

**DEVELOPMENT OF TRANSPORT PHENOMENA
MATHEMATICAL MODELS FOR LINEAR AND
CONCENTRIC MICRODIALYSIS PROBES WITH
DIFFUSION-LIMITED AND CONVECTION-
ENHANCED OPERATIONAL FEATURES**

KHO CHUN MIN

UNIVERSITI SAINS MALAYSIA

2018

**DEVELOPMENT OF TRANSPORT PHENOMENA MATHEMATICAL
MODELS FOR LINEAR AND CONCENTRIC MICRODIALYSIS PROBES
WITH DIFFUSION-LIMITED AND CONVECTION-ENHANCED
OPERATIONAL FEATURES**

by

KHO CHUN MIN

**Thesis submitted in fulfilment of the
requirements for the degree of
Doctor of Philosophy**

September 2018

ACKNOWLEDGEMENT

First of all, I would like to thank God Almighty for blessing me with the strength, knowledge, and perseverance to complete my Ph.D. degree. All the thanks to God Almighty for making my dream of finally acquiring a Ph.D. degree become a reality.

I wish to offer my deepest and sincerest gratitude to my supervisors, Dr. Norazharuddin Shah Bin Abdullah, Prof. Dr. Zainal Arifin Bin Ahmad, and Prof. Dr. Azizan Aziz for their invaluable guidance, inspiration, and credible ideas in my journey towards this degree. I would like to attribute the completion of this thesis to their encouragements and supports. Without them, this thesis would not have been completed. It is my honour to be able to complete this Ph.D. research under their supervision, and I shall eternally be grateful to them.

I would like to express my gratitude to the entire staffs of School of Materials and Mineral Resources Engineering, University Sains Malaysia for providing me with adequate facilities and technical supports that are necessary for my research works. Special thanks to En. Maarof Salleh from School of Industrial Technology, University Sains Malaysia for his assistance in the experimental works of this research.

I am also extremely grateful to the Ministry of Higher Education of Malaysia for their financial support through My Brain 15 sponsorship, as well as other research funds that supported this research work. This research would not have been possible without these funds.

My acknowledgement would not be complete if I omit the names of my dear friends, Dr. Teo Pao Ter and Chan Chee Meng, who have assisted and supported me in their own ways. Thank you for being such good friends and helping me through all those tough times during my studies. I would also like to take this opportunity to extend my thanks to all the good people who have supported me directly or indirectly to complete my studies.

Lastly, I would like to express my warmest and most heartfelt thanks to my family for their continuous love, support, encouragement, and prayers over the long course of my studies. I hoped that this would make you all proud.

TABLE OF CONTENTS

	Page
ACKNOWLEDGEMENT	ii
TABLE OF CONTENTS	iv
LIST OF TABLES	ix
LIST OF FIGURES	x
LIST OF ABBREVIATIONS	xviii
LIST OF SYMBOLS	xix
ABSTRAK	xxi
ABSTRACT	xxiii
CHAPTER ONE: INTRODUCTION	
1.1 Background of microdialysis	1
1.2 Limitations of microdialysis and possible solution approaches	5
1.3 Problem statement	8
1.4 Scope of this thesis	10
1.5 Research objectives	10
1.6 Thesis outline	11
CHAPTER TWO: LITERATURE REVIEW	
2.1 Chapter outline	12
2.2 Principles of microdialysis	13
2.3 Advantages and limitations of microdialysis	14
2.4 Comparison of microdialysis with other in vivo sampling techniques	16
2.5 Development of the microdialysis technique	20
2.6 Set-up and design of microdialysis	24
2.6.1 Set-up of microdialysis	24
2.6.2 Design of microdialysis	25
2.7 Factors affecting the performance of microdialysis	30
2.7.1 Operating conditions of perfused solution	32

2.7.2	Design parameters of microdialysis probes	33
2.7.3	Conditions of the sampling site	36
2.8	Calibration methods for microdialysis	39
2.8.1	Low-flow-rate method	39
2.8.2	No-net-flux method	39
2.8.3	Retrodialysis	41
2.8.4	Internal standard method	42
2.8.5	Endogenous reference method	43
2.9	Recent works on microdialysis	44
2.10	Development of quantitative microdialysis	49
2.10.1	Construction of mathematical models for microdialysis	50
2.10.2	Limitations of previous models	54
2.11	Computational fluid dynamic solutions for microdialysis	57
2.12	Mathematical modelling of transport phenomena in microdialysis	61
2.12.1	Governing equations for the probe lumen	61
2.12.2	Governing equations for semipermeable membrane	64
2.12.2(a)	Diffusion-limited transportation	66
2.12.2(b)	Convection-enhanced transportation	68
2.12.3	Governing equations for the target site	70
2.13	Boundary conditions	72
2.14	Concluding remarks	75

