Rational Bioavailability Design

Optimizing Bioavailability during Lead Optimization with Global Sensitivity Analysis of Physiologically-Based Pharmacokinetic Simulations

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Drug Discovery & Development

About 60-80% of animal studies conducted during Lead Opt

Lead ID and Lead Opt together contribute ~32-35% towards the total cost
Lead Optimization

Chemists manipulate various properties to improve Drugability

Characterisation of promising candidate medicines

Lead identification | Lead optimisation

studied (example)
1000  |  200

Proportion of Animals Used

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Improving Binding Affinity and Potency

Absorption
Permeability
Solubility
Ionizability
Lipophilicity

Distribution
Plasma Protein Binding
Volume of Distribution

Elimination
Intrinsic Clearance
Renal Excretion
Biliary Excretion

%F & Drug-Exposure
PBPK Models may Prove to be most Informative to Optimization

Model inputs are the properties med chemists can optimize

Allometric Scaling

Traditional Pharmacokinetic Model

Compartmental and non-compartmental PK analysis, \textit{in vivo} data modeled \textit{a posteriori}

After animal experiments

QSAR/QSPR

Physiologically-Based Pharmacokinetic Model

Integrate \textit{in silico} and \textit{in vitro}
For Lead Optimization, we must optimize for entire med Chem series

• Typically applied to a few advanced compounds
  – Prioritize expensive animal studies or predict human dose
  – Usually based mainly on experimental inputs
  – Broader studies require global QSAR models
  – Sometimes includes local sensitivity analysis

• Lead optimization requires tuning for entire series
  – Requires global sensitivity analysis (GSA)
  – All inputs calculated from structure
  – These can be local QSAR models
Our Approach Applies GSA to PBPK Modeling

First step is to show reliable results for a congeneric series

1. Select the parameters (measured or predicted)
2. GastroPlus simulations for active med-Chem series
3. Predict the %F and exposure
4. Sample the active property space
5. GastroPlus simulations for sampled points
6. Identify the most sensitive parameters, those affect the %F
7. Lead optimization with emphasis on the identified sensitive parameters

Physicochemical and Biochemical properties:
- Permeability
- Solubility
- Ionizability
- Clearance
- Hydrophobicity
- Protein Binding

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Case Study #1: Dipeptidyl Peptidase-4 Inhibitors

Trouble with Clearance can be overcome by fitted CL

- 49 Compounds: Single congeneric series reported by Merck in various papers
  - RAT in vivo data: %F, CLp
  - Physicochemical prop & in vitro data: --
Case Study #1: Dipeptidyl Peptidase-4 Inhibitors

Trouble with Clearance can be overcome by fitted CL

- 49 Compounds: Single congeneric series reported by Merck in various papers
  - RAT in vivo data: %F, Clp
  - Physicochemical prop & in vitro data: --
Case Study #2: 11\(\beta\)-HSD1 Inhibitors

Hepatocyte CL provides accurate estimate of CL and hence %F

- 81 Compounds: Single congeneric series reported by AstraZeneca in 4 papers
  - RAT in vivo data: %F, CL\(_p\)
  - in vitro data: CL\(_{\text{int(hep)}}\)
Case Study #3: Internal Kinase-“X” Inhibitor series

**In silico inputs are adequate for GSA**

- **61 compounds**: Single congeneric series with experimental data
  - Physicochemical prop & *in vitro* data: (Solubility, Caco2 permeability, Plasma Protein binding, CL\text{int})
  - RAT PK data (%F, AUC, C\text{max}, T\text{max}, CL\text{plasma}, V\text{ss})

![Graphs showing predicted vs measured F (%) for different CL parameters](Image)

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Our Approach can be used Early in Lead Optimization

Kinase Dataset: Chronological Predictions

Model With 18 molecules

Model With 37 molecules

Model With 55 molecules

Number of compounds used to build QSAR model is shown in parenthesis within the inner circle.
Local Models OK w/ only ~15 Rat Data Points

*Increasing training data size, improved performance*

<table>
<thead>
<tr>
<th></th>
<th>Global</th>
<th>Local ~15</th>
<th>Local ~35</th>
<th>Local ~50</th>
<th>Local ~70</th>
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</thead>
<tbody>
<tr>
<td>Kinase-X</td>
<td>63 cpd</td>
<td>2.0 (0)</td>
<td>2.1 (18)</td>
<td>1.5 (37)</td>
<td>1.4 (55)</td>
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<tr>
<td></td>
<td></td>
<td>66 %</td>
<td>68 %</td>
<td>79 %</td>
<td>86 %</td>
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<tr>
<td>HSD1</td>
<td>81 cpd</td>
<td>2.9 (0)</td>
<td>2.6 (18)</td>
<td>1.8 (32)</td>
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<td></td>
<td></td>
<td>37 %</td>
<td>15 %</td>
<td>12 %</td>
<td>7 %</td>
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<tr>
<td>DPP-4</td>
<td>48 cpd</td>
<td>2.6 (0)</td>
<td>1.9 (30)</td>
<td>1.7 (42)</td>
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<tr>
<td></td>
<td></td>
<td>10 %</td>
<td>14 %</td>
<td>14 %</td>
<td>12 %</td>
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</table>

