscopic* regime—dimensions in which one or more of the assumptions of the *classical* regime break down. In particular, we discuss what happens when the Debye length becomes comparable to the size of the electrode and the diffusion region. We then discuss finite particle number fluctuations in the vicinity of the nanoelectrodes. We conclude the Section with a discussion on quantum-dot electrodes and charging and finite-size effects seen in these systems. We move in the next Section to the *single-molecule* limit and discuss the recent advances in the electrochemistry of freely-diffusing single molecules as well as electrochemical scanning probe techniques used in the investigations of immobilized biomolecules. We conclude the chapter with a brief survey of the applications of nanoelectrodes in biosensors and biological systems.

## II. THE CLASSICAL REGIME

We begin our survey of nanoscale electrochemical measurements by focusing on cases in which no new effects appear upon downscaling, but rather where the formalisms that apply on the micrometer scale or higher are sufficient to explain observations. There are basically two different ways in which nanometer-scale dimensions can be introduced into electrochemical systems.

First, it is possible to scale down the size of the working electrode such that its lateral dimensions are nanometric. These experiments are essentially equivalent to those performed at ultramicroelectrodes, except that the smaller dimensions of the electrodes yield further enhancements in performance. These advantages include the ability to achieve a true steady-state in extremely short times, as well as the possibility of reaching higher current densities. The latter is particularly relevant for measuring fast heterogeneous kinetics.

Second, it is possible to create situations in which two or more electrodes or surfaces (each of which may or may not be nanometric in size) are separated by nanometer-scale distances. This has been most famously exploited in thin-layer cells and in the so-called positive feedback mode of scanning electrochemical microscopy (SECM), in which oxidation and reduction taking place at separate, closely spaced electrodes lead to enhanced mass transport.

## 1. Theory

Because heterogeneous kinetics feature prominently in the experiments reviewed below, we begin by briefly reviewing the relevant theory at the level of Butler-Volmer kinetics. While this topic will already be familiar to many readers, we aim through our exposition to bring particular attention to the role played by the electrode geometry in determining the predicted voltammogram shape.

We consider a simple outer-sphere heterogeneous electron-transfer reaction at an electrode surface, $\mathrm{O} + e^- \leftrightarrows \mathrm{R}$. O and R are present in the bulk solution at concentrations $C_\mathrm{O}{}^b$ and $C_\mathrm{R}{}^b$, respectively. We further assume the presence of a large excess of inert salt, such that mass transport in this simple system will be determined by the diffusion of the species O and R to or from the surface. Finally, we also assume for notational simplicity that the diffusion coefficients for O and R have an identical value, $D$. Quite generally for any electrode of finite size immersed in a volume of much larger size in all three dimensions (a condition which nearly always applies to nanoelectrodes immersed in a macroscopic volume), a true steady-state limiting current exists. The total rate of mass transport of O from the bulk solution to the electrode, $J_\mathrm{O}$, can then be written as[17]

$$J_\mathrm{O} = D(C_\mathrm{O}^b - C_\mathrm{O}^e)b \tag{1}$$

Here, $C_\mathrm{O}{}^e$ is the concentration of O at the electrode surface (to be determined further into the calculation), while $b$ is a parameter with units of length that characterizes the electrode geometry. The parameter $b$ can be thought of consisting of two components: a numerical constant that depends only on the *shape* of the electrode, multiplied by a characteristic length that characterizes the *size* of the electrode. Determining the value of $b$ is equivalent to solving the diffusion equation for this particular geometry. A well-known example is a shrouded semi-hemispherical electrode of radius $R$, for which $b = 2\pi R$. The corresponding expression for the rate of mass transport of reduced species R from the electrode surface to the bulk can be written as

$$J_R = D\left(C_R^e - C_R^b\right)b \tag{2}$$

Finally, the heterogeneous kinetics at the electrode surface are described by the Butler-Volmer (BV) expression

$$i = FA(k_f C_{\mathrm{O}}^e - k_b C_{\mathrm{R}}^e) \tag{3}$$

where $i$ is the reduction current at the electrode (using the convention that *reduction* corresponds to a positive current), $F$ is Faraday's constant, $A$ is the area of the electrode, and the forward and backward rates are given by

$$\begin{aligned} k_f &= k^0 \exp(-\alpha f \eta) \\ k_b &= k^0 \exp((1-\alpha) f \eta) \end{aligned} \tag{4}$$