CHAPTER THREE: RESEARCH METHODOLOGY

3.1	Chapter outline	77
3.2	Stage 1: Construction of mathematical models	78
3.2.1	Development of mathematical models for microdialysis	78
3.2.2	Microscopic analysis on the microdialysis probes	87
3.2.3	Development of linear probe models	88
3.2.3(a)	Domain of linear probe models	88

3.2.3(b) Governing equations of linear probe models	90
3.2.3(c) Boundary conditions of linear probe models	94
3.2.3(d) Solutions for linear probe models	102
3.2.4 Development of concentric probe models	103
3.2.4(a) Domain of concentric probe models	103
3.2.4(b) Governing equations of concentric probe models	105
3.2.4(c) Boundary conditions of concentric probe models	108
3.2.4(d) Solutions for concentric probe models	116
3.2.5 Selection of model parameters	117
3.2.6 Analytical procedures for mathematical models	119
3.3 Stage 2: Validation of mathematical models	121
3.3.1 Experimental work for validation of mathematical models	122
3.3.1(a) Materials and equipment	122
3.3.1(b) Microdialysis sampling procedures	123
3.3.1(c) Comparison of simulation results to experimental results	128
3.3.2 Comparison of simulation results from current work to experimental results reported by other researchers	129
3.3.3 Comparison of simulation results from current work to Bungay's Microdialysis Framework	131
3.4 Stage 3: Analysis on the impact of different parameters on the recovery of microdialysis	132
3.5 Concluding remarks	134

CHAPTER FOUR: RESULTS AND DISCUSSIONS

4.1 Chapter outline	136
4.2 Stage 1: Presentation of mathematical models	136
4.2.1 Microscopic analysis on microdialysis probes	137
4.2.2 Presentation of simulation results for linear probe models	146

4.2.2(a)	Concentration profiles of the linear probe models	146
4.2.2(b)	Fluid flow profiles in the linear probe models	151
4.2.2(c)	Analysis of fluid flow and mass transport characteristics in linear probe models	156
4.2.2(d)	Mesh studies on the linear probe models	160
4.2.3	Presentation of simulation results for concentric probe models	163
4.2.3(a)	Concentration profiles of the concentric probe models	163
4.2.3(b)	Fluid flow profiles in concentric probe models	168
4.2.3(c)	Analysis of fluid flow and mass transport characteristics of concentric probe models	173
4.2.3(d)	Mesh studies on the concentric probe models	177
4.2.4	Concluding remarks for Stage 1	180
4.3	Stage 2: Validation of mathematical models	182
4.3.1	Comparison of simulation results from current work to in-house experimental results	182
4.3.2	Comparison of simulation results from current work to experimental results reported in other research	187
4.3.3	Comparison of simulation results from current work to simulation results from Bungay's Microdialysis Framework	190
4.3.4	Concluding remarks for Stage 2	193
4.4	Stage 3: Analysis on the impact of different operational and design parameters on the recovery of microdialysis	194
4.4.1	Variation of modelling parameters related to microdialysis probe	194
4.4.1(a)	Flow rate of perfused solution	194
4.4.1(b)	Diameter of microdialysis probe	203
4.4.2	Variation of modelling parameters related to the membrane	211
4.4.2(a)	Membrane molecular weight cut-off and porosity	211
4.4.2(b)	Membrane tortuosity	226
4.4.2(c)	Membrane thickness	231

4.4.2(d) Membrane length	237
4.4.3 Variation of modelling parameters related to the probe surrounding area (PSA)	243
4.4.4 Concluding remarks for Stage 3	247
CHAPTER FIVE: CONCLUSION	
5.1 Summary of current research work	251
5.2 Statement of novelty	252
5.3 Recommendations for future work	254
REFERENCES	255
APPENDICES	
Appendix A: Summary of Lindefors and Amberg's Model	
Appendix B: Summary of Bungay's Microdialysis Framework	
Appendix C: COMSOL Multiphysics modelling guide	
LIST OF PUBLICATIONS	