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GastroPlus Adapted to %F Prediction for Congeneric Series

**Second step: Global Sensitivity Analysis finds key properties**

1. Select the parameters (measured or predicted)

**Physicochemical and Biochemical properties:**
- Permeability
- Solubility
- Ionizability
- Clearance
- Hydrophobicity
- Protein Binding

2. GastroPlus simulations for active med-Chem series

3. Predict the %F and exposure

4. Sample the active property space

5. GastroPlus simulations for sampled points

6. Identify the most sensitive parameters, those affect the %F

7. Lead optimization with emphasis on the identified sensitive parameters
GSA is Similar to “Design of Experiments”

Instead of 2/3 levels of parameters, we use continuous data

<table>
<thead>
<tr>
<th>Design of Expt</th>
<th>Global Sensitivity Analysis</th>
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<tbody>
<tr>
<td><strong>Temp</strong></td>
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<td><strong>Volume</strong></td>
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<td><strong>Yield</strong></td>
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<td><strong>Run1</strong></td>
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<td><strong>Run2</strong></td>
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<td><strong>Run3</strong></td>
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<td><strong>Run4</strong></td>
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<td><strong>Run13</strong></td>
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</table>
Difficulties Encountered: Applying GSA to PBPK

1. Two pKa’s are adequate to predict accurate pH-Solubility profile

- Two pKa values sandwiching the Isoelectric pH

Allows alignment of pKa’s in GSA and simplifies message to med chemists
Difficulties Encountered: Applying GSA to PBPK (cntd..)

2. Don’t sample impossible property combinations

- Can't use Fourier Amplitude Sensitivity Testing (FAST) or other standard algorithms
- Property sampling points can result in inaccessible combinations by selected series of compounds
Workflow for Sampling Valid Property-Space

Properties from “Drug-like” molecule DB avoids impossible combinations

Simulation using only physicochemical properties, no structural information provided

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What can we Achieve with GSA-PLS Models?

1. To find sensitive properties and their contribution
2. Faster prediction of %F of new compounds (virtual libraries of large number of cmpds)
3. Bioavailability landscape around specific compounds
Results are Unique for Each Series

**Bioavailability (%F)**

- **Kinase-X**
- **11β-HSD1**
- **DPP-4**

**Fraction Absorbed (%Fa)**

- **Sw, pKa2**
- **Sw, Sw**
- **LogP, Sw**
- **Peff, Sw**
- **Peff, LogP**
- **Peff, Peff**
- **Sw**
- **LogP**
- **Peff**

- **Fup, pKa1**
- **Fup, Sw**
- **Fup, LogP**
- **Peff, pKa1**
- **Peff, Fup**
- **Peff, Sw**
- **Peff, LogP**
- **Peff, Peff**
- **pKa1**
- **Fup**
- **Sw**
- **LogP**
- **Peff**
High-Throughput Prediction of %F

%F predicted by PLS models is comparable to G+ prediction (Kinase-X)

The deviation from the line of unity can be attributed to the error in the PLS model.

The series-specific PLS model built using only 8 PC properties:
1. Sol
2. Human Peff
3. A-pKa
4. B-pKa
5. RBP
6. CL_{loc}
7. Fup
8. LogP
Specific Recommendations for Individual Compound

LogP, LogP

CLint
RBP
LogP
Peff

-1.0 -0.5 0.0 0.5 1.0

Only LogP
NVP-XXX000

Only Peff
NVP-XXX001

LogP & Peff Both
NVP-XXX002

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Application in Lead Optimization and Design of New Cmpds

Apply evolutionary algorithm & multi-parameter optimization (activity & prop’s)
Sampling/Library Generation & %F Prediction

Entire workflow can be run within ADMET Predictor 8.5

ADMET Predictor 8.5
- R Group Explosion
- R List explosion
- Combinatorial Library
Conclusions

• PBPK modeling can be successfully used in lead optimization phase
• Use of Intrinsic Clearance, but not plasma clearance results in accurate estimate of %F
  – Using $\text{CL}_{\text{loc}}$, accurate bioavailability can be predicted for new compounds in a chemical series
• *in silico* predictions can be successfully used in absence of measured input properties (new molecules)
• GSA identifies sensitive properties (medchem series specific)
• The approach can be used in early stage of lead optimization
  – Even with 15-18 molecules with Rat PK data
• Sensitive properties can guide molecular design
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• John DiBella
• Walter S. Woltosz

Thousands of “Rats” who sacrificed their lives for betterment of human health
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