Use of AI & ML in Discovery Toxicology

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Machine Intelligence for Quantitative Modeling in Drug Discovery & Development Applications:
16 September 2022
1. What is the problem we are trying to solve?
2. Prediction of pharmacokinetics
3. The changing landscape of safety assessment
4. Applications of machine learning in early discovery toxicology
5. Imaging and toxicology & digital pathology
6. SEND and machine learning
7. Conclusions
What’s the big deal about AI?

Artificial Intelligence has the capability to transform drug discovery…

but…

We need to separate reality from the hype!
The Challenges of Drug Discovery

Complex Disease Targets
Not Sufficiently Selective

Too Long in Body

Adverse Reactions

Poor Absorption

Low Levels in Body

Not Effective Enough

Most Molecules
Do Not Become
Medicines

Side Effects
Unsafe
Unstable
Competition
Impractical To Make
Therapeutic index is often uncertain at candidate nomination

- Efficacy = $f$(potency, exposure)
- Safety = $f$(hazard, exposure)
- Safety and efficacy of a drug is fixed by its dose
- The dose gives a specific time vs concentration curve
- This is solely a property of the molecule selected

Muller & Milton (2012). Nat Rev Drug Discovery
An AI model to predict rat PK

~4000 compounds with *in vivo* rat PK

**Multi-task GCNs**

- Clearance (CL)
- Bioavailability (%F)
- $C_{\text{max}}$
- Half-life ($t_{1/2}$)
- Volume ($V_{ss}$)

**AI model predicts from chemical structure and measured *in vitro* ADME properties**

- Chemical structure is encoded by graph convolutional neural network (GCN)
- *In vitro* ADME and physicochemical properties are used as input features
- *In silico* predictions are used in case of missing *in vitro* data

Yang et al. JCIM 2019
Rat PK model accuracy

Accuracy is evaluated on the test set
Metrics are in log-transformed space for CL, Vss and logit-transformed for F
R² – coefficient of determination
RMSE – root mean square error

Percentage of compounds with 2-3-5-fold error

Good accuracy achieved on key PK parameters CL, F, Vss

<table>
<thead>
<tr>
<th></th>
<th>R²</th>
<th>RMSE</th>
<th>Experimental variability</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL</td>
<td>0.57</td>
<td>0.28</td>
<td>0.18</td>
</tr>
<tr>
<td>F</td>
<td>0.48</td>
<td>0.72</td>
<td>0.55</td>
</tr>
<tr>
<td>Vss</td>
<td>0.50</td>
<td>0.28</td>
<td>0.21</td>
</tr>
</tbody>
</table>

RMSE is close to experimental variability in the data

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Human Clinical data from FDA & EMA

Human clinical data curated according to expert opinions from across the organization

Included:
- Adult healthy volunteers and oncology patients
- Single dose PK for compounds with MW ≤750 Da
- Non-tissue specific measurements

Excluded:
- Patient groups with signs of decreased PK functionality
- Incompatible assay technologies
- Concomitants with potential impact on PK
- *Plus others...*

Building a human PK model

Rat PK & in vitro predictions used as features in the model

- Random forest chosen as method after benchmarking
- Validated on both external and internal clinical data

Three models, AUC, Cmax & Vd are fit for purpose

- Putting performance in context with experimental variability
- Data distributions and availability impact model performance

External validation on FDA and EMA data

Values are log10 transformed
RMSE – root mean square error
Improving human PK predictions

- Use rat and dog PK as part of a *feature set* for modelling human PK
- Utilize power of *transfer learning* to learn from one similar task to another
The changing face of toxicology

New HT multiplexed approaches for studying the effects of molecules on a biological system

Multi-omics technologies becoming mainstream generating 100k+ data points

Data science, machine learning and AI are improving the way we analyze and use data
Common approaches to early safety assessment

- Compounds of interest are tested against a wide range of assays
- Emphasis on **Cardiovascular, Hepatic & CNS (Secondary Pharmacology)**
- High quality compounds will be inactive, or have good selectivity in the *in vitro* safety assays
- Compounds with good selectivity have an increased chance of having large safety margins (Therapeutic Index) in vivo, or in the clinic.

