# Application of Artificial Neural Networks in Pharmacokinetics

**By**

**Joseph Vernon Turner**

**A thesis submitted in fulfilment of**
**the requirements for the degree of**
**Doctor of Philosophy**


**Faculty of Pharmacy**
**The University of Sydney**

March 2003

## Preface

The work described in this thesis was carried out in the Faculty of Pharmacy, The University of Sydney, under the supervision of Assoc Prof Hak-Kim Chan, Dr Desmond J Maddalena, Dr Snezana Agatonovic-Kustrin, and Dr David Cutler. This thesis has not been submitted for a degree at any other university. Full acknowledgement has been made where the work of others has been cited or used. A list of publications is included in support of this thesis.

*Joseph V Turner*

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# Acknowledgments

I wish first to acknowledge the support of my supervisors during the course of this work. I thank Dr David J Cutler for giving me the opportunity to commence my PhD and for his expert guidance over the first three years of this research. I acknowledge the assistance of Assoc Prof Hak-Kim Chan for assuming my supervision after that time. I am sincerely grateful to Dr Desmond J Maddalena for his continuing support over the entirety of this work. Thank you Des for your breadth, encouragement and friendship. Finally, I am indebted to Dr Snezana Agatonovic-Kustrin for her pivotal role in this work. Thank you Nena for your energy, enthusiasm and scientific direction.

I gratefully acknowledge the financial support provided by the Faculty of Pharmacy, The University of Sydney, for the first three years of my candidature.

A number of people past and present of the Faculty of Pharmacy, particularly in Pharmaceutics, have made this a valuable learning experience for me. I especially thank Dr Mahboubeh Hosseini Yeganeh and Dr Lucy DN Sasongko for their welcome friendship and support. Thanks also to Mr Jimmy Xuemin Jiang, Elaine YK Blair, and the number of other students who contributed to our lab N412.

Scientific assistance was provided by Assoc Prof Ian Spence, Mr Mostafa Hosseini, Mr Slade T Matthews, and Dr Jane R Hanrahan, for which I am very grateful.

Many friends have played an integral role in helping me get through this PhD. I express my appreciation to those of you with whom I have lived, played hockey, done gymnastics, ridden bikes, shared and laughed. Each experience rewarding.

Finally, I profoundly thank my parents Vernon and Theresia, my sister Kathleen, and my little brother Damien. You have been my rock and my hope, and your inspiration has carried me so far. This is for you Mum and Dad.

## Publications in Support of this Thesis

Turner JV, Maddalena DJ, Cutler DJ and Agatonovic-Kustrin S (2003). Multiple pharmacokinetic parameter prediction for a series of cephalosporins. *Journal of Pharmaceutical Sciences*, 92(3): 518-525.

Turner JV, Cutler DJ, Spence I and Maddalena DJ (2003). Selective descriptor pruning for QSAR/QSPR studies using artificial neural networks. *Journal of Computational Chemistry*, 24(7):891-897.

Turner JV, Glass BD and Agatonovic-Kustrin S (2003). Prediction of drug bioavailability based on molecular structure. *Analytica Chimica Acta*, 485(1):89-102.

Turner JV, Maddalena DJ and Agatonovic-Kustrin S (in press). Bioavailability prediction based on molecular structure for a diverse series of drugs. *Pharmaceutical Research*.

## Manuscripts Submitted for Publication

Turner JV, Maddalena DJ and Cutler DJ . Pharmacokinetic parameter prediction from drug structure using artificial neural networks.

# Presentations at Scientific Meetings

Turner JV, Maddalena DJ and Agatonovic-Kustrin S. Prediction of bioavailability based on molecular structure. Australasian Pharmaceutical Science Association (APSA) Annual Conference – Melbourne, December 2002. Podium. Abstract p. 99.

Turner JV, Agatonovic-Kustrin S, Maddalena DJ and Cutler DJ. Multiple pharmacokinetic parameter prediction using artificial neural networks. American Association of Pharmaceutical Scientists (AAPS) Annual Conference and Exposition – Toronto, Canada, November 2002. Poster. Abstract published *AAPSPharmSci*, 4(4):T3221 (2002).

Turner JV, Cutler DJ and Maddalena DJ. Prediction of β-adrenoceptor antagonist pharmacokinetics from molecular descriptors using artificial neural networks. The University of Sydney Third College of Health Sciences (CoHS) Research Conference – Leura, September 2002. Miniposter/ Podium. Abstract 27-3.

Turner JV, Agatonovic-Kustrin S, Maddalena DJ and Cutler DJ. Predicting the pharmacokinetics of antibiotics in humans using artificial neural networks. Australian Society for Medical Research (ASMR) Annual Meeting – Sydney, June 2002. Poster. Abstract p. 91.

Turner JV, Cutler DJ and Maddalena DJ. Artificial neural network prediction of pharmacokinetic parameters using descriptors generated from the molecular graph. Australasian Pharmaceutical Science Association (APSA) Annual Conference – Melbourne, December 2001. Podium. Abstract p. 72.

Turner JV, Cutler DJ and Maddalena DJ. Artificial neural network prediction of pharmacokinetic parameters using simple atomic descriptors. Australasian Pharmaceutical Science Association (APSA) Annual Conference – Newcastle, December 2000. Poster. Abstract 89, p. 65.

