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Deep Learning for PK/PD and Disease Progression Time-Course Predictions using Neural-ODE

PAGE 2021

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Topics

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- Neural-ODE as an AI-powered time-course modeling methodology
- PK/PD application:
  - Platelet count under trastuzumab emtansine (T-DM1) treatment
- Disease progression application:
  - Geographic Atrophy (GA)

The beginnings of Differential Equation Modeling

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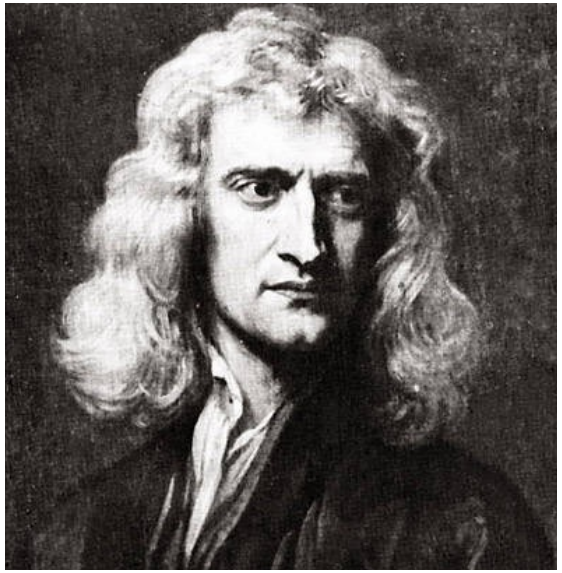
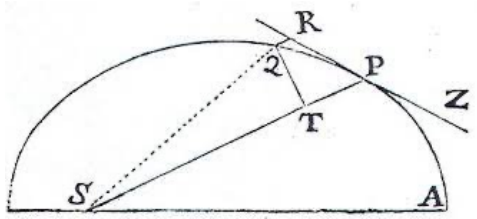
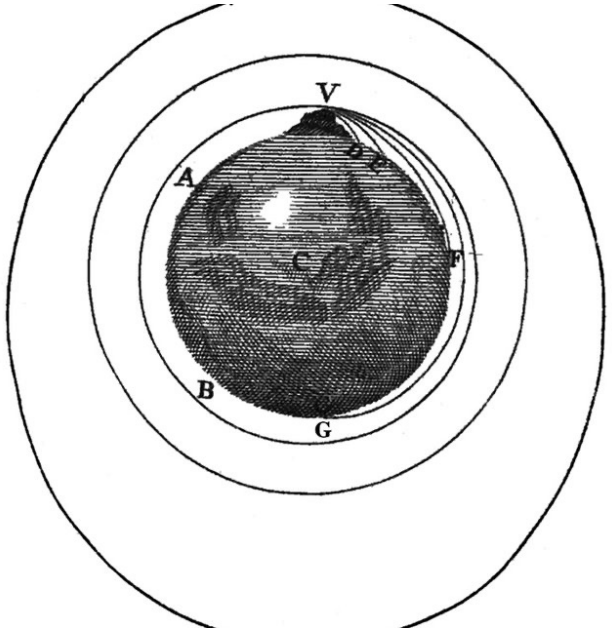


Analysis



Synthesis



Newton's anagram:
"It is useful to solve differential equations"

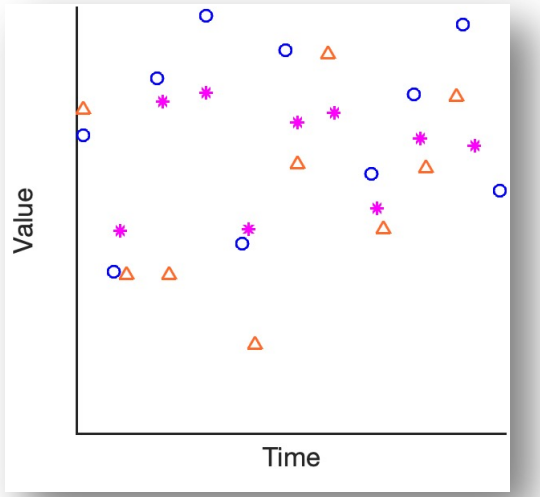
Description of a system divides into two parts:
- Dynamical equations
- Initial conditioins

A beautiful question, Wilczek (2015)

From Data to Model: Human Mind

- The process of modeling

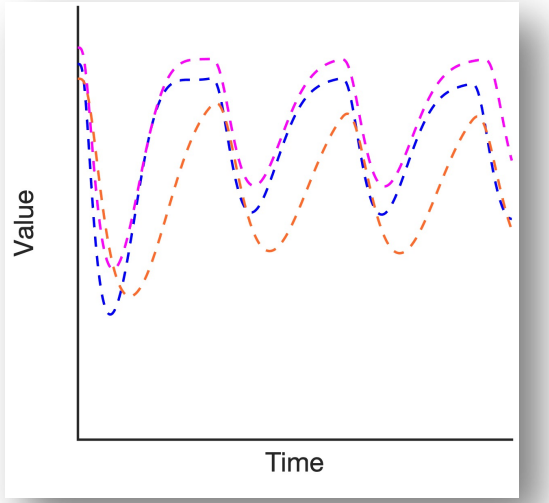
Physical Realm



Concepts
Mechanisms
Equations
Parameters
…

```
DADT(1)=K21*A(2)-K12*A(1)-K10*A(1)
DADT(2)=K12*A(1)-K21*A(2)
DADT(3)=KEO*CP-KEO*A(3)
DADT(4)=-KTR*A(4)+..*(1-EFFPLT)*(BT/A(8))**GAM
DADT(5)=-KTR*A(5)+KTR*A(4)
...
```

