Practical Applications of Deep Learning to Imputation of Drug Discovery Data

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Overview

- **Problems** with pharma data:
  - Define solutions to these problems

- **Alchemite**: A novel deep learning algorithm for *imputation*
  - *Imputation* = *Filling in the blanks*

- **Walkthrough** deep learning imputation on a **real project**:
  - Early screen data
  - Validation
  - Late stage models
  - Comparison with standard QSAR methods

- Larger applications and **future prospects**
Imputation goes beyond QSAR!

- QSAR
- Imputation
- e.g. Random forest

Alchemite
Problems with Pharma Data
Problems with Pharma Data

For a machine learning method to be *practically* useful in QSAR it should handle:

<table>
<thead>
<tr>
<th>Missing Values</th>
<th>Noisy Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple Endpoints</td>
<td>Data Changing with Time</td>
</tr>
</tbody>
</table>
**Missing Values**

- **Problem:**
  - Most algorithms cannot handle missing inputs
  - \( y = f(x_1, ? , x_3, x_4, ?) \)
  - Simple methods to impute give poor quality results e.g. imputation via mean
  - \( y \neq f(x_1, \overline{x}_2, x_3, x_4, \overline{x}_5) \)

- **Solution:**
  - Algorithm should make the most of data present
  - “Fill in” the missing values with sensible predictions
Noisy Data and Confidence in Predictions

• Problem:
  − Pharma data is inherently noisy
  − Input data may not be “true”
  − Model outputs a number with no context

• Solution:
  − Input noise accounted for
  − Predictions should come with confidence values!
  − Highly confident predictions are more valuable than weak ones
  − Provide a big error bar if model doesn’t know the answer
Multiple Endpoints – One Model

• Problem:
  – Many columns in project data: can’t train a model for each one...
  – Activity IC50, EC50: protein, supersome, cell
  – Multiple targets: related, unrelated
  – (ADME) Absorption, distribution, metabolism, and excretion
  – Plasma protein binding, intrinsic clearance, CYP inhibition, permeability, solubility

• Solution:
  – One model to handle everything

(Noisy Fragmented Data)

\[ X_{ij} \]
Changing with Time

• Problem:
  − Data are evolving as project continues
  − Chemical space changes
  − Activity changes i.e. increasingly active
  − Data sparsity changes
    (more ADME, less HTS)
  − Uncertainty changes
    (new assay concentration, finer resolution)

• Solution:
  − Model which extrapolates well
  − Retraining the model as appropriate
Alchemite – A Method for Deep Multiple Imputation
Optibrium and Intellegens Collaborate to Apply Novel Deep Learning Methods to Drug Discovery

Partnership combines Intellegens’ proprietary AI technology with Optibrium’s expertise in predictive modelling and compound design

Imputation of Assay Bioactivity Data Using Deep Learning

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Supporting Information

ABSTRACT: We describe a novel deep learning neural network method and its application to impute assay pIC50 values. Unlike conventional machine learning approaches, this method is trained on sparse bioactivity data as input, typical of that found in public and commercial databases, enabling it to learn directly from correlations between activities measured in different assays. In two case studies on public domain datasets we show that the neural network method outperforms traditional quantitative structure-activity relationship (QSAR) models and other leading approaches. Furthermore, by focusing on only the most confident predictions the accuracy is increased to $R^2 > 0.9$ using our method, as compared to $R^2 = 0.84$ when reporting all predictions.

Whitehead et al.

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Alchemite – A Method for Deep Multiple Imputation

- Originally used to design new materials at the University of Cambridge, UK
  - Design alloys, identify errors in databases
  - Optimising algorithm and applying to drug discovery data

- Take solution of deep neural network $D_{NN}(\bar{x})$ under fixed point iteration
  - $D_{NN}(\bar{x}; W, \beta, \theta) = \bar{x}$, for $\bar{x}$ in training set.

A process: $G[f(\bar{x}), \bar{x}, \Theta]$

Output Predictions and Uncertainty

- Outputs a probability distribution by multiple imputation (1000’s of samples).
  - Network is very quick to train/evaluate: train thousands of networks

Predicted pIC\textsubscript{50} values

Probability

\[ \mu \text{ prediction} \]
\[ \sigma \text{ prediction} \]

Higher moments \( \gamma_1, \gamma_2, \ldots \)
Practical Application of Deep Learning to Project Data
Initial Project Data

- **Two Projects**
  - A: Completed project
  - B: Ongoing project that had recently commenced

<table>
<thead>
<tr>
<th>Project</th>
<th>No. of Cmpds.*</th>
<th>Biochemical Activity Endpoints</th>
<th>Cell-based Activity Endpoints</th>
<th>ADME Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Number</td>
<td>Sparsity (% Filled)</td>
<td>Number</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
</tbody>
</table>

Small number of additional data points for Project B compounds were measured for imputed data points after completion of the models.

