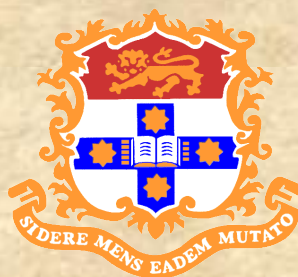


Application of Artificial Neural Networks in Pharmacokinetics

By

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



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

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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)
$\text{clog } P$	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
$t_{1/2}$	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.