Digital Realm



Abstraction

- Signal vs. noise
- Parsimony
- Experience

Recapitulation

- Goodness-of-fit

From Data to Model: the AI Paradigm

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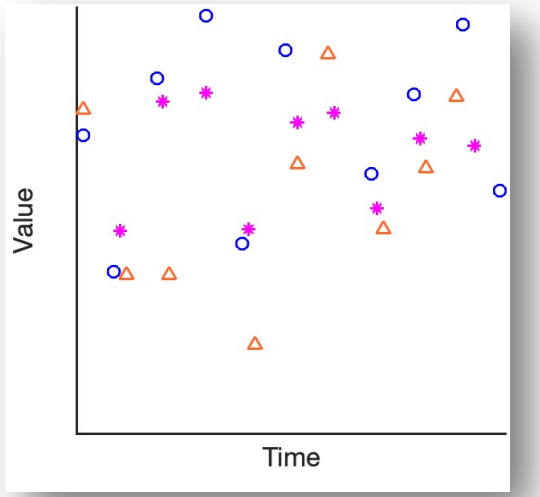
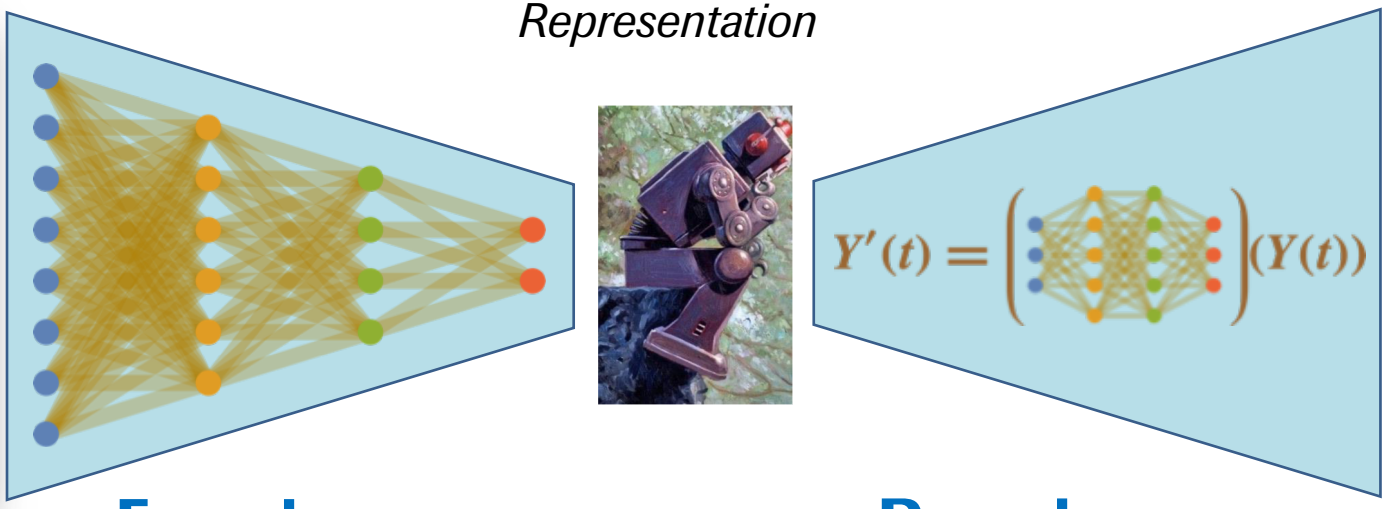
- Using neural nets for data abstraction & reproduction

Physical Realm



Growing data complexity:
+omics
+images
+RWD
+ …

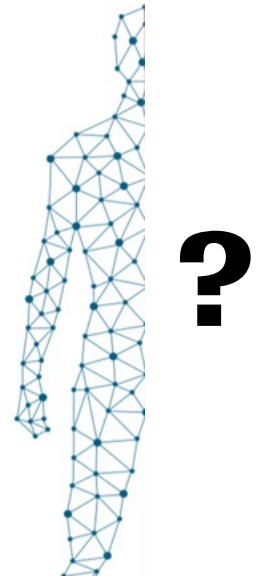
Machine Generated Representation



Encoder
- Data abstraction

Decoder
- Reproduction
- Prediction

Digital Realm



?

Growing needs:
+more medicines
+personalized healthcare
+…

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Platelet count prediction under T-DM1 treatment