* After removal of qualifiers
Overview

• Objectives
  – Compare accuracy of Alchemite model to conventional QSAR models
  – Compare models built on all data simultaneously with those built on individual projects and subsets of data
  – Evaluate Alchemite’s ability to estimate confidence in individual predictions and target the most accurate results

• Three sets of models generated:
  – Two Alchemite models of the individual project data sets
  – A single Alchemite model covering the combined activity and ADME data from both projects
  – Conventional QSAR models of the individual endpoints
    o Random forest, Gaussian processes, radial basis functions and partial least squares
Comparison of Alchemite and QSAR
Single Alchemite model of combined data set

Average $R^2$: QSAR = 0.44, Alchemite = 0.65
Single Model vs Individual Project Models

Single model performs equivalently to individual project models

* Individual project model for ADME properties built and tested on Project A only. Full data set model tested against both projects.
We then received more data on the Project B compounds.

Observed values are outside the range of the initial training set; yet, they are correctly predicted to be inactive.

New active compounds correctly identified as active.

Outlier correctly identified as the prediction with the highest uncertainty.
Identify and Discard the Least-Confident Predictions

Project B – Bioactivity 2

Increasing confidence in prediction

Increasing accuracy

Fraction of data predicted

Root Mean Square Error

- Alchemite
- Theoretical maximum/minimum
- Expected random ±1 standard deviation

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Part 1 - Conclusions

• The single Alchemite model of data for both projects, including biochemical and cell-based activities, and ADME properties significantly outperforms QSAR models

• The performance on independent and prospective test sets is very good and consistent.

• The single Alchemite model performs equivalently to models of individual projects and subsets of the data
  – Can combine data from multiple chemistries and types of endpoints in a single model

• Alchemite can target focus on the most confident and accurate results to use as the basis for decisions

• Next steps... Application to new compounds and data as project progresses
Part 2 - Temporal Prospective Validation

- Received an **additional 874 compounds** for project B
  - Sparse results from real experiments
  - Many additional ADMET datapoints

- Three blocks of temporally coordinated data, B1,2,3:
  - **Model 1**: Trained on all of the original data
  - **Model 2**: Original + B1
  - **Model 3**: Original + B1 + B2
  - Test each model on B3
Project B - Temporal Prospective Validation

Increasing Data

Average Coefficient of Determination

Model Number

Coefficient of Determination

Model Number

Activities + ADME

Mouse PPB

PAMPA Perm.

Kin. Sol.

CYP 2D6

CYP 3A4

Increasing Data
ADME Human Plasma Protein Binding: Predicting Block 3

- Initial models can tell high from low
- Quality of predictions and error models improves with more data
Example of Activity Improving

- Activity
- Good model gets better
- Last model confident identifying active compounds better than μM
Comparison of Alchemite and QSAR

Single Alchemite model of Model 3 data set

Average $R^2$

QSAR was 0.44 now 0.48

Alchemite was 0.65 now 0.72
Part 2 - Conclusions

• Alchemite: Practical application of deep learning
  - Handles missing data and makes the most of extreme levels of sparsity
  - Provides robust uncertainty estimates on predictions
  - One model trained for all project data simultaneously, exploits assay-assay correlations
  - Retrainable to handle all stages of project which changes in time

• Alchemite can focus on the most confident and accurate results

• Alchemite models improve as data is added in a realistic chronological project series
Application to Larger Datasets
Global Pharma Collaboration

- **710,305** compounds
- **2,171** assays totaling **3,568** endpoints
- Covering a **full range** of drug discovery assays, including compound activities and ADME properties

![Graph showing Coefficient of determination for Alchemite™ and Random forest models. Median R² = 0.50 for Alchemite™ and R² = 0.19 for Random forest.](image-url)
Thank you for Listening!

• Thanks to:
  − Tom Whitehead, Gareth Conduit
  − Julian Levell
  − Matthew Segall, Peter Hunt

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