

**9**

**Springer Series on Chemical  
Sensors and Biosensors**

**Methods and Applications**

**Series Editor: G. Urban**

# Springer Series on Chemical Sensors and Biosensors

Series Editor: G. Urban

Recently Published and Forthcoming Volumes

## **Optical Guided-wave Chemical and Biosensors II**

Volume Editors: Mohammed Z.,  
Lakhtakia A.

Vol. 8, 2009

## **Optical Guided-wave Chemical and Biosensors I**

Volume Editors: Mohammed Z.,  
Lakhtakia A.

Vol. 7, 2009

## **Hydrogel Sensors and Actuators**

Volume Editors: Gerlach G., Arndt K. -F.

Vol. 6, 2009

## **Piezoelectric Sensors**

Volume Editors: Steinem C., Janshoff A.

Vol. 5, 2006

## **Surface Plasmon Resonance Based Sensors**

Volume Editor: Homola J.

Vol. 4, 2006

## **Frontiers in Chemical Sensors**

Novel Principles and Techniques

Volume Editors: Orellana G., Moreno-Bondi M. C.

Vol. 3, 2005

## **Ultrathin Electrochemical**

### **Chemo- and Biosensors**

Technology and Performance

Volume Editor: Mirsky V. M.

Vol. 2, 2004

## **Optical Sensors**

Industrial, Environmental  
and Diagnostic Applications

Volume Editors:

Narayanaswamy R., Wolfbeis O. S.

Vol. 1, 2003

# Mathematical Modeling of Biosensors

An Introduction for Chemists and Mathematicians

Volume Authors: Romas Baronas • Feliksas Ivanauskas  
Juozas Kulys

 Springer

Chemical sensors and biosensors are becoming more and more indispensable tools in life science, medicine, chemistry and biotechnology. The series covers exciting sensor-related aspects of chemistry, biochemistry, thin film and interface techniques, physics, including opto-electronics, measurement sciences and signal processing. The single volumes of the series focus on selected topics and will be edited by selected volume editors. The Springer Series on Chemical Sensors and Biosensors aims to publish state-of-the-art articles that can serve as invaluable tools for both practitioners and researchers active in this highly interdisciplinary field. The carefully edited collection of papers in each volume will give continuous inspiration for new research and will point to existing new trends and brand new applications.

ISSN 1612-7617

ISBN 978-90-481-3242-3

e-ISBN 978-90-481-3243-0

DOI: 10.1007/978-90-481-3243-0

Springer Dordrecht Heidelberg London New York

Library of Congress Control Number: 2009931246

© Springer Science+Business Media B.V. 2010

No part of this work may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, microfilming, recording or otherwise, without written permission from the Publisher, with the exception of any material supplied specifically for the purpose of being entered and executed on a computer system, for exclusive use by the purchaser of the work.

*Cover design:* SPi Publisher Services

Printed on acid-free paper

Springer is part of Springer Science+Business Media ([www.springer.com](http://www.springer.com))

## Series Editor

Prof. Dr. Gerald Urban

IMTEK - Laboratory for Sensors  
Institute for Microsystems Engineering  
Albert-Ludwigs-University  
Georges-Köhler-Allee 103  
79110 Freiburg  
Germany  
*urban@imtek.de*

## Volume Authors

Romas Baronas

Feliksas Ivanauskas

Vilnius University  
Dept. Mathematics & Informatics  
Naugarduko 24  
LT-03225 Vilnius  
Lithuania  
*romas.baronas@mif.vu.lt*  
*feliksas.ivanauskas@mif.vu.lt*

Juozas Kulys

Vilnius Gediminas Technical University  
Fac. Fundamental Sciences  
Dept. Chemistry & Bioengineering  
Sauletekio Ave. 11  
LT-10223 Vilnius  
Lithuania  
*JKulys@bchi.lt*

# Preface

Biosensors are analytical devices in which specific recognition of the chemical substances is performed by biological material. The biological material that serves as recognition element is used in combination with a transducer. The transducer transforms concentration of substrate or product to electrical signal that is amplified and further processed. The biosensors may utilize enzymes, antibodies, nucleic acids, organelles, plant and animal tissue, whole organism or organs. Biosensors containing biological catalysts (enzymes) are called catalytical biosensors. These type of biosensors are the most abundant, and they found the largest application in medicine, ecology, and environmental monitoring.

The action of catalytical biosensors is associated with substrate diffusion into biocatalytical membrane and its conversion to a product. The modeling of biosensors involves solving the diffusion equations for substrate and product with a term containing a rate of biocatalytical transformation of substrate. The complications of modeling arise due to solving of partially differential equations with non-linear biocatalytical term and with complex boundary and initial conditions.