In the latter expressions $k^0$ is the standard heterogeneous rate constant, $\alpha$ is the transfer coefficient,[220] $\eta = (E - E^0)$ is the overpotential and $f = F/RT$ with $R$ the gas constant and $T$ the temperature.

Steady-state requires that the rate of mass transport of O, the rate of mass transport of R, and the net rate of electron transfer at the interface be equal: $i = FJ_{\mathrm{R}} = FJ_{\mathrm{O}}$. Applying this condition turns Eqs. (1), (2), and (3) into a set of three algebraic equations in three unknowns (the current $i$ and the two surface concentrations $C_{\mathrm{O}}^e$ and $C_{\mathrm{R}}^e$). These are easily solved, yielding for the current

$$i = \frac{C_{\mathrm{O}}^b e^{-\alpha f \eta} - C_{\mathrm{R}}^b e^{(1-\alpha) f \eta}}{e^{-\alpha f \eta} + e^{(1-\alpha) f \eta} + Db / Ak^0} \cdot FDb \tag{5}$$

For the special case of a pure oxidation reaction, $C_{\mathrm{O}}^b = 0$, this expression takes a simpler form,

$$i = -\frac{i_{\mathrm{lim}}}{1 + e^{-f\eta} + (Db / Ak^0) e^{-(1-\alpha) f \eta}} \tag{6}$$

Here we also introduced the so-called diffusion-limited current, $i_{\mathrm{lim}}$, whose value is given by $i_{\mathrm{lim}} = FDC_{\mathrm{R}}^b b$.

Equation (6) indicates that the relative importance of heterogeneous kinetics compared to mass transport is entirely determined by the dimensionless ratio

$$\lambda = \frac{Ak^0}{Db} \tag{7}$$

a quantity known as the dimensionless rate constant. In the limit of very fast kinetics, $k^0 >> Db/A$ or, equivalently, $\lambda >> 1$, Eq. (6) reduces to the fully reversible result obtained from the Nernst equation. Redox species at the electrode surface are then in local equilibrium with the surface, and the heterogeneous kinetic parameters do not affect the shape of the voltammogram. Once $\lambda$ becomes sufficiently small, however, kinetics begin to have an appreciable impact. As a rule of thumb, this occurs when $\lambda$ decreases below a value of 10.

Very importantly, Eq. (6) indicates that the geometry influences the relative importance of kinetics through two closely related, yet separate, mechanisms. First, it determines the area $A$ and, hence, the total electron transfer rate at a given surface concentration. Second, it influences the rate of mass transport of both R and O, as expressed by the parameter $b$. This makes it clear why electrodes with smaller dimensions are more sensitive to heterogeneous kinetics: for a given shape of electrode, scaling all the dimensions simultaneously by a factor $\gamma$ causes $A$ to change by a factor $\gamma^2$ and $b$ by a factor $\gamma$, leading to a net change of $\lambda$ by a factor $\gamma$. More simply put, shrinking all dimensions by a factor of 10 reduces the electrode area by a factor of 100 and is equivalent to speeding mass transport by a factor of 10.