<table>
<thead>
<tr>
<th>Target Organ</th>
<th>Assay</th>
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</thead>
<tbody>
<tr>
<td><strong>Cardiovascular</strong></td>
<td>hERG</td>
</tr>
<tr>
<td></td>
<td>NaV1.5</td>
</tr>
<tr>
<td></td>
<td>Iks</td>
</tr>
<tr>
<td></td>
<td>Kv4.3</td>
</tr>
<tr>
<td></td>
<td>L-type calcium channel</td>
</tr>
<tr>
<td></td>
<td>Cardiomyocyte</td>
</tr>
<tr>
<td></td>
<td>Structural Cardiovascular Tox</td>
</tr>
<tr>
<td><strong>Hepatic</strong></td>
<td>Glu/Gal Mitochondrial Assay</td>
</tr>
<tr>
<td></td>
<td>High Content Mitotox assay</td>
</tr>
<tr>
<td></td>
<td>Cytotoxicity</td>
</tr>
<tr>
<td></td>
<td>Hepatic Spheroid</td>
</tr>
<tr>
<td></td>
<td>Liver Transporters (BSEP &amp; MRP2)</td>
</tr>
<tr>
<td><strong>Genetic Toxicity</strong></td>
<td>AMES Mutagenicity Test</td>
</tr>
<tr>
<td></td>
<td>In vitro Micronucleus</td>
</tr>
<tr>
<td><strong>Various</strong></td>
<td><strong>Secondary Pharmacology</strong> Panels</td>
</tr>
<tr>
<td></td>
<td>Phospholipidosis</td>
</tr>
<tr>
<td></td>
<td>AhR (CYP1a1)</td>
</tr>
</tbody>
</table>
"Every drug has two actions – the one you know about, and the one you don’t"
Sir John Gaddum 1900-1965

- The off target profile cannot be predicted by the primary therapeutic target
- 75% of adverse drug reactions (ADR) are dose-dependent and predictable from pharmacology (Type AADRs)
- All large pharma adopt broad *in vitro* profiling strategies
Machine learning approaches are improving safety readouts significantly reduce time required for data analysis and increase throughput of the assay.

### Applying machine learning to high content imaging data reveals new insights

<table>
<thead>
<tr>
<th>Interpretation and visualisation of results</th>
<th>Gain insights into data that were not previously available</th>
<th>Generate accurate, unbiased predictions</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Image 1" /></td>
<td><img src="image2.png" alt="Image 2" /></td>
<td><img src="image3.png" alt="Image 3" /></td>
</tr>
<tr>
<td>Suitable for deep learning techniques</td>
<td>Nuclear morphology alone can predict compound MOA</td>
<td>98% compounds correctly classified (Confidence &gt;80%)</td>
</tr>
</tbody>
</table>

Significantly reduce time required for data analysis and increase throughput of the assay.
New technologies for assessing hazards e.g. cell painting

Cell Painting, a high-content image-based assay for morphological profiling using multiplexed fluorescent dyes

Chandrasekaran et al. (2020)

- Cell Painting captures 5 images per cell, 100s of cells per well
- Rich morphological description of cellular states
High throughput imaging for safety profiling

Cell Painting enables compound scoring

...enables chemical clustering

...enables safety prediction

Uniform manifold approximation (UMAP) analysis

UMAP analysis with Mitotox annotation (HepG2 Galactose IC50)
Multi-omics technologies create a “data avalanche”

• Multi-omics allow for the generation of tens of thousands of data points per sample

• Machine learning approaches enable the digestion and use of high dimensional data sets

• Predictions of liver injury across a range of exposures enables the determination of a “safe” dose
<table>
<thead>
<tr>
<th></th>
<th>Human assessment</th>
<th>AI-based assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complexity</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Training Time</td>
<td>years</td>
<td>days</td>
</tr>
<tr>
<td>Time</td>
<td>20min</td>
<td>seconds</td>
</tr>
<tr>
<td>Error rate</td>
<td>10-20%</td>
<td>0.65%</td>
</tr>
</tbody>
</table>
Advanced imaging is changing the way we can understand disease and evaluate drug safety
Standard for Exchange of Nonclinical Data (SEND)

