Microelectrodes
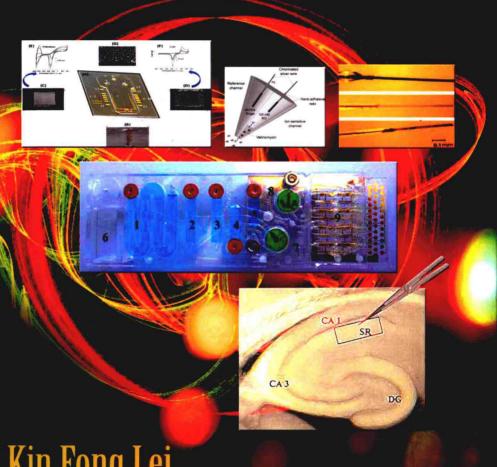
Techniques, Structures for Biosensing and Potential Applications

Kin Fong Lei

Editor

NOVA

MICROELECTRODES

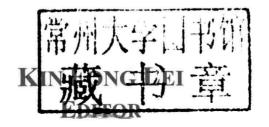# TECHNIQUES, STRUCTURES FOR BIOSENSING AND POTENTIAL APPLICATIONS

KIN FONG LEI
EDITOR

NOVA BIOMEDICAL

New York

For permission to use material from this book please contact us:
Telephone 631-231-7269; Fax 631-231-8175
Web Site: http://www.novapublishers.com

NOTICE TO THE READER

The Publisher has taken reasonable care in the preparation of this book, but makes no expressed or implied warranty of any kind and assumes no responsibility for any errors or omissions. No liability is assumed for incidental or consequential damages in connection with or arising out of information contained in this book. The Publisher shall not be liable for any special, consequential, or exemplary damages resulting, in whole or in part, from the readers' use of, or reliance upon, this material. Any parts of this book based on government reports are so indicated and copyright is claimed for those parts to the extent applicable to compilations of such works.

Independent verification should be sought for any data, advice or recommendations contained in this book. In addition, no responsibility is assumed by the publisher for any injury and/or damage to persons or property arising from any methods, products, instructions, ideas or otherwise contained in this publication.

This publication is designed to provide accurate and authoritative information with regard to the subject matter covered herein. It is sold with the clear understanding that the Publisher is not engaged in rendering legal or any other professional services. If legal or any other expert assistance is required, the services of a competent person should be sought. FROM A DECLARATION OF PARTICIPANTS JOINTLY ADOPTED BY A COMMITTEE OF THE AMERICAN BAR ASSOCIATION AND A COMMITTEE OF PUBLISHERS.

Additional color graphics may be available in the e-book version of this book.

Library of Congress Cataloging-in-Publication Data

Published by Nova Science Publishers, Inc. † New York

MICROELECTRODES

TECHNIQUES, STRUCTURES FOR BIOSENSING AND POTENTIAL APPLICATIONS

LABORATORY AND CLINICAL RESEARCH

Additional books in this series can be found on Nova's website under the Series tab.

Additional e-books in this series can be found on Nova's website under the e-book tab.

Preface

In our living world, the fundamental observing length scale is meter. From human body, organ, tissue, cell, protein, to nucleic acid, the length scale decreases in each stage from meter to micro/nano-meter. In order to observe different objects in various length scales, technique with relatively similar in size should be adopted for accurate observation. Matching of length scales is a fundamental requirement of observation. For example, the invention of optical microscope (the wavelength of visible light is about half a micron) enabled the observation of biological cells and intra cellular components with a spatial resolution larger than 0.2 microns. The ability of micro-scale observation has improved biological research dramatically. In addition, based on the mature development of microfabrication technology, micro-scale electrodes, i.e., microelectrodes, for the electrical observation of activities in micro-scale environment become realizable. This technique opened a new avenue for micro-scale observation and measurement besides optical technique.