The dual role played by geometry can, however, easily mislead our intuition, as we now illustrate through two numerical examples. First, consider the simple case of a shrouded semi-hemispherical electrode of radius $R$, as shown in Fig. 1a. In this case the area is simply given by $A = 2\pi R^2$, while $b = 2\pi R$, as discussed above. In this case Eq. (6) reduces to a more recognizable expression,

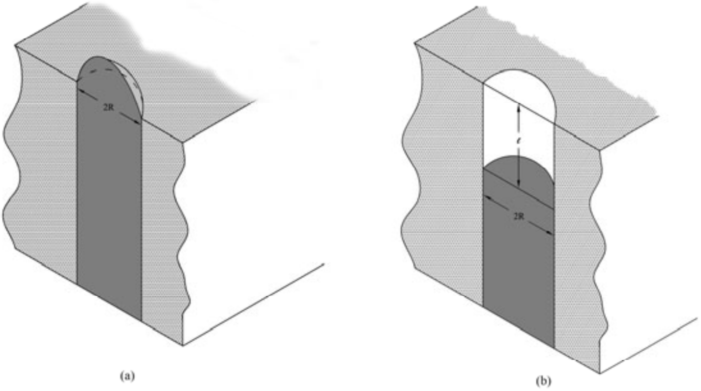

Figure 1. Sketch showing a cross-section of (a) a hemispherical electrode embedded in an insulator and (b) a disk electrode recessed a distance *l* into the surface of the insulator.

$$i = -\frac{i_{\mathrm{lim}}}{1 + e^{-f\eta} + (D/k^0 R)e^{-(1-\alpha)f\eta}} \tag{8}$$

Second, consider a disk electrode that is recessed a distance *l* into the surface, as sketched in Fig. 1b. Solving the diffusion equation for this system yields[18]

$$i_{\mathrm{lim}} = -\frac{4FDC_{\mathrm{R}}^{\mathrm{b}}R}{1 + 4l/\pi R} \approx -\frac{\pi FDC_{\mathrm{R}}^{\mathrm{b}}R^2}{l} \qquad l >> R \tag{9}$$

where the last simplification holds when $l >> R$. Substituting the corresponding values $A = \pi R^2$ and $b = \pi R^2/l$ into Eq. (6) yields for the current

$$i = -\frac{i_{\mathrm{lim}}}{1 + e^{-f\eta} + (D/lk^0)e^{-(1-\alpha)f\eta}} \qquad l >> R \tag{10}$$

While superficially very similar in form to Eq. (8), note that this result is actually independent of the electrode radius *R* (!).

This occurs because, in this case, both the area *A,* and the mass transport parameter *b,* are proportional to $R^2$. Nonetheless, as discussed above, isotropic downscaling of the device dimensions also leads to enhanced mass transport, since in this case the parameter *l* is also scaled down.

The above discussion was meant as a simple introduction to BV kinetics at electrodes with non-trivial geometries. Strictly speaking, this treatment only holds for cases where the symmetry of the electrode is such that the concentrations at the electrode surface, $C_O^e$ and $C_R^e$, are uniform over the electrode surface. In cases where this is not strictly true, such as the system of Eq. (10), a slight numerical error is introduced (which becomes increasingly negligible as $l/R$ increases in that particular example). For a far more general treatment that extends to non-uniform current densities, we refer the reader to the work of Oldham.[19]

## 2. Experimental Approaches to Nanoelectrochemistry

### (*i*) *Fabrication of Nanoelectrodes*

As mentioned in the introduction, the efforts to miniaturize electrodes began in the early 1980s with the advent of microelectrodes and, later, ultra-microelectrodes (UMEs).[20,21]

Many of the advantages that accrued from shrinking electrode sizes from millimeter to micrometer dimensions are also expected to hold as the dimensions are further reduced into the nanometer regime. Nanoscale electrodes allow the extension of electrochemical measurements into new realms of space (cells, nanogaps, etc.) and time. The uncompensated resistance, $R_u$, scales with $1/r$, where $r$ is the radius of the electrode, and the capacitance scales with the area ($r^2$). Thus, the RC time constant of the cell scales with $r$ and, hence, reduces with smaller electrode sizes. With electrodes of $r \sim 100$ nm, one can in principle reduce the cell time constant to lower than 1 ns. Further, the complications arising from uncompensated solution resistance, $iR_u$, are significantly minimized. This feature makes it easier to do electrochemical experiments in media of low conductivity such as highly resistive organic solvents and solutions devoid of any supporting electrolyte. Lastly, the high