The book starts with the modeling biosensors by analytical solution of partial differential equations. Historically this method was used to describe fundamental features of biosensors action though it is limited by substrate concentration, and is applicable for simple biocatalytical processes. Using this method the action of biosensors was analyzed at critical concentrations of substrate and enzyme activity. The substrates conversion in single and multienzyme membranes was studied. The different schemes of substrates conversion which found practical application for biosensors construction were analyzed. The biosensors dynamics was considered at the simplest scheme of biocatalyzer action.

The other part of the book covers digital modeling of biosensors. The biosensors based on amperometric as well as potentiometric transducers are considered. The action of biosensors containing single and multienzymes were modeled using the finite difference technique at nonstationary and steady state. Special emphasis was placed to model biosensors utilizing a complex biocatalytical conversion and biosensors with multipart transducers geometry and biocatalytical membranes structure.

The final part of the book is dedicated to the basic concepts of the theory of the difference schemes for the digital solving of linear diffusion equations which are basis for biosensors modeling.

The book can be recommended for the master and doctoral studies as well as for special studies of biosensors modeling. The Part 3 can also be used for independent study of digital solution of differential equations.

The book was prepared for the period of students teaching by R. Baronas and F. Ivanauskas at Vilnius University and by J. Kulys at Vilnius Gediminas Technical University. The authors acknowledge particular universities for the support of the manuscript preparation. The contribution of the coauthors of the cited publications is highly appreciated.

Vilnius,  
February 2009

*Romas Baronas*  
*Feliksas Ivanauskas*  
*Juozas Kulys*

# Acknowledgements

The authors acknowledge Vilnius University (Romas Baronas and Feliksas Ivanauskas) and Vilnius Gediminas Technical University (Juozas Kulys) for the support of monograph preparation.



# Contents

<b>Introduction</b> .....	xvii
<b>Part I Analytical Modeling of Biosensors</b>	
<b>Biosensor Action</b> .....	3
1 Kinetics of Biocatalytical Reactions .....	3
2 Transducer Function .....	5
3 Scheme of Biosensor Action .....	6
<b>Modeling Biosensors at Steady State and Internal Diffusion Limitations</b> ..	9
1 Biosensors Containing Single Enzyme .....	9
2 Biosensors Containing Multienzymes .....	10
2.1 Consecutive Substrates Conversion .....	10
2.2 Parallel Substrates Conversion.....	14
2.3 Biosensors Utilizing Cyclic Substrates Conversion .....	15
3 Biosensors Utilizing Synergistic Substrates Conversion.....	16
4 Biosensors Based on Chemically Modified Electrodes .....	18
<b>Modeling Biosensors at Steady State and External Diffusion</b>	
<b>Limitations</b> .....	21
1 Biosensor Using Single Enzyme .....	21
2 Biosensors with Multienzymes.....	22
3 Biosensor Utilizing Non Michaelis–Menten Enzyme.....	23
<b>Modeling Biosensors Utilizing Microbial Cells</b> .....	27
1 Metabolite Biosensor .....	27
2 BOD Biosensor .....	30
<b>Modeling Nonstationary State of Biosensors</b> .....	33
1 Potentiometric Biosensors .....	33
2 Amperometric Biosensors .....	34

## Part II Numerical Modeling of Biosensors

<b>Mono-Layer Mono-Enzyme Models of Biosensors</b> .....	43
1 Mathematical Model of an Amperometric Biosensor .....	44
1.1 Governing Equations .....	44
1.2 Initial and Boundary Conditions .....	45
1.3 Dimensionless Model .....	46
2 Characteristics of the Biosensor Response .....	47
2.1 Biosensor Current .....	47
2.2 Biosensor Sensitivity .....	48
2.3 Maximal Gradient of the Current .....	48
2.4 Response Time .....	49
3 Finite Difference Solution .....	50
3.1 Numerical Approximation of Equations .....	50
3.2 Calculation Procedure .....	51
3.3 Validation of Numerical Solution .....	53
3.4 Numerical Error Analysis .....	57
4 Peculiarities of the Biosensor Response .....	60
4.1 Effect of the Enzyme Membrane Thickness .....	60
4.2 Stability of the Response .....	63
4.3 The Response Versus the Substrate Concentration .....	64
4.4 The Response Versus the Maximal Enzymatic Rate .....	66
4.5 Choosing the Enzyme Membrane Thickness .....	68
4.6 Biosensor Resistance .....	70
4.7 Maximal Gradient of the Current .....	71
5 Flow Injection Analysis .....	72
5.1 Mathematical Model .....	73
5.2 Numerical Solution .....	73
5.3 Biosensor Response .....	75
5.4 Peculiarities of the Biosensor Response .....	77
5.5 Sequential Injection Analysis .....	80
6 Biosensors with Chemical Amplification .....	81
6.1 Mathematical Model .....	82
6.2 Finite Difference Solution .....	84
6.3 Concentration Profiles .....	85
6.4 Peculiarities of the Biosensor Response .....	86
7 Potentiometric Biosensors .....	91
7.1 Mathematical Model .....	91
7.2 Biosensor Response .....	92
7.3 Finite Difference Solution .....	93
7.4 Validation of Numerical Solution .....	94
7.5 Simulated Biosensor Response .....	95
7.6 Peculiarities of the Biosensor Response .....	98