This book presents the techniques, structures, and applications of using microelectrodes in micro-scale environment. It covers a board spectrum of topics and the state of the art in the field. As such, the book is divided into four sections, comprising 11 chapters written by recognized experts from leading groups around the world. The first section (from chapter 1 to 3) is intended to introduce the fundamental theories, key concepts, novel materials, and fabrication techniques of microelectrodes. The second section (from chapter 4 to 6) is designed to present the microelectrodes for molecular and cellular monitoring applications. The concept of microfluidic system is brought to build a well-controlled integrated system for biological sensing. The third section (from chapter 7 to 9) discusses the microelectrodes for physiological monitoring applications. Different structures of the microelectrodes are adopted for different measuring environments. The fourth section (from

chapter 10 to 11) presents the microelectrodes for environmental applications. Reader will gain a unique perspective on the challenges and emerging opportunities in the technology of microelectrodes.

We hope our readers find this book to be a useful and would like to thank all of our authors for sharing their recent results and advances in this exciting field.

Kin Fong Lei
Chang Gung University, Taiwan
October 2013

Contents

Chapter 1

Digital Simulation of Electrochemistry at Microelectrodes

Dieter Britz[1],*and Jörg Strutwolf*[2],†

[1]Department of Chemistry, Aarhus University, Åarhus C, Denmark
[2]Institute of Organic Chemistry, University of Tübingen,
Tübingen, Germany

Abstract

Finite difference methods for solving diffusion equations associated with microelectrodes in electrochemical systems are described and reviewed. Different types of electrode geometries and configurations are considered, such as microelectrodes used in scanning electrochemical microscopy, microelectrode arrays and dual microelectrode systems in parallel and generator-collector mode, and hydrodynamic systems. The generation of problem adapted space grids is described. Examples are given

*E-mail address:britz@chem.au.dk
†E-mail address: joerg.strutwolf@uni-tuebingen.de

for a few geometries which lend themselves to conformal mapping to raise simulation efficiency.

PACS: 02.70.Bf

Keywords: Finite difference methods, Electrochemistry, ultramicroelectrodes, diffusion equation, electrode arrays

AMS Subject Classification: 65L12, 35-04

1. Introduction

Ultramicroelectrodes (hereafter UMEs) have been in use since at least 1948 [1–3], at that time for use mainly in studying nerve cells. The electrodes used by Hodgkin et al might be considered too large to be accepted as UMEs, at a diameter of 16 μm, and similarly for the Saito paper (15 μm). However, specifications for exactly what dimensions an UME must have, vary. Thus, Fleischman et al [4] write that a UME must have "one dimension less than 1-10 μm", whereas Heinze, on page 255 of the same volume, considers a radius of less than 20 μm as small enough and Bard and Faulkner [5, p.169] set the limit at 25 μm. One of the early works in the area, by Lines et al [6] used disks of 30 μm diameter. This might be considered the upper limit on "ultramicro". Oja et al [7] wrote a recent review of nanosized electrodes.

In vivo applications continue [8–16] (see also Chapter 8 in this volume), but from about 1981, applications to electroanalytical chemistry have dominated the field, starting with the seminal note by Wightman [17], although there had been some published work before this [9, 18]. Some general reviews have been written [4, 19–21], as well as some focussed on mathematical treatments of the behaviour of these electrode systems [22, 23].

Most in vivo biological applications make use of carbon fibres (see the above references), but for electroanalytical work, disks and bands appear to be preferred although cylindrical electrodes (fibres) are advantageous. Bands and cylinders share the benefits of one ultramicro-dimension and thus a fast approach to steady state [22] but compared to the disk shape they allow larger currents and thus greater signal to noise ratios [22].

Hereafter, the term "electrode" will be assumed to mean one of ultramicro size in at least one dimension.

For the disk electrode, the article by Wightman [17] is often cited as the

source, and his design is more or less the one still used today. However, Saito [24] made a disk electrode with a diameter smaller than 1 μm with essentially the same construction, and indeed refers to even earlier works such as [3]. Interestingly, Saito writes that in order to avoid convection effects, the diameter of the disk should be less than 1 μm. Immunity to convection effects is one of the benefits of these very small electrodes. The 1968 Saito paper is often referred to for the derivation of the steady state current at an inlaid disk, and here too there are earlier works, such as that of Soos and Lingane [25], possibly ignored because their derivation deals with an inlaid electrode of general shape, of which the circular disk is just one example; but their result is the same as Saito's.