NEURAL-PK/PD MODELING

Deep Learning Methodology enabling PK/PD Model Discovery

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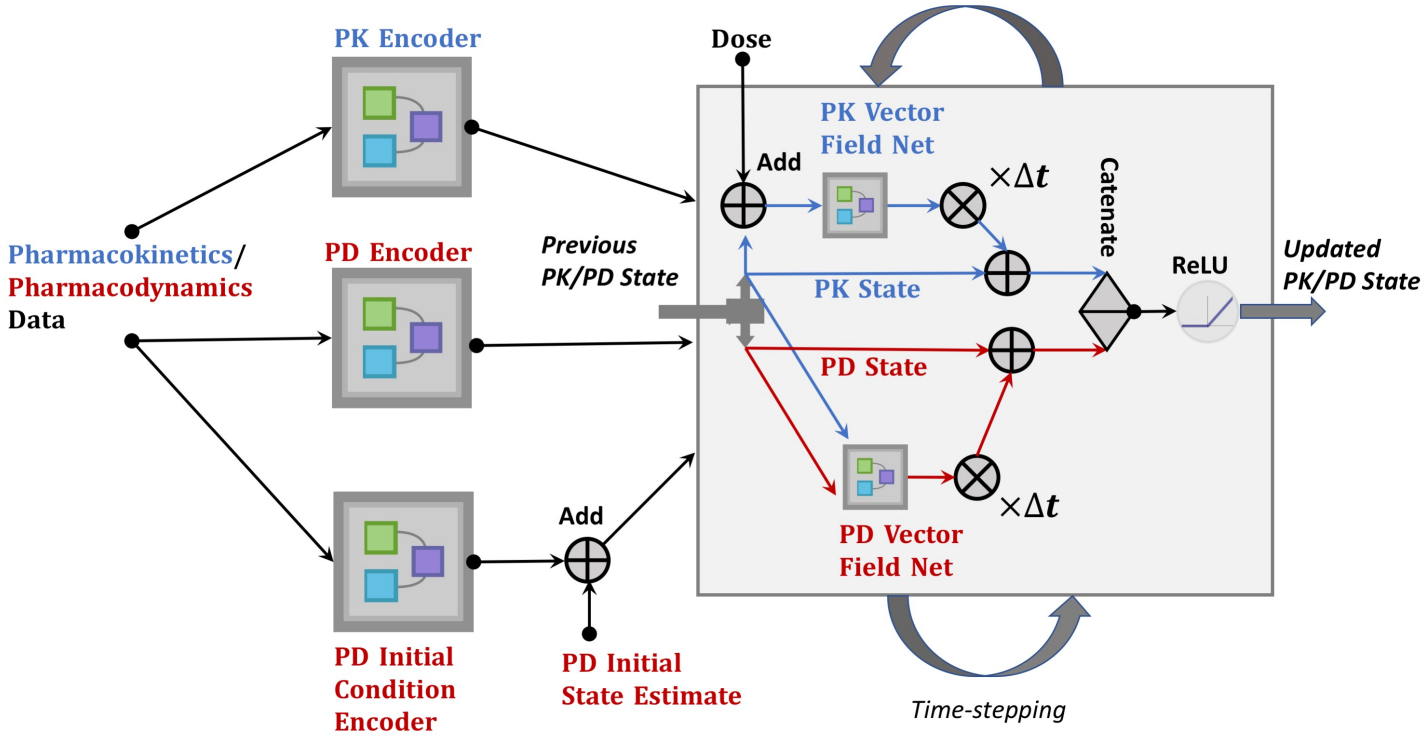
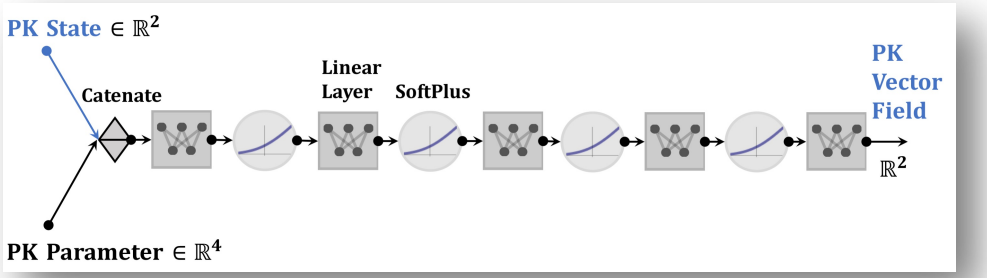
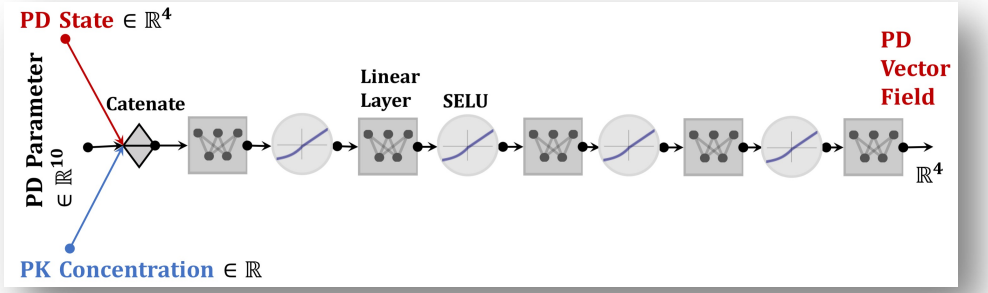
- Network architecture incorporates key causal assumptions:
  - Dosing drives PK
  - PK drives PD



PK Vector Field Net



PD Vector Field Net

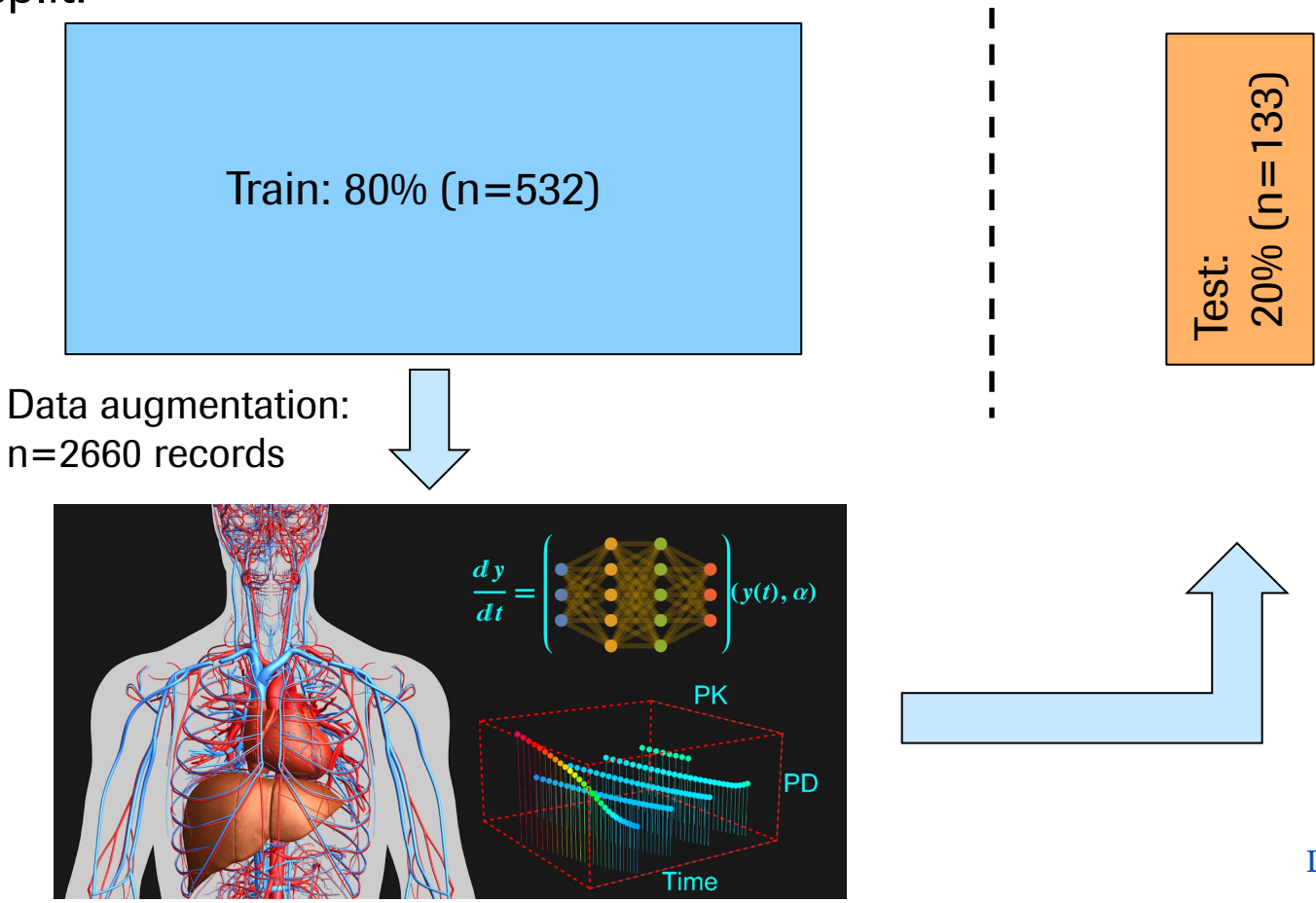


Lu *et al*, Nature Machine Intelligence (2021)

