AI-Partnered Dynamical Model Discovery for Precision Medicine

FDA-MCERSI Workshop on Application of AI/ML for Precision Medicine
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James Lu, Distinguished AI Scientist
Clinical Pharmacology, Genentech
Q: How to adapt dynamical modeling (pharmacokinetics/pharmacodynamics, disease progression, ...) to complex high-dim data for precision medicine?

- Leverage **AI as Partner** in dynamical model discovery
Expanding the Language of Dynamical Modeling

**Human Mind**

\[ TS(t) = TS_0 \times (\exp(-KS_t) + \exp(KG_t) - 1) \]

.....

**Language:**
Mathematical expressions

**Inductive bias:**
Form of equations

**Artificial Neural Networks**

\[ \frac{d y(t)}{dt} = \begin{pmatrix} \text{Neural network} \end{pmatrix} (y(t), p) \]

**Language:**
Neural networks

**Inductive bias:**
Network architecture
AI as Partner in Dynamical Model Discovery

Classical Modeling

abstraction

F = m \times a

dynamical law

AI-Partnered Modeling

Pharmacology Informed Neural Network

encoder

generator

decoder

\frac{d y(t)}{d t} = f(y(t), p)
Hallmarks of *Pharmacology-Informed* Neural Network Architectures

**Pharmacology Concepts**
- Express *causal* relationships between dose, PK, PD
- Leverage population data to learn the *dynamical law*
- Enable “what-if” simulations

**Neural Networks**
- Learn to obtain useful abstractions of patient data
- Learn to improve model as the amount of data increases
Pharmacology-Informed: Expressing Causal Relationships within Neural Network

Causal chain

Dose

autonomous dynamics

PK

PD

system perturbation

Dosing input

\[
\frac{dy_{PK}(t)}{dt} = \left(\text{network}\right)(y_{PK}(t), p_{PK})
\]

\[
\frac{dy_{PD}(t)}{dt} = \left(\text{network}\right)(y_{PD}(t), y_{PK}(t), p_{PD})
\]
AI-Partnered Dynamical Modeling for Personalized PK/PD Prediction

Deep learning prediction of patient response time course from early data via neural-pharmacokinetic/pharmacodynamic modelling

James Lu\textsuperscript{1,2}, Brendan Bender\textsuperscript{1}, Jin Y. Jin\textsuperscript{1,2} and Yuanfang Guan\textsuperscript{1,2}

![Diagram illustrating the process from longitudinal clinical data to personalized PK/PD predictions.](image)

Longitudinal clinical data $\xrightarrow{\text{Neural-PK/PD Model}}$ $\frac{dy(t)}{dt} = (y(t), p)$ $\xrightarrow{\text{Observed individual PK/PD data}}$ Predicted PK/PD profiles

Personalized PK/PD Predictions
Enabling Improved Personalized Predictions from Early Data

**Data**

**Encoder**

**Actual or “what-if” dosing**

\[
\frac{dy(t)}{dt} = \sum_{i=1}^{n} dose(i) \delta(t - T_i) + \begin{pmatrix} \text{patient embedding} \\ p \end{pmatrix} (y(t), p)
\]

**Decoder**

**Simulation**

**Individual patient predictions**

**Comparison of Predictivity**

<table>
<thead>
<tr>
<th></th>
<th>Observation window</th>
<th>Prediction window</th>
<th>Population PK/PD</th>
<th>Neural-PK/PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>R2</td>
<td>t&lt;42 day</td>
<td>t≥42 day</td>
<td>0.39±0.02</td>
<td>0.52±0.01</td>
</tr>
<tr>
<td>R2</td>
<td>t&lt;21 day</td>
<td>t≥42 day</td>
<td>-</td>
<td>0.45±0.02</td>
</tr>
</tbody>
</table>
Precision Medicine in Oncology: the Emergence of Multimodal Data

Adapted from: Boehm et al, Nature Reviews Cancer (2022)
Al-Partnered Tumor Dynamics Neural-ODE Model for Personalized Predictions

**Data**
- Sum-of-Longest Diameters (SLD)
- Encoder
- Decoder

\[
\frac{dy(t)}{dt} = \phi(y(t), p)
\]

- Patient embedding
- XGBoost
- Overall Survival

**Prediction**

Benefits:
- Unbiased tumor dynamic predictions from early data
- Improved patient survival prediction at individual level (metric: c-index)
- Potential to link up with Al models for multimodal data in an explainable manner
Enhancing Tumor Dynamics Predictions by Incorporating High Dimensional Data

RNAseq data

Gene network

Early tumor data

Graph encoder

Neural-ODE Decoder

\[
\frac{dy(t)}{dt} = (y(t), p)
\]

Tumor dynamics prediction

Zichen Wang

Omid Bazgir

Marc Hafner
Summary

- Dynamical modeling of modern high volume data calls for partnership with AI

- Pharmacology-informed neural network architectures enable construction of models in a principled way

- AI-partnered Neural-ODEs on PK/PD and disease progression data demonstrate ability to enhance personalized predictions

- Integrating Graph Neural Networks with Neural-ODEs in a pharmacology-informed manner shows significant promise for fusing -omics with dynamical data
**Acknowledgement**

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- Zichen Wang

**University of Michigan**
- Yuanfang Guan
- Kaiwen Deng

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**Pharmacology Informed Neural Network**

\[
\frac{dy(t)}{dt} = \left(\begin{array}{c}
\end{array}\right)(y(t), p)
\]

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**THANK YOU!**