Bard and Faulkner [5] provide some useful descriptions of ultramicro-sized electrodes and some of the theory for disks, hemispheres, bands and cylinders. Examples of early band electrodes are seen (again) in the 1968 Saito paper [24] and the work of Kovach et al [26]; the so-called line electrode ("Strichelektrode"), a strip on the outside of a rotating cylinder [27] might be regarded as an early band electrode. Ring electrodes on the inner side of a tube were described by Bernstein et al [28] and a ring electrode similar in construction was described by MacFarlane and Wong [29]. Other electrode geometries include a cone standing in an insulating plane (these are often but not exclusively used as the probe tip in scanning electrochemical microscopy, SECM) [11,30–32], and a conical electrode tip on the end of an insulating cone was described by McNally and Wong [12] and Chan and Wong [33] and has been simulated [34]. Disks can also be recessed into or protruding from the insulating plane [35–40] or lie at the bottom of an open conical well [41–43]. The term "lagooned electrode" was used by Oldham [44] and Baranski [45] for disks at the bottom of a well with a small opening. Pairs of electrodes near each other can be used for generator-collector systems to probe reaction mechanisms, and Barnsley wrote a review of these [46]. Interdigitated band arrays serve the same purpose [47–49].

UMEs are often the electrodes in hydrodynamic systems. Albery et al wrote a review of digital simulation of such systems [50]. Some of the earliest simulation papers taking into account two dimensions are due to Anderson et al [51–53], dealing with an electrode on the floor of a channel with a flowing electrolyte (see later). It is not however clear in that paper how wide the band was. There is extensive work on channel electrodes [54–59]. Other hydrodynamic systems include a jet impinging on an electrode [60–66]. Channel flow systems have been simulated extensively [40, 51–53, 67–104]. Wall-jet simula-

tions include [50, 105–117].

Ultramicroelectrodes are, as mentioned above, used in SECM, usually in the form of disks or cones on a flat plane [31, 118–121] and simulations include [122–152]. Most of these used commercial simulation packages such as COMSOL Multiphysics® [153] (formerly FEMLAB). When investigators write their own programs, they appear mostly to use ADI [154] (see below) in order to avoid large two-dimensional systems of equations [125–129, 132–134, 138, 140–143, 150, 155]

It was immediately recognised [156] that arrays of electrodes would produce larger currents and many arrays were designed, and still are [16, 41, 43, 157–163]. Some of the earliest works were concerned with partially covered or blocked electrode surfaces [164–168] which essentially form an array of small disks. Reller et al [168] concluded that at short times, the total current is the sum of the individual currents and at long times, the total current is proportional to the total area. Partially blocked electrodes continue to attract attention [169–175]. Theoretical works on arrays or ensembles of UMEs deal with the question of how the density of the array affects the performance [161, 176, 177].

There is considerable interest in UMEs under polymer layers containing an enzyme, such that a substrate outside the polymer layer partitions into the layer and gets converted by an enzyme reaction into a product, which reacts at the electrode and is detected either amperometrically or potentiometrically. There is a large literature on this; some reviews are [178–181].

2. Simulations of Single UMEs

In this section, examples of the simulation of the behaviour of some selected UMEs are provided.

2.1. Grids

For most of these simulations, the critical stage is the generation of the grid, as pointed out by Yang et al [182, p. 366]. They describe rectangular grids as "structured, orthogonal", meaning that the grid is divided into equally spaced points. This is ideal but cannot always be realised. Indeed, grids with unequally spaced points are the norm with UME simulations, because most UMEs show a strong edge effect [183–185], meaning that the current density, and concentration gradients, are greatest at electrode edges. Grids will be described for each

example.