Clinical Data: Train and Test

- Compiled data: longitudinal platelet response from 665 patients
  - Phase I: *various doses and schedules*
  - 3×Phase II, 1×Phase III: *3.6 mg/kg, Q3W*

- Train and test split:



Lu *et al*, Nature Machine Intelligence (2021)

The Prediction Task

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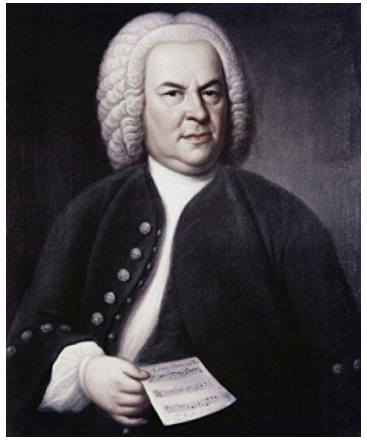
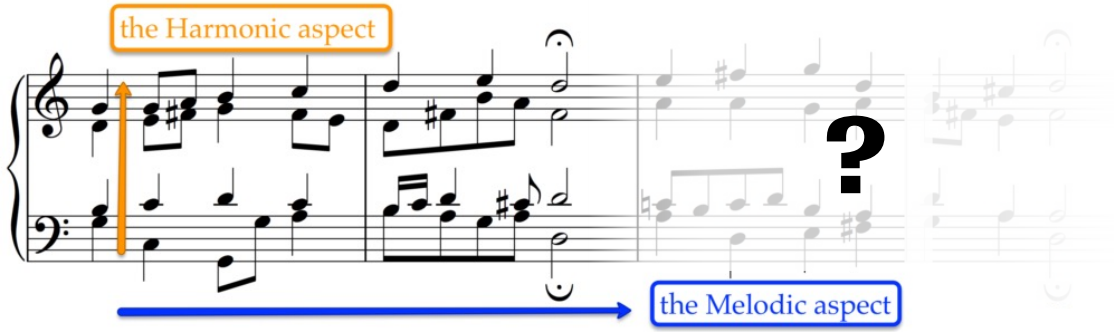
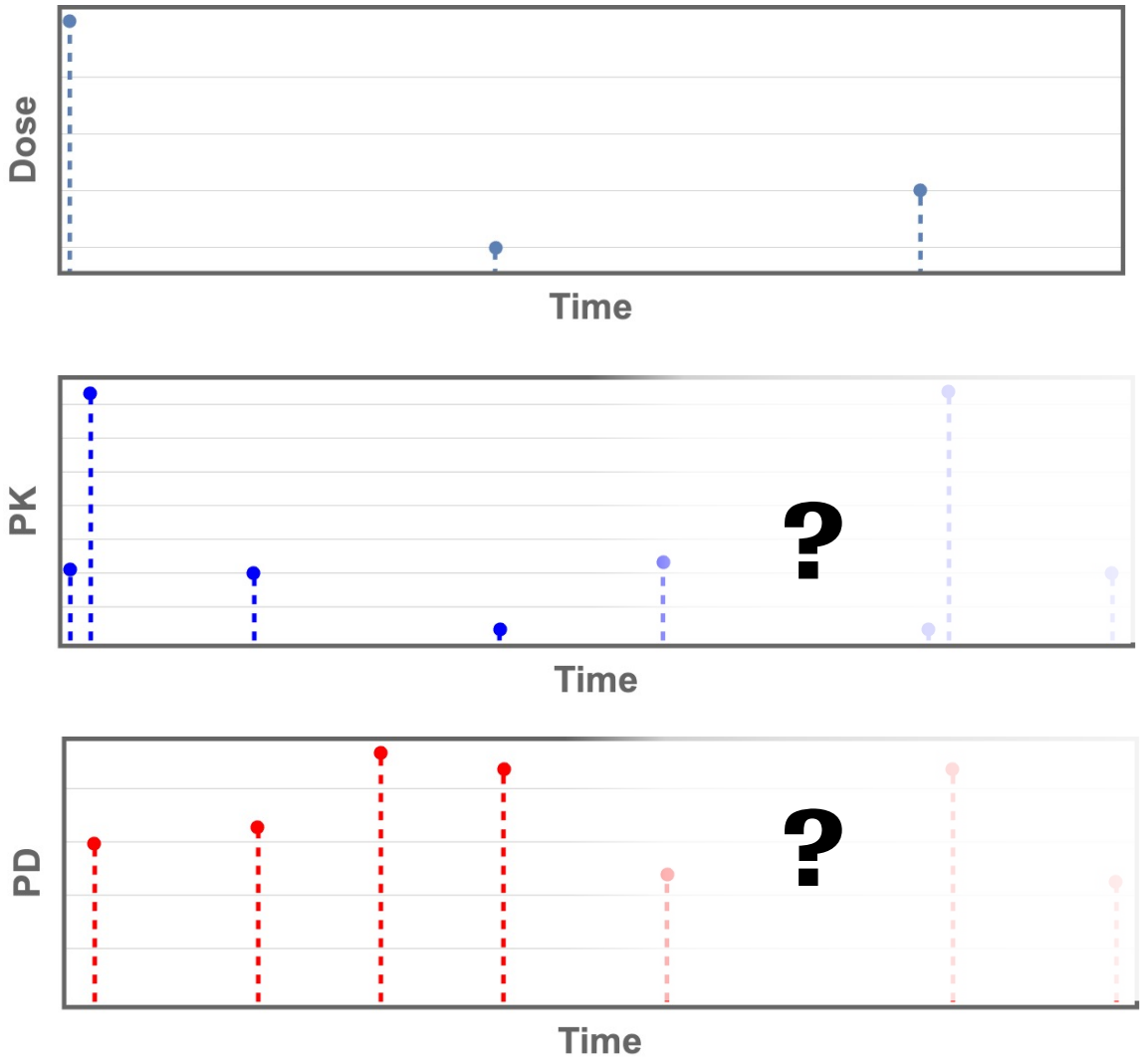
- Music analogy





