Predicting hERG Potassium Channel Affinity with Artificial Neural Network Ensembles

Adam C. Lee, Grazyna Fraczkiewicz, Robert Fraczkiewicz, Robert D. Clark, and Walter S. Woltosz

Simulations Plus, Inc., 42505 10th Street West, Lancaster, CA 93534, USA (www.simulations-plus.com)

Introduction

Modeling hERG inhibition has gained significant popularity since 2005, when the FDA recognized the correlation between hERG inhibition and a prolonged QT interval by issuing guidance for the evaluation of new non-antiarrhythmic drugs against the hERG channel. Long QT syndrome or LQTS is a risk factor for ventricular tachyarrhythmias and sudden death.

Here we present the evolution of our hERG inhibition model in consecutive releases of ADMET Predictor™. Examples detailing the impact of new and evolving descriptors on a TOX hERG's applicability domain and performance on internal and external data are provided. Focus is given to a particularly interesting case where an earlier release of ADMET Predictor outperformed its successor on a client's proprietary data. Finally, we discuss how we are improving model selection criteria through the use of descriptor sensitivity analysis with artificial neural network ensembles in combination with a better understanding of the model's applicability domain, based on the World Drug Index.

ECG and Cardiac Action Potential

Inhibition of If (delayed rectifier current) correlates with LQTS


Model Performance for ADMET Predictor v. 3.0–5.5

The training and test sets of v4.0 and v5.0 are equivalent. Nine of the ten metrics measuring the test set in v5.0 are constant vs v4.0 and v3.0.

An external data set from a large pharmaceutical company: patch clamp measurements on HEK293 cells transfected with hERG

Model Selection & Conclusions

Model selection occurs using a combination the following normalized elements:

Take home messages:
1. Model selection criteria play a vital part when selecting a useful model
2. Two criteria that often go overlooked
   a. balanced statistics between the training/test sets
   b. understanding of the overall applicability domain
3. When selecting models, especially those built from a small training set, it pays dividends to focus on and maximize the applicability domain.
4. Manual patch clamp measurements produce the highest quality hERG data, but useful insights was gained by including data from displacement assays

Training Set Effects

The data used to construct our earlier hERG inhibition models (v3.0–5.0) were restricted to values obtained by patch clamp studies on mammalian cell lines composed primarily of human embryonic kidney (HEK) cell lines. We hypothesized that expanding that bias would improve the model performance on external data (HEK293).

That hypothesis was tested by building new models for version 5.5 using data sets consisting of measurements for patch clamp assays alone or in combination with values obtained by displacement assay (e.g., of [3H]-dofetilide), which have been shown to correlate well with patch clamp results (Murphy, S.M. J. Pharm. Tox. Meth. 2006, 54, 42-55).

The figures and table below show results for models based on earlier versions of ADMET Predictor as well as for three different combinations of data types, denoted “HEK Patch Clamp,” “Mammalian 1” and “Mammalian 2”: HEK Patch Clamp vs Mammalian 1 vs Mammalian 2.

Comparison of Descriptors and Model Architectures v3.0–5.0

Although different descriptor selection methods were used when building the models with ADMET Predictor v3.0 (Genetic Algorithm) and v4.0-5.0 (Input Gradient), five descriptors were common to each model and the first four ranked among the top 8 descriptors according to our descriptor sensitivity analysis.

1. (Topological) Distance between the center of mass and the most distant atom
2. (Atomization) Fraction of aromatic rings in ionization states with no net charge
3. (Ionization) Absolute value of the average across all cationic species of the net formal negative charge
4. (Constitutional) Number of amide groups
5. (Constitutional) Number of distinct m-systems, excluding lone pairs

Model Neurons Common Descriptors

v5.0 2 6 11 19
v4.0 2 7 18 11
v3.0 0 1 19 1

Network architectures are defined by the number of neurons present and the number of inputs (descriptors) used. # of weights = neurons*(inputs+2) +1

TOX hERG Applicability Domain and WDI

% Data Outside the Applicability Domain

Model

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