2.2. Methods

The simulation method must be considered, and here there is a variety of choices. If one does not want to write programs, there are packages available, such as Digisim [186], DigiElch [187], and ELSIM [188], which all use finite differences. Finite elements are used in other packages such as the general simulation software COMSOL Multiphysics® [153], formerly known as FEMLAB. Some of these packages have their limits in what experiments can be simulated or in the simulation parameters allowed and sometimes suffer from lower accuracy than lab-written programs can achieve. This is the approach favoured by the present authors, who mostly write their own programs, using Fortran 90/95. Language is however a personal choice, other useful and popular ones being C++ or indeed Pascal or MATLAB® [189]. The choice is often dictated by whether a compiler can be obtained cheaply or free.

Algorithms used are also a personal choice. One generally seeks to solve a partial differential equation of the type

$$\frac{\partial c}{\partial t} = D\nabla^2 c \tag{1}$$

where c is the concentration of a species of interest, t is the time, D a diffusion coefficient. We ignore the possibility of homogeneous chemical reactions, in order to keep things simple. The particular form of the right-hand side (RHS) depends on the geometry of the system to be simulated (see below) and usually involves spatial first and second derivatives. These are easily approximated by weighted sums of values at a number of points (see a text on this [190], but some examples will be given below). The various algorithms differ mainly in how the left-hand side (LHS), the time derivative, is handled, and the choice affects the discretisation of the RHS as well. We present here a brief description of some of these, but see [190] for details.

The simplest method is the explicit method, for which (1) is discretised as a forward difference. At the grid point i (confining ourselves for the moment to one spatial dimension), we have

$$\frac{c_i' - c_i}{\delta t} = D\delta_x^2 c_i \tag{2}$$

where the notation is that c_i' is the concentration to be computed for the next time step of size δt, and δ_x^2 denotes the discrete approximation operator for the second spatial derivative. Note that the RHS makes use of the present, known, c_i. This is the "explicit" or Euler method originally adapted for electrochemistry by Feldberg [191, 192]. Feldberg treats the diffusion space as a number of boxes, whereas the present authors prefer to focus on the grid points [193]. Discretisation of the *pde* at all points in the grid (index i) leads to a system of linear equations to be solved. For the explicit method, each point can be simply computed. The method suffers from a limit on the parameter $\lambda = D\delta t/h^2$, where h is the spatial interval. For stability, λ must not exceed 0.5. Larger values of this parameter lead to errors growing indefinitely with the number of iterations. Even with a proper choice, the method is rather inefficient, being $O(\delta t)$, meaning that decreasing the time interval leads only to a proportional decrease in the simulation error. A method that is stable for all λ is the modified Euler or backwards implicit method (BI) [194], which inserts the unknown c' in the RHS:

$$\frac{c_i' - c_i}{\delta t} = D\delta_x^2 c_i' \ . \tag{3}$$

This is an implicit method because of the unknown on both sides, and is also only $O(\delta t)$, but is stable for all λ and does have the pleasant feature of an error that decreases smoothly with the number of iterations, rather than in an oscillatory manner. The equations that result from this (and all other implicit methods) each have several unknowns and need to be solved as a system. The order can be raised by using extrapolation [195], introduced into electrochemical simulation by Strutwolf and Schoeller [196]. The essence of this is that at each step, several computations are made with a number of partial steps, and then to combine them in a particular way. There are several variants, the simplest being that in which one computes a result, let us say $c^{(1)}$, using a single step of length δt, then another, $c^{(2)}$, using two consecutive steps of length $\delta t/2$, and then applying the extrapolation formula

$$c' = 2c^{(1)} - c^{(2)} \ . \tag{4}$$

It can be shown that this eliminates the $O(\delta t)$ error and leaves an $O(\delta t^2)$ error, which is an improvement, allowing larger time intervals for a given target accuracy. The method can be driven to even higher orders, see [195, 196].