schoolofcomposition.com

- PK/PD data



Neural-PK/PD Recapitulates Qualitative Dynamics

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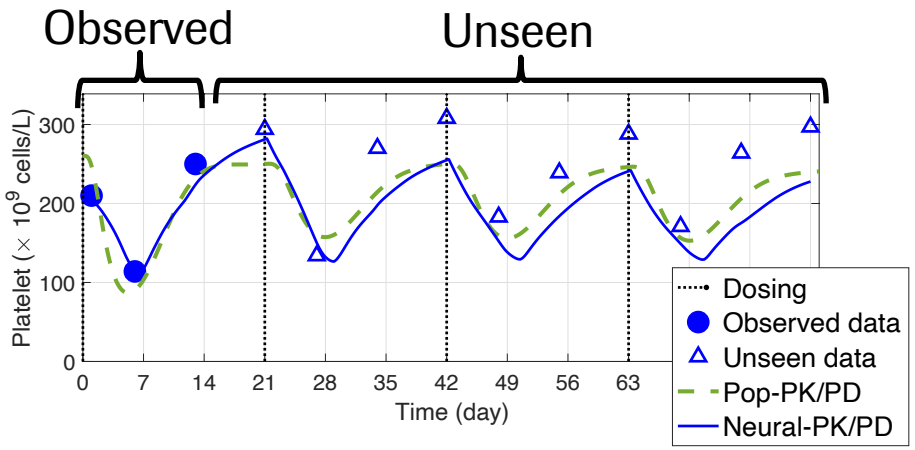
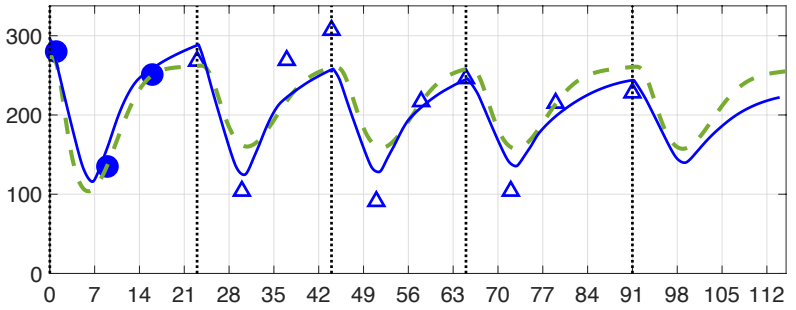
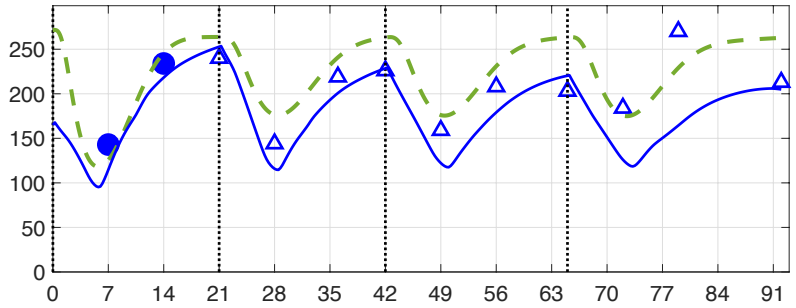
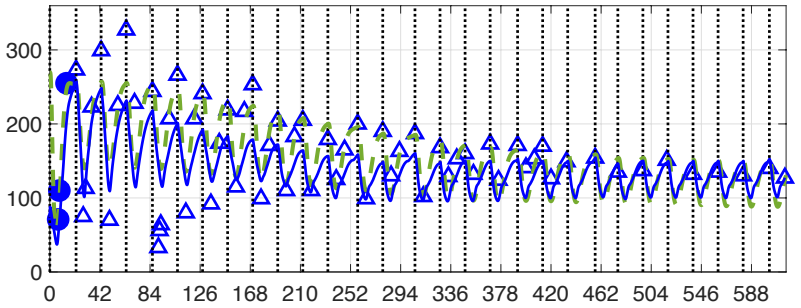
- Comparable to prior population-PK/PD model (Bender *et al*) based on the Friberg formulation