LIST OF TABLES

	Page
Table 2.1 Advantages and limitations of the design for most commercially available microdialysis probe	34
Table 2.2 Example of modelling works that are constructed based on medical devices in recent years	59
Table 2.3 List of equations for solute diffusivity in a solvent as derived by previous researchers	67
Table 3.1 Parameters for the simulation of microdialysis sampling in this research work	118
Table 3.2 List of equipment for the experimental set-up of microdialysis sampling	122
Table 3.3 Recovery of APAP and caffeine for each linear probe from in vitro microdialysis sampling experimental work	130
Table 3.4 Modelling parameters for the recovery of APAP	130
Table 3.5 Modelling parameters for the recovery of caffeine	130
Table 4.1 Measurements of microdialysis probe structure provided by manufacturer	139
Table 4.2 SEM micrographs and surface porosity analysis on various spots of the membrane surface	142
Table 4.3 Cell Pe number at selected points in the linear probe models	159
Table 4.4 Comparison of the effect of different mesh size schemes on the number of mesh generated, number of degree of freedom that has to be solved, time taken to solve the model and simulated recovery for linear probe models	162
Table 4.5 Cell Pe number at selected points in the concentric probe models	176
Table 4.6 Comparison of the effect of different mesh size schemes on the number of mesh generated, number of degree of freedom that has to be solved, time taken to solve the model and simulated recovery for concentric probe models	179
Table 4.7 Comparison of experimental results to simulation results for microdialysis sampling conducted under different operational and design parameters	184
Table 4.8 Comparison of the relative recoveries (RR) estimated from BMF and the present work under various perfused solution flow rates	191

LIST OF FIGURES

		Page
Figure 1.1	Schematic illustration for the concept of microdialysis (a) and retrodialysis (b)	3
Figure 2.1	Schematic illustration of a microdialysis during in vivo sampling	13
Figure 2.2	Illustration of the set-up for push-pull perfusion	17
Figure 2.3	Schematic illustration for the set-up for OFM	19
Figure 2.4	Illustration of set-up for offline microdialysis sampling, with (a) syringe pump with control unit, (b) collect and storage unit, (c) probe, (d) experimental subject, and (e) life support unit/temperature controller	25
Figure 2.5	Schematic illustration of various microdialysis probe designs, with (a) linear, (b) loop or u-shaped, (c) concentric, (d) side-by-side, and (e) shunt	28
Figure 2.6	Plot of relative and absolute recoveries for microdialysis sampling	31
Figure 2.7	Example of regression plot for no-net-flux method	40
Figure 2.8	Number of publication per year on microdialysis related topics, according to the information on PubMed	44
Figure 2.9	2D-illustration of a MetaQuant probe	47
Figure 2.10	Modelling geometry of concentric probe model	55
Figure 3.1	Flowchart representing the phased of preliminary work prior to constructing mathematical model for microdialysis	81
Figure 3.2	Illustration of the (a) linear probe and (b) concentric probe in 3D, which are simplified to 2D axial-symmetry	83
Figure 3.3	Flowchart representing the procedures for constructing modelling framework for microdialysis probes	86
Figure 3.4	Schematic illustration of the linear probe model that includes the dimensions of domain, dimensions of each subdomain, and fluid flow direction in the probe lumen	89
Figure 3.5	Schematic illustration of the concentric probe model that includes the dimensions of domain, dimensions of each subdomain, and fluid flow direction in the probe lumen	104
Figure 3.6	Image of the microdialysis set-up for the experimental work	124

Figure 3.7	Flowchart for the procedures of the microdialysis sampling experimental work, divided into several distinct steps	124
Figure 3.8	HPLC system for glucose concentration analysis	127
Figure 3.9	Flowchart representing the research activities for present work	135
Figure 4.1	Optical images of a concentric probe showing (a) the 1cm long membrane area, b) the tip of concentric probe, c) the membrane with inner shaft, and d) membrane-outer shaft connection	137
Figure 4.2	Optical images of a linear probe showing (a) the 1cm long membrane area, (b) inlet connecting tube-membrane connection, (c) membrane of linear probe, and (d) outlet connecting tube-membrane connection	138
Figure 4.3	SEM micrographs showing the cross-sectional diameter and thickness of inner cannula structure in a concentric microdialysis probe with 265 × magnifications	140
Figure 4.4	SEM micrographs showing the cross-sectional diameter and thickness of the membrane in linear microdialysis probe with 500 × magnifications	140
Figure 4.5	Images of the completed framework for DL linear probe model showing concentration profile and diffusive flux, with (a) showing the full-scaled plot, while the enlargement (b) shows the concentration and diffusive flux around the membrane area	147
Figure 4.6	Images of the completed framework for CE linear probe model showing concentration profile and diffusive flux, with (a) showing the full-scaled plot, while the enlargement (b) shows the concentration and diffusive flux around the membrane area	148
Figure 4.7	Concentration distribution across axial membrane area of the DL linear probe model ($z = 3.0-4.0$ cm) for convection-enhanced model, from axial symmetry interface to a radial distance of 0.6 mm	149
Figure 4.8	Concentration distribution across axial membrane area of the CE linear probe model ($z = 3.0-4.0$ cm) for convection-enhanced model, from axial symmetry interface to a radial distance of 0.6 mm	149
Figure 4.9	Fluid velocity profile in the DL linear probe model at (a) inlet of connecting tube-membrane connection, (b) midpoint of membrane lumen area, and (c) outlet of connecting tube-membrane tube connection	152