Another stable method is that due to Crank and Nicolson (CN) [197], where

one inserts both present and future values in the RHS:

$$\frac{c'_i - c_i}{\delta t} = \frac{D}{2}\left(\delta_x^2 c_i + \delta_x^2 c'_i\right). \tag{5}$$

This is of $O(\delta t^2)$. The method is often considered as "semistable" because it usually leads to oscillating errors, which can render a simulation useless because, even though the errors are damped with increasing numbers of iterations, this damping might not have proceeded sufficiently at a time when a result is wanted. It is possible to largely eliminate the oscillations by various techniques [198, 199]. Possibly the best method is to subdivide the first step into a number of smaller steps (the Pearson method [200]).

A method that combines the smooth error decay of BI and the second- (or higher-)order behaviour of extrapolation and CN, is the backward differentiation formula (BDF) [201, 202], introduced to electrochemistry under the name FIRM by Mocak and Feldberg [203]. Here one uses more points in time, including past values. In the simplest second-order three-point variant, discretisation becomes

$$\frac{'c_i - 4c_i + 3c'_i}{2\delta t} = D\delta_x^2 c'_i \tag{6}$$

in which $'c_i$ is the value at $t - \delta t$, computed in a previous step. It might be considered as another modification of BI, as the RHS contains only unknown concentration c'_i. Equation (6) is $O(\delta t^2)$ and it can, with more past points, be driven up to sixth order, but as the order is increased by using more points, the error response becomes more and more oscillatory and for more than 7 points, the method is unstable. It will be appreciated at once that there is a problem at the start of a simulation, where no past value exists. There are various strategies for handling this [204], the simplest being to set this value to the initial value and, at the nth step in time, assigning the result to $(n - \frac{1}{2})\delta t$ [203], which, surprisingly, gives rather accurate results [205, 206]. A perhaps more logical start, here called the "rational" start, is to start with a BI step, then go to three-point BDF, then four-point and so on. The present authors favour three-point BDF, so just a single BI step is required, continuing with BDF after that.

For two- (and higher-) dimensional systems, where we have points arranged in two or more dimensions, we also have derivatives in all directions, which complicates the discretised RHS and often leads to rather large systems of equations to be solved. All the above methods can be used, but for very fine grids, solution of the system of equations is best carried out by a sparse solver, such

as MA28 [207, 208] or Y12M [209, 210]. The large systems can be avoided by using the alternating direction implict (ADI) method [154, 211] introduced into electrochemical simulation by Heinze [212] (see below, Sect.2.5.2).

2.3. Derivative Approximations

In the previous section, two- and three-point time derivative approximations were provided. Here we focus on spatial derivatives.

For direct simulations in the given geometry of a two-dimensinal system, it has been found that three-point approximations are competitive, in terms of computing time for a given target accuracy [213]. This was counter-intuitive but apparently due to the internal workings of the sparse solver used to solve the rather large systems of equations resulting from these simulations. For systems that lend themselves to conformal mapping and thus rectangular grids with (commonly) equal spacing of the grid points, larger stencils are of advantage, and it was found that often, five or seven point stencils are optimal. For these, it makes no sense to attempt to seek expressions for the approximations, and instead, the coefficients should be computed on the spot. That is, for a sequence of n points at positions $x_1, x_2, \ldots, x_n$, a given (first or second) derivative is approximated by a weighted sum of the node values, $\sum_{i=1}^{n} w_i u_i$, where w_i is the ith weight and u_i the value at the ith stencil point (perhaps unknown). The weighting coefficients can be conveniently computed using the Fornberg algorithm [214] (a `Fortran` subroutine implementation and one in `C++` due to L. Bieniasz (private communication) can be obtained from the authors). However, we provide two examples of the coefficients for equally spaced points, with interval size h, here: the three-point approximation at point indexed with i is

$$\delta_x^2 \approx \frac{1}{h^2} \left(c_{i-1} - 2c_i + c_{i+1} \right) \tag{7}$$

and for five points we have

$$\delta_x^2 \approx \frac{1}{12h^2} \left(-c_{i-2} + 16c_{i-1} - 30c_i + 16c_{i+1} - c_{i+2} \right). \tag{8}$$

These are central differences, and are $O(h^2)$ and $O(h^4)$, respectively. One-sided approximations are also needed for point on or near the edges, and these are best obtained using the Fornberg algorithm, within a given simulation program.