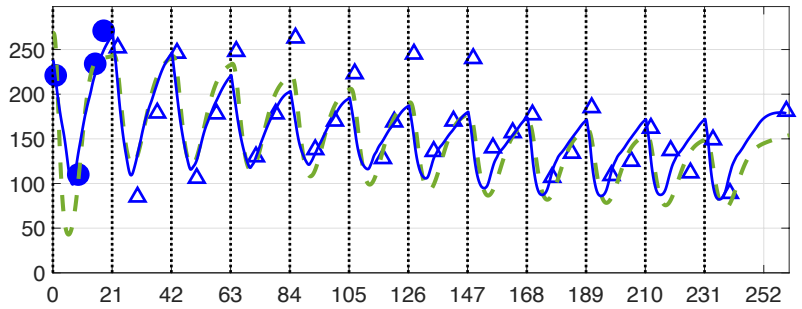
6 test patients shown

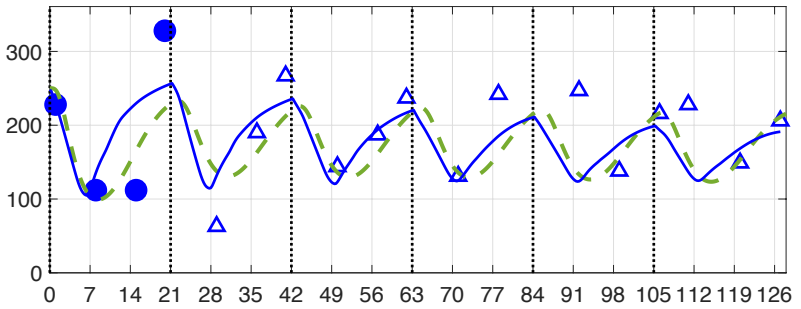












Neural-PK/PD Enables Accurate Individual Predictions

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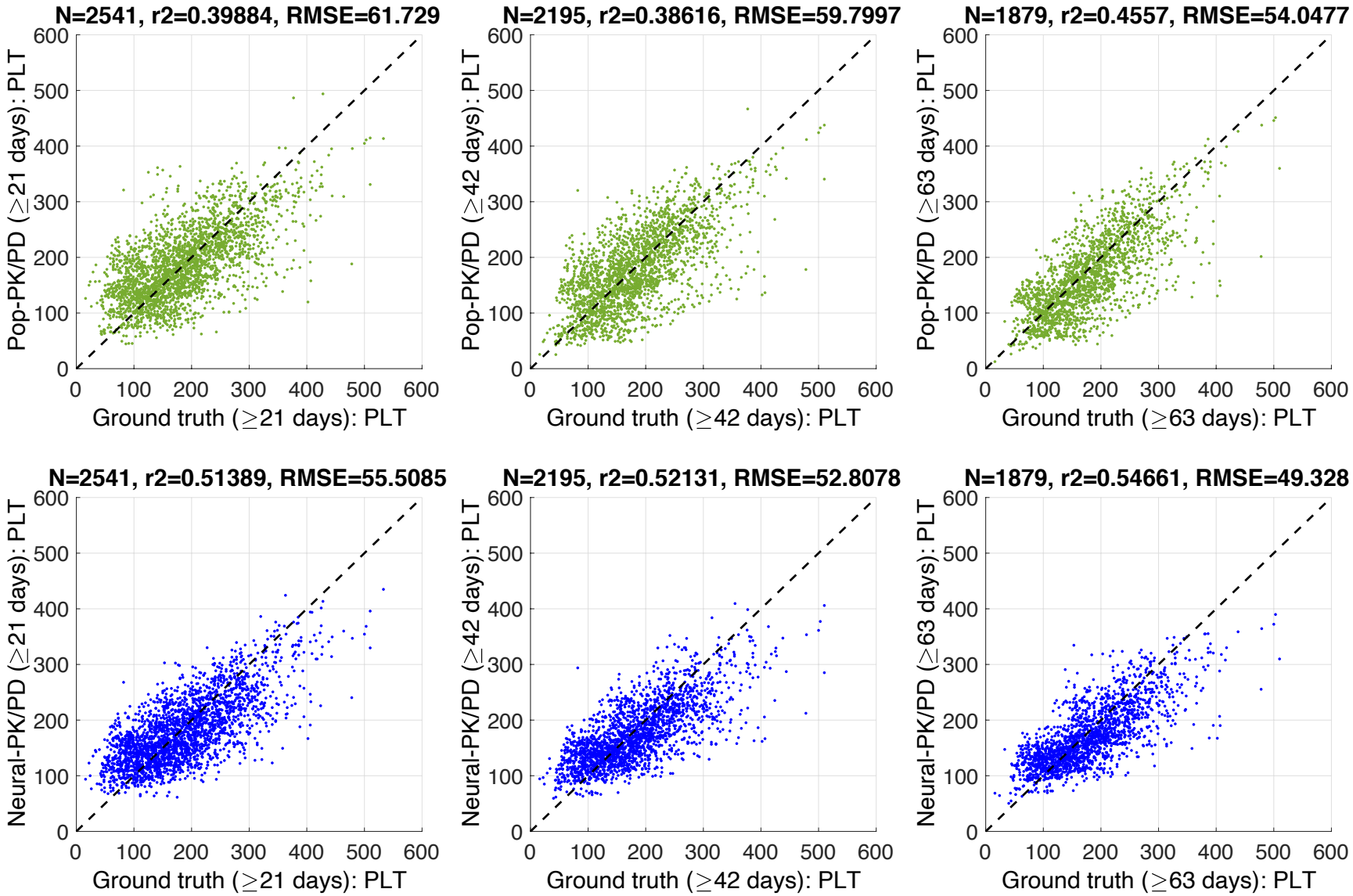
	Observing Cycle 1	Observing Cycles 1 & 2	Observing Cycles 1 to 3
Population PK/PD	N=2541, r2=0.39884, RMSE=61.729	N=2195, r2=0.38616, RMSE=59.7997	N=1879, r2=0.4557, RMSE=54.0477
Neural PK/PD	N=2541, r2=0.51389, RMSE=55.5085	N=2195, r2=0.52131, RMSE=52.8078	N=1879, r2=0.54661, RMSE=49.328



Neural-PK/PD Simulation of Dose Schedules

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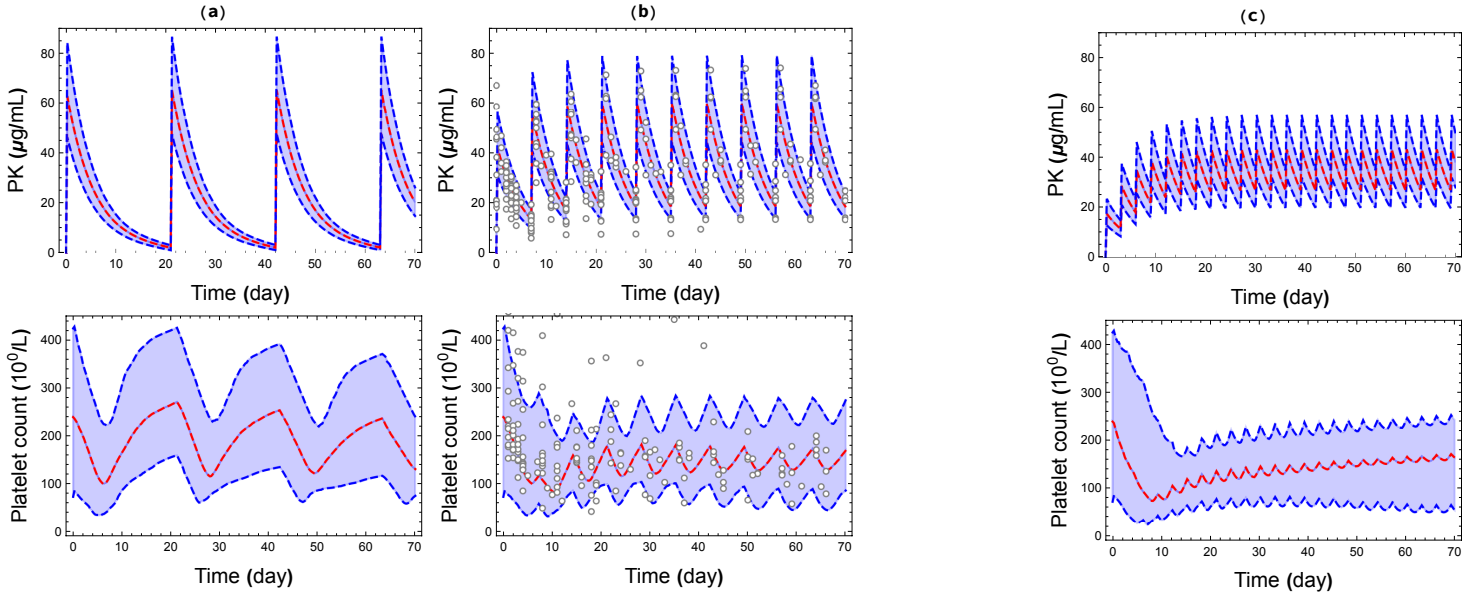
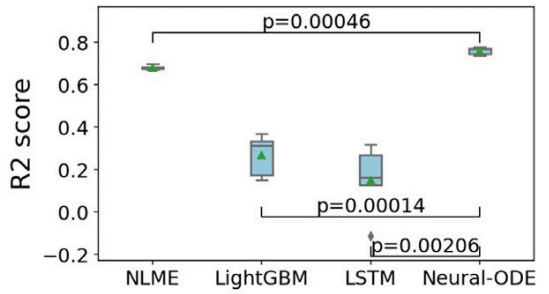
- Can the deep learning model generalize to unseen dose schedules?

