



Universiteit  
Leiden  
The Netherlands

## Pharmacokinetic and pharmacodynamic analysis in anesthesia : a modeling odyssey

Olofsen, E.

### Citation

Olofsen, E. (2017, June 21). *Pharmacokinetic and pharmacodynamic analysis in anesthesia : a modeling odyssey*. Retrieved from <https://hdl.handle.net/1887/50818>

Version: Not Applicable (or Unknown)

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

Downloaded from: <https://hdl.handle.net/1887/50818>

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

Cover Page



Universiteit Leiden



The handle <http://hdl.handle.net/1887/50818> holds various files of this Leiden University dissertation

**Author:** Olofsen, E.

**Title:** Pharmacokinetic and pharmacodynamic analysis in anesthesia : a modeling odyssey

**Issue Date:** 2017-06-21

# Population Pharmacokinetic and Pharmacodynamic Analysis in Anesthesia

*A Modeling Odyssey*

Erik Olofsen

© E. Olofsen, 2017, Leiden, The Netherlands

ISBN 978-90-827007-0-1

Cover design inspired by “2001: A Space Odyssey”, by S. Kubrick and by A.C. Clarke

Typeset with  $\text{\LaTeX}$  via “tbook” by T. Bronger

Printed by Puntgaaf Drukwerk, Leiden, The Netherlands

# Population Pharmacokinetic and Pharmacodynamic Analysis in Anesthesia

*A Modeling Odyssey*

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 woensdag 21 juni 2017  
klokke 16.15 uur

door

Erik Olofsen  
geboren te Amsterdam  
in 1963

Promotor: prof. dr. A. Dahan

Copromotor: dr. M. Niesters

Promotiecommissie: prof. dr. L.P.H.J. Aarts

prof. dr. ing. P.H.C. Eilers (Erasmus MC, Rotterdam)

prof. dr. J.M.A. van Gerven

prof. dr. H.-J. Guchelaar

prof. dr. C.A.J. Knibbe (St. Antonius Hospital, Nieuwegein)

prof. dr. T.W. Schnider (Kantonsspital St. Gallen, Switzerland)

dr. E.Y. Sarton

dr. M. van Velzen

# Contents

<b>1</b>	<b>Introduction</b>	<b>1</b>
1.1	A Modeling Odyssey . . . . .	1
1.2	The Limits of Agreement . . . . .	2
1.3	An Information Theoretic Criterion . . . . .	3
1.4	The Kalman Filter . . . . .	3
1.5	The Entropy of Permutations . . . . .	4
1.6	Location, Location, Location, of the Sampling Site . . . . .	5
1.7	NONMEM and Beyond the Infinite . . . . .	5
<b>2</b>	<b>Improvements in the Application and Reporting of Advanced Bland-Altman Methods of Comparison*</b>	<b>7</b>
2.0.1	Definitions and Notation . . . . .	8
2.0.2	Estimation Methods for the Limits of Agreements . . . . .	9
2.0.3	Confidence Intervals for the Limits of Agreements . . . . .	10
2.1	Methods . . . . .	10
2.1.1	Implementation . . . . .	10
2.1.2	Output of the Analyses . . . . .	11
2.1.3	Diagnostic Plots . . . . .	11
2.1.4	Validation Study . . . . .	12
2.1.5	Application . . . . .	12
2.2	Results . . . . .	12
2.2.1	Validation Study . . . . .	12
2.2.2	Application . . . . .	16
2.3	Discussion . . . . .	16
2.3.1	The Methods of Comparison . . . . .	16
2.3.2	Mixed-Effects Models . . . . .	18
2.3.3	Explanatory Simulations . . . . .	18
2.3.4	Towards a Standard Format of Reporting . . . . .	19
2.3.5	The JavaScript Library . . . . .	19
2.3.6	Conclusion . . . . .	21
2.A	Appendix: Derivations . . . . .	21
2.A.1	The Model . . . . .	21
2.A.2	The Mean of the Differences . . . . .	22
2.A.3	Limits of Agreement and Their Confidence Intervals . . . . .	23
2.A.4	The Pooled Data Method . . . . .	24
2.A.5	The Standard True Value Varies Method . . . . .	25

---

\* E Olofsen, A Dahan, G Borsboom, G Drummond, *J Clin Monit Comput* 2015; 29:127-139