Turner JV, Cutler DJ and Maddalena DJ. Simple atomic descriptors for artificial neural network prediction of pharmacokinetic parameters. The University of Sydney Second College of Health Sciences (CoHS) Research Conference – Leura, November 2000. Miniposter/Podium. Abstract 25-2.

# Abbreviations

| | |
|---|---|
| 1D | one-dimensional |
| 2D | two-dimensional |
| 3D | three-dimensional |
| ADME | absorption, distribution, metabolism, excretion |
| AI | artificial intelligence |
| ANN | artificial neural network |
| AS | artificial structured |
| $C_A$ | arterial drug concentration |
| $C_b$ | concentration of drug in body |
| CD | compact disc |
| $CL$ | clearance (total) |
| $CL_{NR}$ | clearance (nonrenal) |
| clog $P$ | calculated log $P$ |
| $CL_R$ | clearance (renal) |
| $C_p$ | concentration of drug in plasma |
| $C_t$ | concentration of drug in tissue |
| $C_V$ | venous drug concentration |
| CYP | cytochrome P450 |
| $D_b$ | amount of drug in the body |
| ER | efficiency ratio |
| $ER$ | extraction ratio |
| $f_b$ | fraction bound to plasma proteins |
| $f_e$ | fraction excreted in urine |
| GA | genetic algorithm |
| GI | gastrointestinal |
| GNN | genetic neural network |
| HLB | hydrophilic-lipophilic balance |
| HOMO | highest occupied molecular orbital |
| HT | high-throughput |
| ICRMW | inverse cube-root of molecular weight |
| ISRMW | inverse square-root of molecular weight |
| LFER | linear free energy related |
| LOO | leave-one-out |

| | |
|---|---|
| LUMO | lowest unoccupied molecular orbital |
| MLP | multilayer perceptron |
| MLR | multilinear regression |
| MR | molar refractivity |
| MW | molecular weight |
| NCE | new chemical entity |
| PBPK | physiologically-based pharmacokinetic |
| PSA | polar surface area |
| $P_{t:b}$ | tissue/blood partition coefficient |
| $P_{t:p}$ | tissue/plasma partition coefficient |
| $Q$ | blood flow |
| QSAR | quantitative structure-activity relationship |
| QSPkR | quantitative structure-pharmacokinetic relationship |
| QSPR | quantitative structure-property relationship |
| $r_{cv}$ | cross-validation correlation |
| RBF | radial-basis function |
| RMS | root mean squared |
| $r_t$ | training correlation |
| $r_{tes}$ | testing correlation |
| $r_{val}$ | validation correlation |
| S:N | signal to noise ratio |
| SD | standard deviation |
| SOM | self-organising map |
| SPR | structure-property relationship |
| SWR | stepwise regression |
| $t_{½}$ | half life |
| $V_{ss}$ | volume of distribution at steady state |
| WDI | World Drug Index |
| $w_{meaningful}$ | meaningful weight value |
| $w_{meaningless}$ | meaningless weight value |

# Abstract

Drug development is a long and expensive process. It is often not until potential drug candidates are administered to humans that accurate quantification of their pharmacokinetic characteristics is achieved. The goal of developing quantitative structure-pharmacokinetic relationships (QSPkRs) is to relate the molecular structure of a chemical entity with its pharmacokinetic characteristics. In this thesis artificial neural networks (ANNs) were used to construct *in silico* predictive QSPkRs for various pharmacokinetic parameters using different drug data sets.

Drug pharmacokinetic data for all studies were taken from the literature. Information for model construction was extracted from drug molecular structure. Numerous theoretical descriptors were generated from drug structure ranging from simple constitutional and functional group counts to complex 3D quantum chemical numbers. Subsets of descriptors were selected which best modeled the target pharmacokinetic parameter(s).

Using manual selective pruning, QSPkRs for physiological clearances, volumes of distribution, and fraction bound to plasma proteins were developed for a series of β-adrenoceptor antagonists. All optimum ANN models had training and cross-validation correlations close to unity, while testing was performed with an independent set of compounds. In most cases the ANN models developed performed better than other published ANN models for the same drug data set.

The ability of ANNs to develop QSPkRs with multiple target outputs was investigated for a series of cephalosporins. Multilayer perceptron ANN models

were constructed for prediction of half life, volume of distribution, clearances (whole body and renal), fraction excreted in the urine, and fraction bound to plasma proteins. The optimum model was well able to differentiate compounds in a qualitative manner while quantitative predictions were mostly in agreement with observed literature values. The ability to make simultaneous predictions of important pharmacokinetic properties of a compound made this a valuable model.

A radial-basis function ANN was employed to construct a quantitative structure-bioavailability relationship for a large, structurally diverse series of compounds. The optimum model contained descriptors encoding constitutional through to conformation dependent solubility characteristics. Prediction of bioavailability for the independent testing set were generally close to observed values. Furthermore, the optimum model provided a good qualitative tool for differentiating between drugs with either low or high experimental bioavailability.

QSPkR models constructed with ANNs were compared with multilinear regression models. ANN models were shown to be more effective at selecting a suitable subset of descriptors to model a given pharmacokinetic parameter. They also gave more accurate predictions than multilinear regression equations.

This thesis presents work which supports the use of ANNs in pharmacokinetic modeling. Successful QSPkRs were constructed using different combinations of theoretically-derived descriptors and model optimisation techniques. The results demonstrate that ANNs provide a valuable modeling tool that may be useful in drug discovery and development.