8	Enzyme Inhibition .....	103
8.1	Substrate Inhibition .....	103
8.2	Effect of Substrate Inhibition .....	105
8.3	Product Inhibition .....	108
8.4	Effect of Product Inhibition .....	109
	<b>One-Layer Multi-Enzyme Models of Biosensors .....</b>	<b>113</b>
1	Biosensors Response to Mixture of Compounds .....	114
1.1	Mathematical Model .....	114
1.2	Solution of the Problem .....	116
1.3	Generation of Data Sets .....	117
1.4	Concluding Remarks .....	120
2	Biosensors Acting in Trigger Mode .....	120
2.1	Mathematical Models .....	121
2.2	Finite Difference Solution .....	126
2.3	Simulated Response .....	128
2.4	Peculiarities of the Response .....	129
2.5	Concluding Remarks .....	136
	<b>Multi-Layer Models of Biosensors .....</b>	<b>139</b>
1	Multi-Layer Approach .....	140
1.1	Mathematical Model of Multi-Layer System .....	141
1.2	Numerical Approximation .....	143
1.3	Three-Layer Model .....	145
2	Two-Compartment Model .....	147
2.1	Mathematical Model .....	147
2.2	Transient Numerical Solution .....	150
2.3	Validation of Numerical Solution .....	152
2.4	Simulated Biosensor Responses .....	153
2.5	Effect of the Diffusion Layer .....	155
2.6	The Nernst Diffusion Layer .....	157
2.7	Dimensionless Model .....	160
2.8	Impact of the Diffusion Module .....	162
3	Biosensors with Outer Porous Membrane .....	163
3.1	Mathematical Model .....	164
3.2	Numerical Simulation .....	166
3.3	Effect of the Porous Membrane .....	168
3.4	Concluding Remarks .....	171
4	Biosensors with Selective and Outer Perforated Membranes .....	172
4.1	Mathematical Model .....	173
4.2	Numerical Simulation .....	176
5	Biosensors Based on Chemically Modified Electrode .....	178
5.1	Mathematical Model .....	178
5.2	Numerical Simulation .....	182
5.3	Dimensionless Model .....	184

5.4	Simulated Biosensor Action .....	186
5.5	Impact of the Diffusion Module .....	189
5.6	Impact of the Substrate Concentration .....	191
5.7	Concluding Remarks .....	192
6	Optical and Fluorescence Biosensors .....	193
6.1	Mathematical Model .....	193
6.2	Numerical Simulation .....	197
6.3	Simulated Biosensor Action .....	198
6.4	Impact of the Substrate Concentration .....	201
	<b>Modeling Biosensors of Complex Geometry .....</b>	<b>203</b>
1	Biosensor Based on Heterogeneous Microreactor .....	204
1.1	Structure of Modeling Biosensor .....	204
1.2	Mathematical Model .....	206
1.3	Numerical Simulation .....	211
1.4	Effect of the Tortuosity of the Microreactor Matrix .....	214
1.5	Effect of the Porosity of the Microreactor Matrix .....	214
1.6	Concluding Remarks .....	216
2	Biosensor Based on Array of Microreactors .....	217
2.1	Principal Structure of Biosensor .....	217
2.2	Mathematical Model .....	219
2.3	Numerical Simulation .....	222
2.4	Effect of the Electrode Coverage with Enzyme .....	225
2.5	Concluding Remarks .....	227
3	Plate-Gap Biosensor .....	228
3.1	Principal Structure of Biosensor .....	228
3.2	Mathematical Model .....	229
3.3	Governing Equations .....	230
3.4	Initial Conditions .....	231
3.5	Boundary and Matching Conditions .....	231
3.6	Biosensor Response .....	232
3.7	Numerical Simulation .....	233
3.8	Effect of the Gaps Geometry .....	236
3.9	Concluding Remarks .....	236
4	Biosensors with Selective and Perforated Membranes .....	237
4.1	Principal Structure of Biosensor .....	238
4.2	Mathematical Model .....	239
4.3	Numerical Simulation .....	242
4.4	Effect of the Perforation Topology .....	245
4.5	Concluding Remarks .....	246