Figure 4.10	Fluid velocity profile in the CE linear probe model at (a) inlet of connecting tube-membrane connection, (b) midpoint of membrane lumen area, and (c) outlet of connecting tube-membrane tube connection	153
Figure 4.11	Fluid velocity profile across the probe lumen of DL linear probe model ($r = 0-0.12$ mm), from inlet to outlet of the membrane area ($z = 3.0-4.0$ cm)	154
Figure 4.12	Fluid velocity profile across the probe lumen of CE linear probe model ($r = 0-0.12$ mm), from inlet to outlet of the membrane area ($z = 3.0-4.0$ cm)	154
Figure 4.13	Fluid velocity profile for CE linear probe model from the membrane ($r = 0.12-0.16$ mm) to a PSA radial distance of 1.2 mm ($r = 0.16-1.20$ mm), across the membrane axially ($z = 3.0-4.0$ cm)	155
Figure 4.14	Cell Re profile for DL linear probe model at (a) inlet of connecting tube-membrane connection, (b) midpoint of lumen area, and (c) outlet of connecting tube-membrane tube connection	157
Figure 4.15	Cell Re profile for CE linear probe model at (a) inlet of connecting tube-membrane connection, (b) midpoint of lumen area, and (c) outlet of connecting tube-membrane tube connection	158
Figure 4.16	Images of the linear probe models generated from different predefined mesh size scheme of (a) extra fine, (b) fine, (c) normal, (d) coarse, and (e) extra coarse	161
Figure 4.17	Images of the completed framework for DL concentric probe model showing concentration profile and diffusive flux, with (a) showing the full-scaled plot, while the enlargement (b) shows the concentration and diffusive flux around the membrane area	164
Figure 4.18	Images of the completed framework for CE concentric probe model showing concentration profile and diffusive flux, with (a) showing the full-scaled plot, while the enlargement (b) shows the concentration and diffusive flux around the membrane area	165
Figure 4.19	Concentration distribution across axial membrane area of the DL concentric probe model ($z = 3.00-3.97$ cm), from axial symmetry interface to a radial distance of 0.60 mm	166
Figure 4.20	Concentration distribution across axial membrane area of the CE concentric probe model ($z = 3.00-3.97$ cm), from axial symmetry interface to a radial distance of 0.60 mm	166

Figure 4.21	Fluid velocity profile in the DL concentric probe model around (a) probe tip, (b) midpoint of probe lumen, and (c) membrane-shaft connecting point	169
Figure 4.22	Fluid velocity profile in the CE concentric probe model around (a) probe tip, (b) midpoint of probe lumen, and (c) membrane-shaft connecting point	170
Figure 4.23	Fluid velocity profile across the probe lumen of DL concentric probe model ($r = 0-0.12$ mm), from membrane-shaft connecting point to the tip of the membrane ($z = 3.0-3.97$ cm)	171
Figure 4.24	Fluid velocity profile across the probe lumen of CE concentric probe model ($r = 0-0.12$ mm), from membrane-shaft connecting point to the tip of the membrane ($z = 3.0-3.97$ cm)	171
Figure 4.25	Fluid velocity profile for CE concentric probe model from the membrane ($r = 0.12-0.16$ mm) to a PSA radial distance of 1.2 mm ($r = 0.16-1.20$ mm), across the membrane axially ($z = 3.0-3.97$ cm)	172
Figure 4.26	Cell Re profile for DL concentric probe model around (a) probe tip, (b) midpoint of probe lumen, and (c) membrane-shaft connecting point	174
Figure 4.27	Cell Re profile for CE concentric probe model around (a) probe tip, (b) midpoint of probe lumen, and (c) membrane-shaft connecting point	175
Figure 4.28	Images of the concentric probe models generated from different predefined mesh size scheme, with (a) extra fine, (b) fine, (c) normal, (d) coarse, and (e) extra coarse	178
Figure 4.29	Calibration curve for HPLC analysis of glucose samples	183
Figure 4.30	Residual plot for experimental RR values and simulated RR values from DL models	186
Figure 4.31	Residual plot for experimental RR values and simulation RR values from CE models	186
Figure 4.32	Comparison of APAP and caffeine recovery from three different linear microdialysis probe labelled as probe 1, 2, and 3, to the simulated recovery of DL and CE linear probe model	188
Figure 4.33	Residual plot for simulation results (RR) of BMF versus DL concentric probe model	192