- Nonclinical data standard developed by Clinical Data Interchange Standards Consortium (CDISC)
- Guide for organization, structure and format of electronic data files
- Data for individual/pooled animals
- SEND became a requirement for submissions to the FDA for studies started on or after:
  - 18th December 2016 for NDA, and
  - 18th December 2017 for IND

2.3 THE SENDIG STANDARD DOMAIN MODELS

The following standard domains with their respective domain codes have been defined or referenced by the CDISC SEND Team in this document:

Special-Purpose Domains (Section 5)
- Demographics – DM
- Subject Elements – SE
- Comments – CO

Interventions General Observation Class (Section 6.1)
- Exposure – EX
- Disposition – DS
- Organ Measurements – OM
- Palpable Masses – PM
- Pharmacokinetics Concentrations – PC
- Pharmacokinetics Parameters – PP
- Subject Characteristics – SC
- Tumor Findings – TF
- Vital Signs – VS
- ECG Test Results – EG

Events General Observation Class (Section 6.2)
- Body Weights – BW
- Body Weight Gains – BG
- Clinical Observations – CL
- Death Diagnosis – DD
- Food and Water Consumption – FW
- Laboratory Test Results – LB
- Macroscopic Findings – MA
- Microscopic Findings – MI
- Trial Sets – TX
- Trial Summary – TS
- Pooling – POOLDEF

Findings General Observation Class (Section 6.3)
- Organ Measurements – OM
- Palpable Masses – PM
- Pharmacokinetics Concentrations – PC
- Pharmacokinetics Parameters – PP
- Subject Characteristics – SC
- Tumor Findings – TF
- Vital Signs – VS
- ECG Test Results – EG

Trial Design Domains (Section 7)
- Trial Elements – TE
- Trial Arms – TA
- Relationship Datasets (Section 8)
  - Supplemental Qualifiers – SUPP--datasets
  - Related Records – RELREC

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SEND data harmonization is challenging

Before using SEND formatted data, it requires extensive harmonization:

- Unit standardization
- Correcting misspellings
- Grouping of similar terms
- Removing low frequency terms
- Removing rows with missing data in important columns
Example: Histopathology (MI domain) data challenges

- It is hard for non-experts to know which of these terms have the same meaning
- Are any terms meaningless in toxicity context?
  - E.g., PIGMENTED MACROPHAGE
- Other organs have similar situation

Example: male rat heart findings

<table>
<thead>
<tr>
<th>Term</th>
<th>Count</th>
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</thead>
<tbody>
<tr>
<td>NORMAL</td>
<td>612</td>
</tr>
<tr>
<td>UNREMARKABLE</td>
<td>257</td>
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<tr>
<td>INFILTRATION, MONONUCLEAR CELL</td>
<td>30</td>
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<tr>
<td>DEGENERATION/NECROSIS</td>
<td>18</td>
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<tr>
<td>INFILTRATE</td>
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<tr>
<td>CARDIOMYOPATHY</td>
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<tr>
<td>NECROSIS/INFLAMMATORY CELL INFILTRATE,</td>
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<tr>
<td>CARDIOMYOCYTE</td>
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<tr>
<td>MINERALIZATION</td>
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<tr>
<td>NECROSIS</td>
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<td>INFILTRATE, INFLAMMATORY CELL, MYOCARDIUM</td>
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<td>MONONUCLEAR CELL INFILTRATE/FIBROSIS</td>
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<tr>
<td>INFLAMMATION, EPICARDIUM</td>
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<tr>
<td>PIGMENTED MACROPHAGE</td>
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<tr>
<td>INFLAMMATION, MONONUCLEAR CELL</td>
<td>1</td>
</tr>
</tbody>
</table>

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ML models enable efficient compound design

Integrated into Augmented Drug Design tools to improve speed and efficiency in DMTA cycle

Help design compounds with better safety and PK properties early in drug discovery

Modelling human PK gives confidence in preclinical translation to the patient
Why is now the time for change?

“Artificial intelligence will not replace scientists, but those who don’t use AI will be replaced by those who do.”
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