**Part III Numerical Methods for Reaction–Diffusion Equations**

**The Difference Schemes for the Diffusion Equation** ..... 249

1 The Grids ..... 250

    1.1 An Equidistant Grid in the Straight ..... 251

    1.2 A Non-equidistant Grid in a Straight ..... 251

    1.3 The Equidistant Grid in a Plane ..... 252

    1.4 The Non-equidistant Grid in a Plane ..... 253

    1.5 The Grid in a Multidimensional Case ..... 253

2 The Approximation of the Function Derivatives ..... 254

    2.1 The Derivative of the First Order ..... 254

    2.2 The Approximation of the Second Order Derivative ..... 256

    2.3 The Approximation of the Second Order Derivative  
        on a Non-equidistant Grid ..... 256

3 The Explicit Difference Scheme ..... 258

    3.1 The Calculation of a Solution ..... 261

    3.2 The Convergence and the Stability ..... 262

4 The Implicit Difference Scheme ..... 264

    4.1 The Convergence and the Stability ..... 266

    4.2 The Calculation of a Solution ..... 266

5 The Elimination Method for the System of Linear Equations ..... 268

    5.1 Stability of the Elimination Method ..... 271

6 The Crank–Nicolson Difference Scheme ..... 271

    6.1 The Calculation of a Solution ..... 273

    6.2 The Convergence and the Stability ..... 274

7 The Difference Scheme with the Weights ..... 274

    7.1 The Convergence and the Stability ..... 276

8 The Crank–Nicolson Difference Scheme  
on Non-equidistance Grid ..... 276

    8.1 The Calculation of a Solution ..... 278

    8.2 The Convergence and the Stability ..... 279

9 The Explicit Difference Scheme  
in the Cylindrical Coordinates ..... 280

    9.1 The Calculation of a Solution ..... 281

    9.2 The Convergence and Stability ..... 282

10 The Crank–Nicolson Difference Scheme in the Cylindrical Coordinates .. 282

    10.1 The Calculation of a Solution ..... 283

    10.2 The Convergence and Stability ..... 285

11 The Discontinuous Diffusion Coefficient ..... 285

12 The Explicit Difference Scheme ..... 287

    12.1 The Calculation of a Solution ..... 288

13 The Crank–Nicolson Difference Scheme ..... 288

    13.1 The Calculation of a Solution ..... 289

<b>The Difference Schemes for the Reaction–Diffusion Equations</b> .....	293
1 The Boundary-Value Problem for the System of Reaction– Diffusion Equations.....	293
2 The Explicit Difference Scheme .....	295
2.1 The Calculation of a Solution.....	296
2.2 The Convergence and the Stability .....	297
3 The Non-linear Crank–Nicolson Type Difference Scheme .....	298
3.1 Calculation of a Solution.....	299
3.2 The Convergence and the Stability .....	303
4 The Linear Crank–Nicolson Type Difference Scheme .....	303
4.1 The Calculation of a Solution.....	304
4.2 The Convergence and the Stability .....	307
5 Law of Conservation of Mass .....	307
6 The Alternating Directions Method .....	309
6.1 Calculation of a Solution.....	311
6.2 The Convergence and the Stability .....	312
7 The Explicit Method for the Multidimensional Problems .....	312
7.1 The Calculation of a Solution.....	314
7.2 The Convergence and the Stability .....	315
<b>References</b> .....	317
<b>Index</b> .....	329
<b>About Authors</b> .....	333

# Introduction

The action of biocatalytical biosensors can be modeled with partial differential equations (PDE) of substrates and products diffusion and conversion in biocatalytical membranes. This book deals with biosensors modeling using analytical and digital solution of the PDE. The intrinsic logics of the book is to evaluate critical parameters and conditions that determinate the biosensors response. Since the analytical solutions of PDE describing biosensors action is possible at limited conditions the modeling of complex biosensor action are performed using digital solution of PDE.