Figure 4.34	Residual plot for simulation results (RR) of BMF versus CE concentric probe model	192
Figure 4.35	The relative recovery of glucose simulated under different perfused solution flow rates for both linear probe and concentric probe models	195
Figure 4.36	Concentration profile in DL linear probe model for various flow rates (0.1-10.0 $\mu\text{L min}^{-1}$) over radial distance of $r = 0-0.5$ mm	197
Figure 4.37	Concentration profile in CE linear probe model for various flow rates (0.1-10.0 $\mu\text{L min}^{-1}$) over radial distance of $r = 0-0.5$ mm	197
Figure 4.38	Concentration profile in DL concentric probe model for various flow rates (0.1-10.0 $\mu\text{L min}^{-1}$) over radial distance of $r = 0-0.5$ mm	198
Figure 4.39	Concentration profile in CE concentric probe model for various flow rates (0.1-10.0 $\mu\text{L min}^{-1}$) over radial distance of $r = 0-0.5$ mm	198
Figure 4.40	Maximum Re of DL linear probe model, CE linear probe model, DL concentric probe model and CE concentric probe model at perfused solution flow rates of 1-10 $\mu\text{L min}^{-1}$	201
Figure 4.41	Surface plots representing the concentration distribution for the liner probe models with probe radius of a) 0.1 mm, b) 0.2 mm, c) 0.3 mm, and d) 0.5 mm	204
Figure 4.42	Surface plots representing the concentration distribution for the concentric probe models with probe radius of a) 0.1 mm, b) 0.2 mm, c) 0.3 mm, and d) 0.5mm	205
Figure 4.43	Simulated RR of linear and concentric probe models under probe radius of 0.1-0.5 mm at perfused solution of 0.3 $\mu\text{L min}^{-1}$ and 5.0 $\mu\text{L min}^{-1}$	206
Figure 4.44	Perfused solution velocity profile in linear probe models with different probe radius	207
Figure 4.45	Perfused solution velocity profile in concentric probe models with different probe radius	207
Figure 4.46	Surface plots representing the concentration distribution for the concentric probe models with probe radius of a) 0.1 mm, b) 0.2 mm, c) 0.3 mm, d) 0.4 mm and e) 0.5mm	209

Figure 4.47	Simulated RR of concentric probe models under inner shaft radius of 0.04-0.44 mm at perfused solution of 0.3 $\mu\text{L min}^{-1}$ and 5.0 $\mu\text{L min}^{-1}$	210
Figure 4.48	Simulated RR for DL and CE linear probe model under porosity of 0.1-0.7 and pore diameter of 5-100 nm at 0.5 $\mu\text{L min}^{-1}$ perfused solution flow rate	213
Figure 4.49	Simulated RR for DL and CE concentric probe model under porosity of 0.1-0.7 and pore diameter of 5-100 nm at 0.5 $\mu\text{L min}^{-1}$ perfused solution flow rate	213
Figure 4.50	Simulated RR for DL and CE linear probe model under porosity of 0.1-0.7 and pore diameter of 5-100 nm at 5.0 $\mu\text{L min}^{-1}$ perfused solution flow rate	215
Figure 4.51	Simulated RR for DL and CE concentric probe model under porosity of 0.1-0.7 and pore diameter of 5-100 nm at 5.0 $\mu\text{L min}^{-1}$ perfused solution flow rate	215
Figure 4.52	Simulated RR for DL and CE linear probe model at different perfused solution flow rates under different membrane porosity and pore diameter	217
Figure 4.53	Simulated RR for DL and CE concentric probe model at different perfused solution flow rates under different membrane porosity and pore opening diameter	217
Figure 4.54	Fluid velocity in the membrane and PSA for CE linear probe model and CE concentric probe model at 0.1 $\mu\text{L min}^{-1}$	219
Figure 4.55	Fluid velocity in the membrane and PSA for CE linear probe model and CE concentric probe model at 5.0 $\mu\text{L min}^{-1}$	219
Figure 4.56	The total flux of the membrane for DL and CE linear probe model at point $r = 0.14$ mm, $z = 3.5$ cm under different membrane porosity, pore diameter and flow rates	222
Figure 4.57	The total flux of the membrane for DL and CE concentric probe model at point $r = 0.14$ mm, $z = 3.5$ cm under different membrane porosity, pore opening diameter and flow rates	222
Figure 4.58	Plot of membrane Pe under different perfused solution flow rates with membrane porosity (ϵ) of 0.7 and average pore diameter (dp) of 100 nm for CE linear probe model and CE concentric probe model	224
Figure 4.59	Simulated RR with different membrane tortuosity for DL linear probe model, CE linear probe model, DL concentric probe model and CE concentric probe models under different flow rates of 0.5 $\mu\text{L min}^{-1}$ and 2.0 $\mu\text{L min}^{-1}$	227