Simulation: Q3W **Simulation: Q1W** **Simulation: Q3D (untested)**



- Not all machine learning models can generalize well:

Q3W to Q1W: PK Prediction



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Geographic Atrophy (GA)

DISEASE PROGRESSION MODELING

Creating Digital Twins for GA Disease Progression

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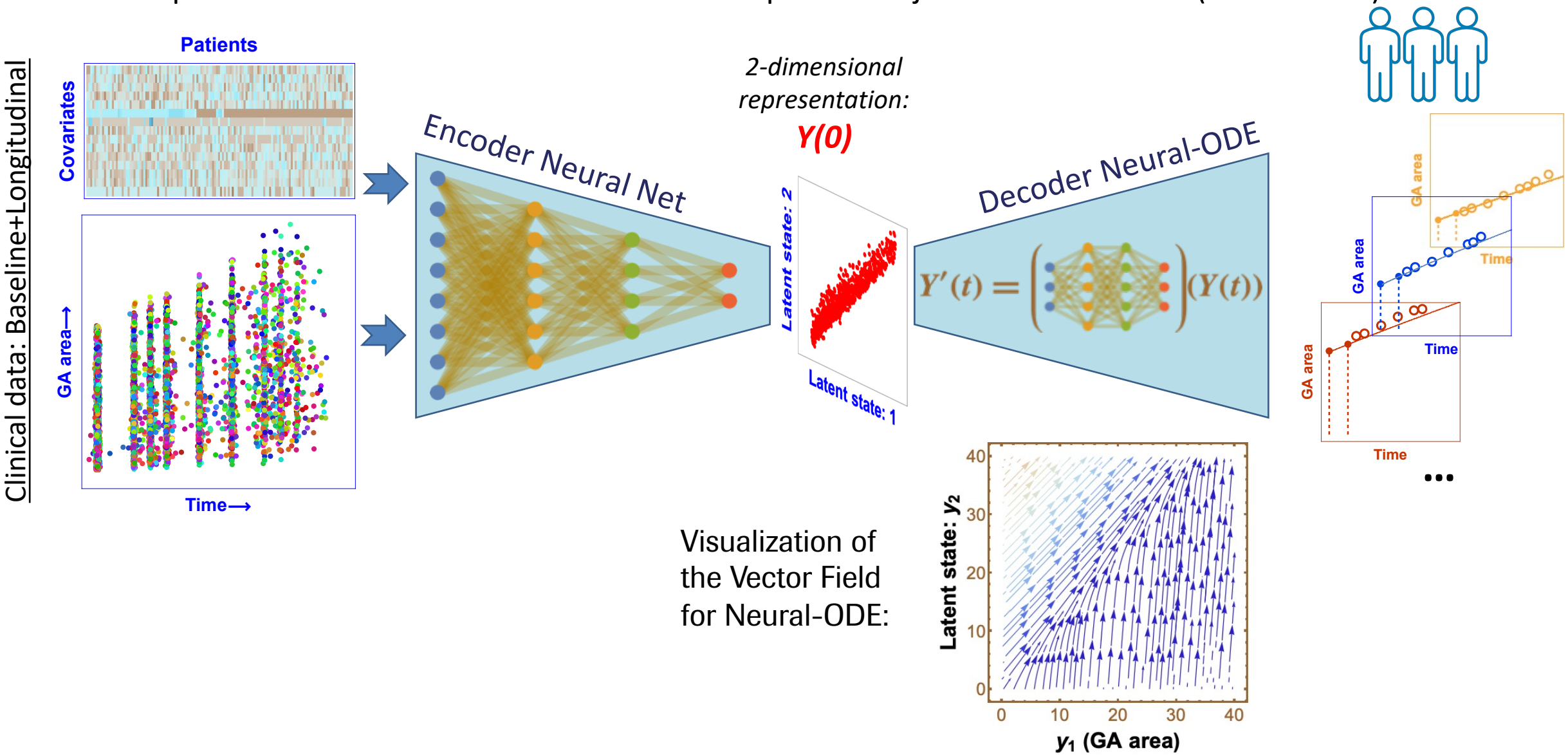
- Develop Neural-ODE model to forecast individual patient trajectories of GA area (if untreated)



