Guided Application of Med Chem Rules to Generate ‘Good’ Ideas

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Overview

• Generating compound ideas
  – Stimulating the search for high quality compounds

• Defining ‘good’
  – Searching for a balance of properties

• Example application
  – Lead to drug

• Conclusions
Generating Compound Ideas
Stimulating the search for high quality compounds
A New Generation of Possibilities

• Traditionally have a scarcity of data
  – Time consuming and expensive to generate data
  – Easy to think of more ideas than can be synthesised and tested
  – Manually analyse all of the available data to select compounds

• With predictive models and ‘multi-parameter optimisation’, it is easy to evaluate very large numbers of ideas

• New scenario – scarcity of ideas
  – Limited by an individual’s ability to conceive and input new ideas

• Generate new ideas to stimulate exploration of chemistry
  – *In silico* analysis helps to prioritise ideas for detailed consideration
Generating Compound Ideas
Applying Med. Chem. ‘Transformation Rules’

• Compounds generated must ‘make sense’ from a medicinal chemistry perspective

• Apply ‘transformation rules’, derived from medicinal chemistry experience, to initial compound*
  – Library of >200 transformation
  – Not only functional group replacement but also framework transformations

Validation of Transformation Set

• Applied to a set of 3211 small molecule drugs
  – Downloaded from DrugBank (www.drugbank.org.ca)

• Generally applicable
  – Each transformation applied to 31% of drugs on average

• Generate wide range of ideas
  – Average of 182 new compounds generated per drug

• Chemical relevant
  – 1500 randomly selected generated compounds inspected visually by medicinal chemists
  – Average of >94% of compounds were acceptable (range 93% – 95.6%)
Iterative Application

Exponential Growth!
Controlling the Process

- Specify initial structure
- A region can be selected to be fixed (no changes allowed)
- Select transformations to apply
- Transformations can be managed for specific objectives
- Apply multiple generations of transformations
- Bias selection in favour of property or score
- Oral CNS Scoring Profile
- High
- Generations: 1
- Selection:
  - Property: Oral CNS Scoring Profile
  - High
  - Method:
    - Threshold: 0.0
    - Number: 50
    - Percentage: 50

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Prioritise Ideas for Detailed Consideration
Defining ‘Good’
Searching for a balance of properties
The Objectives

• Identify chemistries with an optimal **balance** of properties

• Quickly identify situations when such a balance is not possible
  – Fail fast, fail cheap
  – Only when **confident**
Balancing Properties
Defining your objectives

<table>
<thead>
<tr>
<th>Property</th>
<th>Desired Value</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>NK2 pKi</td>
<td>8 -&gt; inf</td>
<td></td>
</tr>
<tr>
<td>log5</td>
<td>&gt; 1</td>
<td></td>
</tr>
<tr>
<td>HIA category</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>logP</td>
<td>0 -&gt; 5</td>
<td></td>
</tr>
<tr>
<td>hERG pIC50</td>
<td>&lt;= 5</td>
<td></td>
</tr>
<tr>
<td>2C9 pKi</td>
<td>&lt;= 6</td>
<td></td>
</tr>
<tr>
<td>2D6 affinity category</td>
<td>low medium</td>
<td></td>
</tr>
<tr>
<td>PPB category</td>
<td>low</td>
<td></td>
</tr>
<tr>
<td>BBB category</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>BBB log([brain]:[blood])</td>
<td>&lt;= -0.5</td>
<td></td>
</tr>
</tbody>
</table>

Importance of Uncertainty

Desired value > Threshold

Property Y

UNDESIRABLE

DESI RABLE

A  B  C

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Importance of Uncertainty

Desired value > Threshold

Property Z

UNDESIRABLE

DESIABLE
StarDrop Prioritisation: Probabilistic Scoring

- **Property data**
  - Experimental or predicted

- **Criteria for success**
  - Relative importance

- **Uncertainties in data**
  - Experimental or statistical

- **Score (Likelihood of Success)**
- **Confidence in score**

Error bars show confidence in overall score. Bottom 50% may be rejected with confidence, as error bars overlap.
Balancing Quality and Diversity
Chemical Space
Example Application
Lead to Drug
Example Application
Duloxetine Lead

• Goal:
  – Orally available serotonin reuptake inhibitor

• 172 compounds in first generation
  – 3 generations ~1.7M compounds!
  – Used only top 10% of each

• Prioritised with respect to following profile

<table>
<thead>
<tr>
<th>Property</th>
<th>Desired Value</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotonin Transporter (log Kᵢ)</td>
<td>≤ 1</td>
<td></td>
</tr>
<tr>
<td>log5</td>
<td>&gt; 1</td>
<td></td>
</tr>
<tr>
<td>HIA category</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>BBB log([brain]:[blood])</td>
<td>-0.2 -&gt; 1</td>
<td></td>
</tr>
<tr>
<td>P-gp category</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>hERG pIC₅₀</td>
<td>≤ 6</td>
<td></td>
</tr>
<tr>
<td>2C9 pKi</td>
<td>≤ 6</td>
<td></td>
</tr>
<tr>
<td>2D6 affinity category</td>
<td>low, medium</td>
<td></td>
</tr>
<tr>
<td>PPB category</td>
<td>low</td>
<td></td>
</tr>
</tbody>
</table>
Results

Snake plot

Score Distribution by Generation

Score

Compounds ordered by score

Duloxetine
Summary of Results

• Duloxetine is among top-scoring compounds
  - Statistically equivalent to best compound
  - ~86% confident better than lead

• Top ranked compounds:
  - ~94% confident better than lead
  - c.f. Litoxetine
Explores a Diverse Range of Solutions
Conclusions

• A robust approach to guiding decisions on compound selection and design must take into account:
  − Multiple criteria with different degrees of importance
  − Uncertainty in the underlying data
  − A balance of diversity and ‘quality’

• Coupled with automated idea generation can stimulate the search for high quality compounds
  − Rigorously explore chemistry around new hits
  − Generate new strategies to improve properties
  − Identify patent busting possibilities

• Encode new transformation rules to capture and transfer knowledge
  − Personal experience or in-house chemistries
  − Define groups of transformations tailored to specific objectives

• More information:
  − www.optibrium.com
  − matt.segall@optibrium.com
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