Figure 4.60	Concentration profiles over radial distance ($r = 0-0.5$ mm) under different membrane tortuosity (1.0-2.5) for DL linear probe model	229
Figure 4.61	Concentration profiles over radial distance ($r = 0-0.5$ mm) under different membrane tortuosity (1.0-2.5) for CE linear probe model	229
Figure 4.62	Concentration profiles over radial distance ($r = 0-0.5$ mm) under different membrane tortuosity (1.0-2.5) for DL concentric probe model	230
Figure 4.63	Concentration profiles over radial distance ($r = 0-0.5$ mm) under different membrane tortuosity (1.0-2.5) for CE concentric probe model	230
Figure 4.64	Simulated RR with different membrane thickness for DL linear probe model, CE linear probe model, DL concentric probe model and CE concentric probe models under flow rates of $0.5 \mu\text{L min}^{-1}$ and $2.0 \mu\text{L min}^{-1}$	232
Figure 4.65	Concentration profiles over radial distance ($r = 0-0.6$ mm) under different membrane thickness for DL linear probe model	234
Figure 4.66	Concentration profiles over radial distance ($r = 0-0.6$ mm) under different membrane thickness for CE liner probe model	234
Figure 4.67	Concentration profiles over radial distance ($r = 0-0.6$ mm) under different membrane thickness for DL concentric probe model	235
Figure 4.68	Concentration profiles over radial distance ($r = 0-0.6$ mm) under different membrane thickness for CE concentric probe model	235
Figure 4.69	Simulated RR with different membrane length for DL linear probe model, CE linear probe model, DL concentric probe model and CE concentric probe models under flow rates of $0.5 \mu\text{L min}^{-1}$ and $2.0 \mu\text{L min}^{-1}$	238
Figure 4.70	Concentration profiles over radial distance ($r = 0-0.5$ mm) under different membrane length for DL linear probe model	240
Figure 4.71	Concentration profiles over radial distance ($r = 0-0.5$ mm) under different membrane length for CE linear probe model	240
Figure 4.72	Concentration profiles over radial distance ($r = 0-0.5$ mm) under different membrane length for DL concentric probe model	241

Figure 4.73	Concentration profiles over radial distance ($r = 0-0.5$ mm) under different membrane length for CE concentric probe model	241
Figure 4.74	Simulated RR with different thickness of PSA for DL linear probe model, CE linear probe model, DL concentric probe model and CE concentric probe models under flow rates of $0.5 \mu\text{L min}^{-1}$ and $2.0 \mu\text{L min}^{-1}$	244
Figure 4.75	Concentration profiles over radial distance ($r = 0-0.5$ mm) under different thickness of PSA DL linear probe model	245
Figure 4.76	Concentration profiles over radial distance ($r = 0-0.5$ mm) under different thickness of PSA CE linear probe model	245
Figure 4.77	Concentration profiles over radial distance ($r = 0-0.5$ mm) under different thickness of PSA DL concentric probe model	246
Figure 4.78	Concentration profiles over radial distance ($r = 0-0.5$ mm) under different thickness of PSA CE concentric probe model	246

LIST OF ABBREVIATIONS

APAP	acetaminophen
BMF	Bungay's Microdialysis Framework
CE	convection-enhanced
CFD	computational fluid dynamics
DL	diffusion-limited
ECS	extracellular space
EF	extraction fraction
FEM	finite element method
GUI	graphical user interface
HPLC	high-performance liquid chromatography
MWCO	molecular weight cut-off
NS	Navier-Stokes equations
OFM	open flow microperfusion
OM	optical microscope
PAN	polyacrylonitrile
PC	polycarbonate
PDE	partial differential equation
Pe	Péclet number
PES	polyethersulfone
PSA	probe surrounding area
Re	Reynolds number
RR	relative recovery
SEM	scanning electron microscopy