Prediction of Individual Patients on a Test Set

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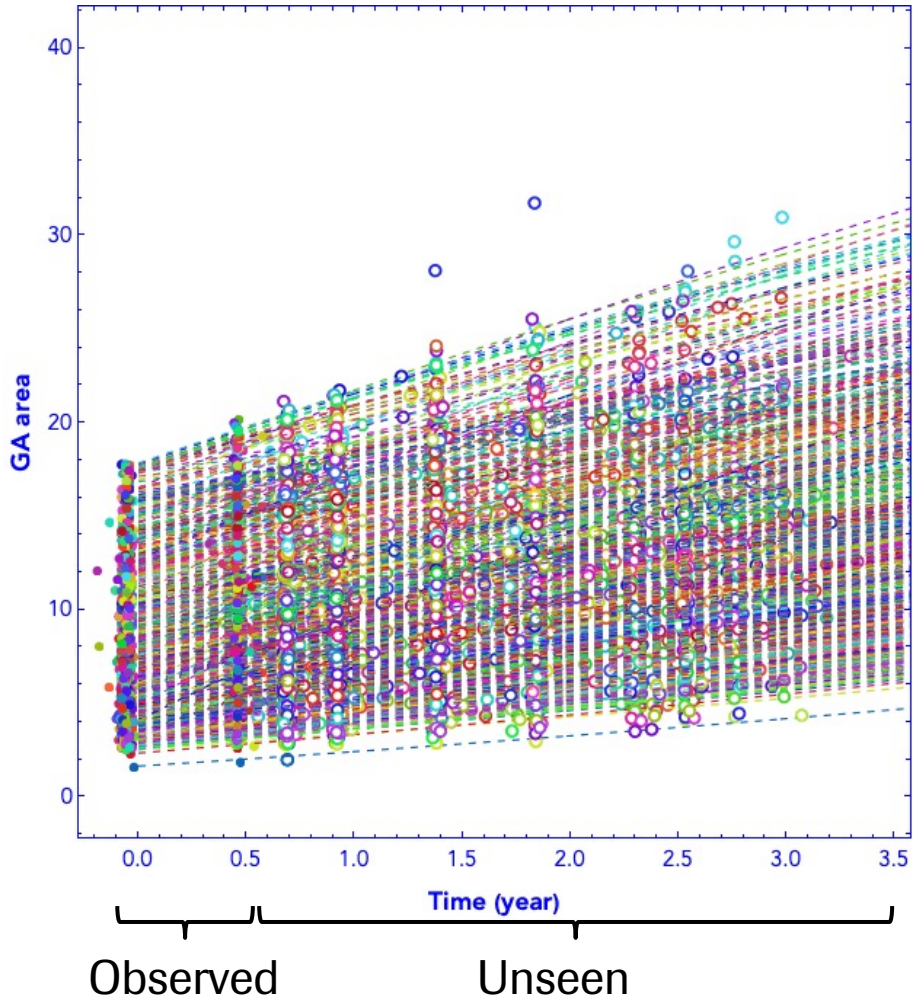
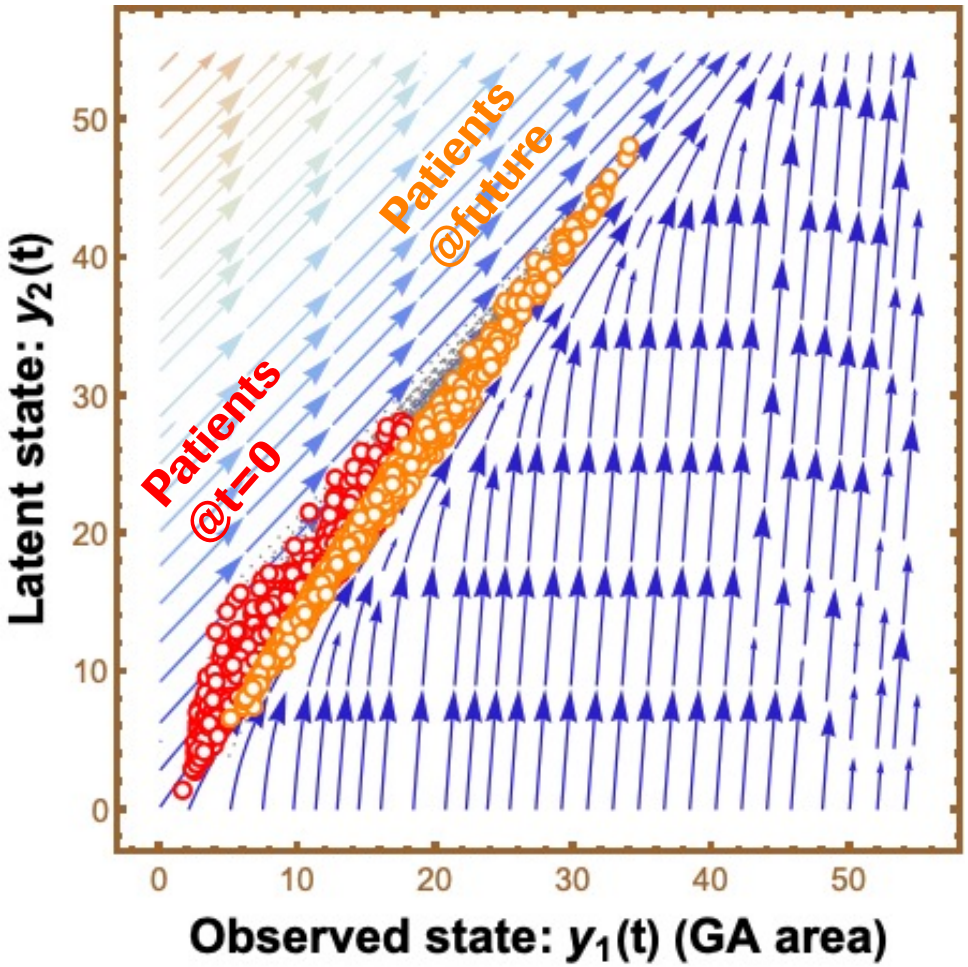
- Using Neural-ODE to predict subsequent GA areas from the first two observations:

Time-Course



Disease State



Conclusions

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- Neural-ODE is a natural and versatile approach to fuse Dynamical Systems with Deep Learning
  - Pharmacological assumptions can be built into the architecture
  - Applicable to both PK/PD and Disease Progression settings
  - Can readily incorporate multi-modal data using the language of neural networks

Acknowledgement

- CEP Innovation Fund
- Genentech: Logan Brooks, Gengbo Liu, Kai Liu, CPLT & Amita Joshi
- University of Michigan: Kaiwen Deng
- Ann Arbor Algorithms: Xinyuan Zhang

“Any sufficiently advanced technology is indistinguishable from magic.”

– Arthur C. Clark