The first part of the book is dedicated to the modeling biosensors by analytical solution of partial differential equations. First chapter of Part I contains tutorial introduction of kinetics of biocatalytical reactions, transducer function of biosensors and a general scheme of biosensor action. In second chapter of Part I the modeling biosensors at steady state and internal diffusion limitation is considered with special contribution to varies schemes of enzymes action. Third chapter of Part I concerns the modeling of biosensors at steady state and external diffusion limitations. The action of biosensor containing single enzyme, biosensors with multienzyme and biosensor utilizing non Michaelis–Menten enzyme kinetics was analyzed. Fourth chapter of Part I contains results of modeling biosensors utilizing microbial cells acting as specific biocatalytical or unspecific biochemical oxygen demand microreactor. The main task of fifth chapter of Part I is to analyze limited cases of biosensors modeling at nonstationary state at some critical concentrations of substrate when analytical solution of PDE was performed. The non stationary response of amperometric as well as potentiometric biosensor was analyzed.

At the end of the first part advantages and disadvantages of analytical modeling of biosensors are shown. The largest advantage of aproximal analytical solution is a possibility to get analytical solution of PDE. The disadvantages include limited concentration interval of reactive components, not applicable to biosensors with complex biocatalytical schemes, very complex solution of non stationary state, lack of analytical solution for complex initial and boundary conditions.

In the second part of the book the corresponding reaction–diffusion problems are solved using digital modeling. The solving PDE was performed using the finite difference technique. First chapter of Part II covers mathematical models with nonlinear reaction kinetics. The biosensors are assumed to be flat electrodes

having a mono-layer of an enzyme applied onto the electrode surface. Coupling the enzyme-catalyzed reaction in the enzyme layer (enzyme membrane) with the one-dimensional-in-space diffusion, the mathematical models are described by the non-stationary reaction-diffusion equations. The biosensors based on amperometric as well as potentiometric transducers are considered. The batch and the injection modes of the biosensor operation are modeled in this chapter. The biosensors utilizing the amplification by the conjugated electrochemical and the enzymatic substrates conversion are also investigated. This chapter ends with the modeling of the biosensors with the substrate as well as the product inhibition. The initial boundary value problems are solved numerically by applying the finite difference technique.

Second chapter of Part II deals with the mathematical models of two types of amperometric multi-enzyme biosensors. One type of the biosensors utilizes enzymatic reactions assuming no interaction between the analyzed substrates and the reaction products. The mathematical model of such biosensors is to simulate the biosensor response to a mixture of compounds (substrates). The second type of the biosensors utilizes the enzymatic reaction followed by a cyclic product conversion. Two kinds of the product regeneration in the two-enzyme biosensors are analyzed: enzymatic and electrochemical.

Third chapter of Part II covers multi-layer mathematical models. The biosensors acting in slightly-stirred buffer solutions are described by two-compartment mathematical models. The biosensor operation is analyzed with a special emphasis to the Nernst diffusion layer. This chapter also discusses the multienzyme systems, where the enzymes are immobilized separately in different active layers packed in a sandwich like multi-layer arrangement. The effect of the diffusion limitation to the substrate is investigated when inert outer membranes are applied to stabilize the enzyme layer and to prolong the calibration curve of the biosensor. This chapter also presents the mathematical models of the amperometric biosensor based on the chemically modified electrode as well as of the peroxidase-based optical biosensor.

Fourth chapter of Part II considers modeling of biosensors for which a two-dimensional-in space domain is required to describe mathematically the biosensor action. Firstly, an amperometric biosensor based on a carbon paste electrode encrusted with a single microreactor is considered. Then, an analytical system based on an array of enzyme microreactors immobilized on a single electrode is investigated. Carbon paste porous electrodes are also investigated by applying a plate-gap model. The last section of the this chapter focuses on the modeling of a practical amperometric biosensor containing the selective and the perforated membranes. The perforated membrane is analyzed with a special emphasis to the geometry of the membrane perforation.

Contemporary numerical methods for solving problems of the mathematical chemistry are gaining increasing popularity. The aim of first chapter of Part III is to introduce the reader with the relevant facts about the basic concepts of the theory of the difference schemes for the linear diffusion equations. The linear diffusion equations play an important and crucial role in most models of a biosensor theory. The most popular simple and together effective difference schemes for the linear diffusion equations are presented here. This method is being frequently used in solving



applied problems not only by professional mathematicians, but also by laymen. The concepts presented below are of a primary nature and are sufficient for the solution of the problems of the biosensor. In this book the notations of [222] are mainly applied. The many aspects of the numerical methods for the solution of the partial differential equations are presented in [5, 12, 187, 216].

The difference schemes are extensively applied to the solution of a biosensor problems in second chapter of Part III. This chapter is devoted to various difference approximations of the reaction–diffusion equations. The difference technique, developed in a previous chapter, is employed for the construction of the difference schemes. The main subject of investigation is the system of two nonlinear reaction–diffusion equations in one and two dimensional in space cases.