LIST OF SYMBOLS

A	surface area of semipermeable membrane (m^2)
c	molar concentration (mol m^{-3})
c_0	initial analyte concentration (mol m^{-3})
$c_{\text{dialysate}}$	analyte concentration in dialysate (mol m^{-3})
$c_{\text{perfusate}}$	analyte concentration in perfusate (mol m^{-3})
c_{PSA}	initial analyte concentration in PSA (mol m^{-3})
c_{site}	analyte concentration at target site (mol m^{-3})
C_f	empirical inertia coefficient
D	diffusivity of solute ($\text{m}^2 \text{s}^{-1}$)
D_{AB}	diffusivity of chemical substance A in solvent B ($\text{m}^2 \text{s}^{-1}$)
D_g	diffusivity of glucose ($\text{m}^2 \text{s}^{-1}$)
D_m	diffusion coefficient of membrane ($\text{m}^2 \text{s}^{-1}$)
D_{PL}	diffusivity of analytes in the probe lumen ($\text{m}^2 \text{s}^{-1}$)
D_{PSA}	diffusivity of analytes in the PSA ($\text{m}^2 \text{s}^{-1}$)
D_T	diffusion coefficient of tissue ($\text{m}^2 \text{s}^{-1}$)
g	gravity constant (m s^{-2})
I	identity matrix
k	permeability (m^2)
k_B	Boltzmann constant ($\text{m}^2 \text{kg s}^{-2} \text{K}^{-1}$)
K_0	mass transfer coefficient
L_c	characteristic length (m)
N_c	convective flux with respect to a stationary axis ($\text{mol m}^{-2} \text{s}^{-1}$)
N_d	diffusive flux with respect to a stationary axis ($\text{mol m}^{-2} \text{s}^{-1}$)
N_p	total flux in the probe lumen ($\text{mol m}^{-2} \text{s}^{-1}$)
p	pressure ($\text{kg m}^{-1} \text{s}^{-2}$)

Q	volumetric flow rate ($\text{m}^3 \text{s}^{-1}$)
Q_0	initial perfused solution flow rate ($\text{m}^3 \text{s}^{-1}$)
R	internal radius of connecting tube /inner shaft (m)
r	radial distance from centreline/axial-symmetrical interface (m)
r_p	average radius of membrane pore (m)
r_s	average radius of analyte molecules (m)
s	mass source of concerned substance ($\text{kg m}^{-3} \text{s}^{-1}$)
T	temperature (K)
u_0	average fluid velocity (m s^{-1})
u_r	radial fluid velocity (m s^{-1})
u_z	axial fluid velocity (m s^{-1})
\vec{u}	fluid velocity vector (m s^{-1})
\vec{u}_L	fluid velocity vector for linear probe model (m s^{-1})
\vec{u}_c	fluid velocity vector for concentric probe model (m s^{-1})
v	initial fluid velocity at inlet (m s^{-1})
$V_{bp,B}$	molar volume of solvent B at its boiling point ($\text{m}^3 \text{mol}^{-1}$)
ε	porosity
μ	dynamic viscosity of fluid ($\text{kg m}^{-1} \text{s}^{-1}$)
$\xi_{d,i}$	hindrance factor
ρ	fluid density (kg m^{-3})
τ	membrane tortuosity
φ	ratio of extracellular space volume to in vivo target site volume
ψ	associate parameter of solvent interactions

**PEMBANGUNAN MODEL MATEMATIK FENOMENA PENGANGKUTAN
JISIM UNTUK KUAR MIKRODIALISIS LELURUS DAN SEPUSAT DENGAN
MENGUNAKAN CIRI KENDALIAN YANG TERHAD KEPADA RESAPAN
DAN YANG DIPERTINGKATKAN DENGAN PEROLAKAN**