2.A.6	The Modified True Value Varies Method . . . . .	26
2.A.7	The True Value Constant Method . . . . .	27
2.A.8	Generation of Simulation Data . . . . .	27
<b>3</b>	<b>Using Akaike's Information Theoretic Criterion in Mixed-Effects Modeling of Pharmacokinetic Data: A Simulation Study<sup>†</sup></b>	<b>29</b>
3.1	Methods . . . . .	30
3.1.1	A Hypothetical Pharmacokinetic Model . . . . .	30
3.1.2	Individual Data Modeling and Simulation . . . . .	30
3.1.3	Population Data Modeling and Simulation . . . . .	31
3.1.4	Statistical Analysis . . . . .	32
3.1.5	Selection of Parameter Values . . . . .	32
3.2	Results . . . . .	33
3.3	Discussion . . . . .	37
3.3.1	Akaike's <i>versus</i> the Conditional Akaike Information Criterion . . . . .	37
3.3.2	Akaike's <i>versus</i> the Bayesian Akaike Information Criterion . . . . .	37
3.3.3	Model Selection Criterion AIC and Predictive Performance . . . . .	38
3.3.4	Regression Weights as Functions of the Model Output . . . . .	38
3.3.5	Model Selection Uncertainty . . . . .	38
3.3.6	Limitations of the Study . . . . .	39
3.4	Conclusion . . . . .	40
3.A	Appendix: Supplementary Material . . . . .	40
<b>4</b>	<b>Stochastic Pharmacokinetic-Pharmacodynamic Analysis of the Effect of Transdermal Buprenorphine on Electroencephalogram and Analgesia<sup>‡</sup></b>	<b>45</b>
4.1	Methods . . . . .	46
4.1.1	Study Design . . . . .	46
4.1.2	Data Analysis . . . . .	48
4.2	Results . . . . .	49
4.2.1	EEG Spectrum and Pain Response . . . . .	49
4.2.2	PK-PD Analysis . . . . .	50
4.3	Discussion . . . . .	57
4.3.1	Variations in Absorption Rate . . . . .	60
4.3.2	EEG Ratio as Biomarker of Opioid Effect . . . . .	60
4.4	Conclusions . . . . .	61
<b>5</b>	<b>Population Analysis of Kalman-Filtered Permutation Entropy of the Electroencephalogram<sup>§</sup></b>	<b>63</b>
5.1	Methods . . . . .	63
5.1.1	Ordinal Statistics and the Calculation of the Permutation Entropy .	63
5.1.2	Parameters and Ties . . . . .	65
5.1.3	Application to Real EEG signals . . . . .	66
5.1.4	PK-PD Modeling . . . . .	67

<sup>†</sup> E Olofsen, A Dahan, *F1000Research* 2015; 2:71

<sup>‡</sup> A E Olesen, E Olofsen, T Andresen, C Graversen, A M Drewes, A Dahan, *Anesth Analg* 2015; 121:1165–1175

<sup>§</sup> Parts have been published in E Olofsen, J W Sleigh, A Dahan, *Br J Anaesth* 2008; 101:810–821, 2008, and E Olofsen, *PAGE* 2011: Abstract #2202

5.1.5 Two Extended Kalman Filters . . . . .	68
5.1.6 Simulation Study . . . . .	69
5.2 Results . . . . .	69
5.2.1 Application to Real EEG signals . . . . .	69
5.2.2 Simulation Study . . . . .	73
5.3 Discussion . . . . .	74
<b>6 Arterial and Venous Pharmacokinetics of Morphine-6-Glucuronide and Impact of Sampling Site on Pharmacodynamic Parameter Estimates<sup>¶</sup></b>	<b>77</b>
6.1 Methods . . . . .	78
6.1.1 Subjects . . . . .	78
6.1.2 Study Design . . . . .	78
6.1.3 Pharmacokinetic Analysis . . . . .	78
6.1.4 Simulation Studies . . . . .	79
6.2 Results . . . . .	81
6.3 Discussion . . . . .	86
6.A Appendix: Linking Venous Compartments . . . . .	87
<b>7 Summary and Conclusions</b>	<b>89</b>
7.1 Expected and Unexpected Findings . . . . .	89
7.2 The 95% Confidence Intervals of the Limits of Agreement . . . . .	89
7.3 Akaike's Information Theoretic Criterion . . . . .	90
7.4 Kalman-Filtered Concentrations and Measures of Analgesia . . . . .	90
7.5 Kalman-Filtered Surrogate EEG Measures of Anesthesia . . . . .	91
7.6 Sampling Site Bias . . . . .	91
7.7 NONMEM: User, stop. Stop, will you? Stop, User. Will you stop User? Stop, User. <sup>¶</sup> . . . . .	92
<b>Bibliography</b>	<b>92</b>
<b>Addenda</b>	<b>101</b>
Samenvatting . . . . .	101
Curriculum Vitae . . . . .	107
List of Publications . . . . .	109

<sup>¶</sup> E Olofsen, R Mooren, E van Dorp, L Aarts, T Smith, J den Hartigh, A Dahan, *Anesth Analg* 2010; 111:626-632

<sup>¶</sup> Adapted quote of HAL (<http://www.imdb.com/title/tt0062622/quotes>)

