



Universiteit  
Leiden  
The Netherlands

## **Prediction of spatial-temporal brain drug distribution with a novel mathematical model**

Vendel, E.

### **Citation**

Vendel, E. (2019, December 17). *Prediction of spatial-temporal brain drug distribution with a novel mathematical model*. Retrieved from <https://hdl.handle.net/1887/81579>

Version: Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/81579>

**Note:** To cite this publication please use the final published version (if applicable).

Cover Page



Universiteit Leiden



The following handle holds various files of this Leiden University dissertation:  
<http://hdl.handle.net/1887/81579>

**Author:** Vendel, E.

**Title:** Prediction of spatial-temporal brain drug distribution with a novel mathematical model

**Issue Date:** 2019-12-17

# **Prediction of spatial-temporal brain drug distribution with a novel mathematical model**

Esmée Vendel

ISBN: 978-94-028-1795-9

©2019 Esmée Vendel

Omslagontwerp: Remco Wetzels

Printed by Ipskamp printing

# **Prediction of spatial-temporal brain drug distribution with a novel mathematical model**

Proefschrift

ter verkrijging van  
de graad van Doctor aan de Universiteit Leiden,  
op gezag van Rector Magnificus prof. mr. C.J.J.M. Stolker,  
volgens besluit van het College voor Promoties  
te verdedigen op dinsdag 17 december 2019  
klokke 13:45 uur

door

**Esmée Vendel**  
geboren te Haarlem  
in 1991

Promotores:	Prof. dr. Roeland M.H. Merks	
	Prof. dr. Elizabeth C.M. de Lange	
Copromotor:	Dr. Vivi Rottschäfer	
Promotiecommissie:	Prof. dr. Aad W. van der Vaart	(Voorzitter)
	Prof. dr. Arjen Doelman	(Secretaris)
Overige commissieleden:	Prof. dr. Gianne Derks	(University of Surrey)
	Prof. dr. Charles Nicholson	(New York University School of Medicine)

This research has been carried out at the Mathematical Institute of Leiden University in the Analysis and Dynamical Systems group in collaboration with the Systems Biomedicine and Pharmacology group at Leiden Academic Centre of Drug Research and with ties to the Scientific Computing group at Centrum Wiskunde & Informatica (CWI).

# Contents

<b>1</b>	<b>Introduction</b>	<b>1</b>
1.1	Processes that govern drug distribution within the brain . .	5
1.2	Models on drug distribution into and within the brain . . .	8
1.2.1	Prediction of local drug concentrations of drug within the brain using a new mathematical model . . . . .	9
1.3	Thesis outline . . . . .	15
<b>2</b>	<b>Review: Modelling drug distribution within the brain</b>	<b>17</b>
2.1	Introduction . . . . .	18
2.2	Factors affecting drug distribution within the brain . . . . .	19
2.2.1	Brain-specific properties . . . . .	19
2.2.2	Drug-specific properties . . . . .	26
2.2.3	Processes affecting drug distribution within the brain	29
2.2.4	Factors that may lead to spatial differences in concentration- time profiles of drugs in the brain . . . . .	38
2.3	Existing models on the local distribution of drugs in the brain	40
2.3.1	Modelling drug transport through the brain capillary system . . . . .	40
2.3.2	Modelling drug transport across the BBB . . . . .	43
2.3.3	Modelling drug transport within the brain ECF . . .	46
2.3.4	Modelling intra-extracellular exchange . . . . .	52
2.3.5	Modelling drug binding kinetics . . . . .	53
2.3.6	Modelling drug metabolism in the brain . . . . .	55
2.3.7	Modelling drug exchange between compartments . .	55
2.3.8	Integration of model properties . . . . .	59
2.4	The need for a refined mathematical model on spatial drug distribution within the brain . . . . .	61
<b>3</b>	<b>A 2D model to improve the prediction of drug distribution within the brain</b>	<b>67</b>
3.1	Introduction . . . . .	68

3.2	The 2D brain unit . . . . .	75
3.2.1	Formulating the model based on the physiology of the brain . . . . .	75
3.2.2	Modelling drug transport through the brain ECF . . . . .	77
3.2.3	Modelling drug transport across the BBB . . . . .	79
3.2.4	Model values and units . . . . .	81
3.3	Model results . . . . .	81
3.3.1	The effect of drug binding on the concentration-time profiles of drug in the brain ECF . . . . .	83
3.3.2	The effect of the kinetics of drug binding to specific binding sites on drug concentrations within the brain ECF . . . . .	85
3.3.3	The influence of BBB permeability on the concentration profiles of drug in the brain ECF . . . . .	88
3.3.4	The local drug distribution within the brain unit . . . . .	91
3.4	Discussion . . . . .	95
<b>4</b>	<b>A 3D model to further improve the prediction of brain drug distribution</b>	<b>101</b>
4.1	Introduction . . . . .	102
4.2	The 3D brain unit . . . . .	104
4.2.1	Formulation of the 3D brain unit . . . . .	107
4.2.2	Description of drug distribution in $U_{pl}$ . . . . .	108
4.2.3	Description of drug distribution in $U_{ECF}$ . . . . .	109
4.2.4	Boundary conditions . . . . .	110
4.2.5	Model parameter values and units . . . . .	112
4.3	Model results . . . . .	112
4.3.1	The effect of the brain capillary blood flow velocity on brain ECF PK within the 3D brain unit . . . . .	114
4.3.2	The effect of active BBB transport on the drug concentrations within the brain ECF . . . . .	118
4.3.3	The effect of the brain capillary blood flow velocity in the presence of active BBB transport . . . . .	121
4.4	Discussion . . . . .	126
<b>5</b>	<b>The 3D brain unit network in health and disease conditions</b>	<b>135</b>
5.1	Introduction . . . . .	136
5.2	The 3D brain unit network model . . . . .	137
5.2.1	Model formulation of the 3D brain unit network . . . . .	138
5.2.2	Description of drug distribution in $U_{pl}$ . . . . .	140



---

5.2.3	Description of drug distribution in $U_{ECF}$ . . . . .	140
5.2.4	Boundary conditions . . . . .	141
5.2.5	Model parameter values and units . . . . .	142
5.3	Model results . . . . .	142
5.3.1	Simulated changes in brain capillary density . . . . .	146
5.3.2	Simulated BBB functionality in health and disease conditions . . . . .	147
5.3.3	Simulated changes in specific binding site density . . . . .	152
5.3.4	Combining properties . . . . .	157
5.3.5	Examples for a number of existing drugs . . . . .	158
5.4	Discussion . . . . .	162
<b>6</b>	<b>General discussion and future perspectives</b>	<b>171</b>
6.1	General discussion . . . . .	172
6.1.1	Model input . . . . .	172
6.1.2	Model methods . . . . .	173
6.1.3	Model results . . . . .	174
6.2	Refinement of descriptions of drug transport into and within the brain . . . . .	175
6.2.1	BBB transport . . . . .	175
6.2.2	Intra-brain distribution . . . . .	177
6.3	Towards a subject-specific 3D brain model . . . . .	180
6.4	Upscaling the 3D brain model . . . . .	182
6.5	Summary . . . . .	183
	<b>References</b>	<b>184</b>
	<b>Acknowledgements</b>	<b>213</b>