ABSTRAK

Mikrodialisis merupakan satu teknik pensampelan yang terkenal dalam bidang penyelidikan perubatan, lazimnya digunakan untuk mengukur kepekatan bahan kimia dalam tisu. Namun, kelemahan utama teknik ini ialah jumlah bahan kimia yang dikumpulkan (iaitu perolehan) tidak konsisten. Ini turut menimbulkan komplikasi lain, seperti keperluan untuk mengendalikan pra-larian dan kalibrasi. Salah satu cara untuk menyelesaikan kelemahan ini adalah dengan memahami kebatasan pengangkutan jisim dalam sistem mikrodialisis dengan meneliti bagaimana setiap parameter operasi mempengaruhi perolehan mikrodialisis. Satu pendekatan umum adalah melalui pemodelan matematik. Walaupun sudah ada beberapa model matematik untuk mikrodialisis, model-model itu hanya menumpu untuk memberi nilai perolehan yang tepat, sementara ciri-ciri lain seperti aliran bendalir dalam mikrodialisis diabaikan. Objektif utama kerja penyelidikan ini adalah untuk membangunkan model-model matematik unsur terhingga yang dapat memberi simulasi yang tepat bagi susuk kepekatan dan aliran bendalir dalam mikrodialisis. Model-model ini dibina berdasarkan kuar mikrodialisis lurus dan sepusat. Domain model-model ini tertumpu pada komponen utama mikrodialisis, iaitu kuar mikrodialisis, membran yang dipasang pada kuar, dan kawasan di sekitar kuar (PSA). PSA ini terdiri daripada medium tetap yang mengandungi analit untuk penyelidikan, iaitu glukosa. Pengangkutan jisim dalam model-model ini diwakili oleh persamaan perolakan dan resapan, manakala sifat aliran bendalir diwakili oleh persamaan Navier-Stokes. Hasil simulasi model-model yang dibentangkan

turut menunjukkan persetujuan yang baik dengan keputusan eksperimen. Analisis regresi antara perolehan simulasi dan perolehan eksperimen memberi nilai R-kuadrat $\geq 98.5\%$ untuk setiap model. Dengan menggunakan model-model yang dibentangkan, kelebihan dan kelemahan setiap parameter operasi untuk persampelan mikrodialisis telah diteliti. Sebagai contohnya, pensampelan mikrodialisis untuk glukosa di bawah kadar aliran cecair perfusi $1.0 \mu\text{L min}^{-1}$ dengan menggunakan kuar mikrodialisis lurus and sepusat (panjang membran 10 mm, pemotongan berat molekul 30 kDa) menghasilkan perolehan sebanyak 30.98% dan 36.67%. Mengurangkan kadar aliran cecair perfusi kepada $0.5 \mu\text{L min}^{-1}$ akan meningkatkan perolehan kepada 55.77% dan 60.72%, tetapi pada masa yang sama, masa pensampelan juga akan meningkat. Di samping itu, walaupun pengangkutan jisim melalui membran dalam kuar mikrodialisis secara tradisinya didefinisikan sebagai proses yang terhad kepada resapan, adalah ditunjukkan dalam kerja ini bahawa di bawah keadaan kadar aliran cecair perfusi dalam kuar yang tinggi, keliangan membran yang tinggi, dan saiz liang membran yang besar, perolakan akan menunjukkan pengaruh yang signifikan kepada perolehan mikrodialisis. Dengan itu, persamaan resapan yang dipertingkatkan dengan perolakan adalah diperlukan untuk mewakili pengangkutan jisim merentasi membran dalam kuar mikrodialisis.

**DEVELOPMENT OF TRANSPORT PHENOMENA MATHEMATICAL
MODELS FOR LINEAR AND CONCENTRIC MICRODIALYSIS PROBES
WITH DIFFUSION-LIMITED AND CONVECTION-ENHANCED
OPERATIONAL FEATURES**

ABSTRACT

Microdialysis is a well-known sampling technique in medical researches, most commonly used to measure the concentration of chemicals in the extracellular space of tissues. However, despite being a well-established technique, microdialysis often gives inconsistent amounts of chemicals collected from the sampling site (i.e. recovery). This would give rise to other complications, such as the requirement of pre-runs and calibrations. In order to resolve this issue, it is necessary to understand the mass transport limitations of microdialysis set-up, by scrutinizing how each operational and design parameters of the microdialysis set-up affect the recovery. One common approach is through mathematical modelling. Although there are already several mathematical modelling works on microdialysis, those works would focus only on providing accurate estimations of the recovery, while other features such as fluid flows are neglected. The main objective of this research work is to develop finite element mathematical models that could provide accurate simulations of concentration and fluid flow profiles for microdialysis. These models were constructed based on linear and concentric microdialysis probes. Modelling domain of these mathematical models would focus on the microdialysis probes, the membrane attached to the probes, and the probe surrounding area (PSA). The PSA for this research work is a quiescent medium filled with the analyte to be recovered, which is glucose. Mass transport properties in the models are represented by convection-diffusion equations, while fluid flows are represented by Navier-Stokes equations. It is shown that the developed mathematical