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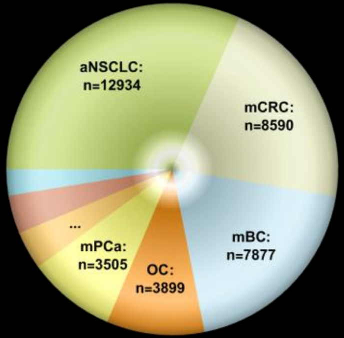
AI-Partnered Dynamical Model Discovery for Precision Medicine

FDA-MCERSI Workshop on Application of AI/ML for Precision Medicine
February 17, 2023

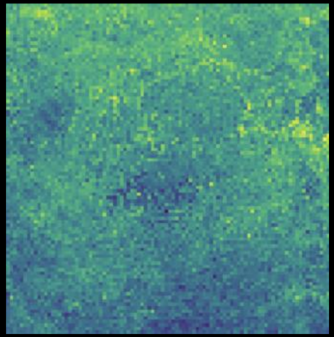
James Lu, Distinguished AI Scientist
Clinical Pharmacology, Genentech

Data Deluge in the Digital Age

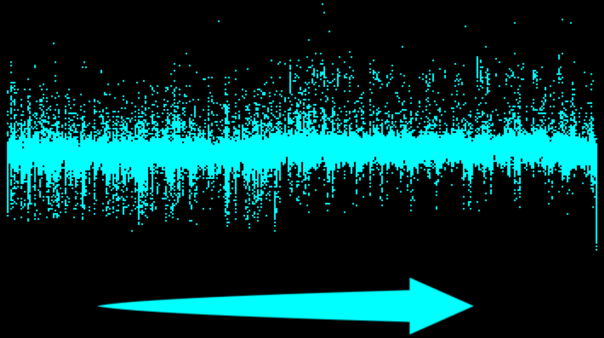
>40,000



>20,000



>1,000,000



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

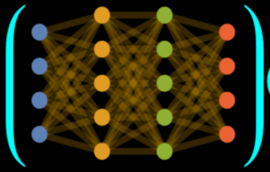
Human Mind

TS(t)=TS0×(exp(-KS×t)+exp(KG×t)-1)

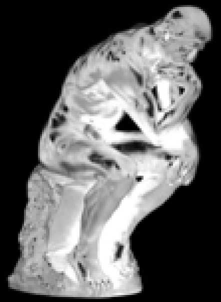
.....

Artificial Neural Networks

$$\frac{dy(t)}{dt} =$$



$$(y(t), p)$$



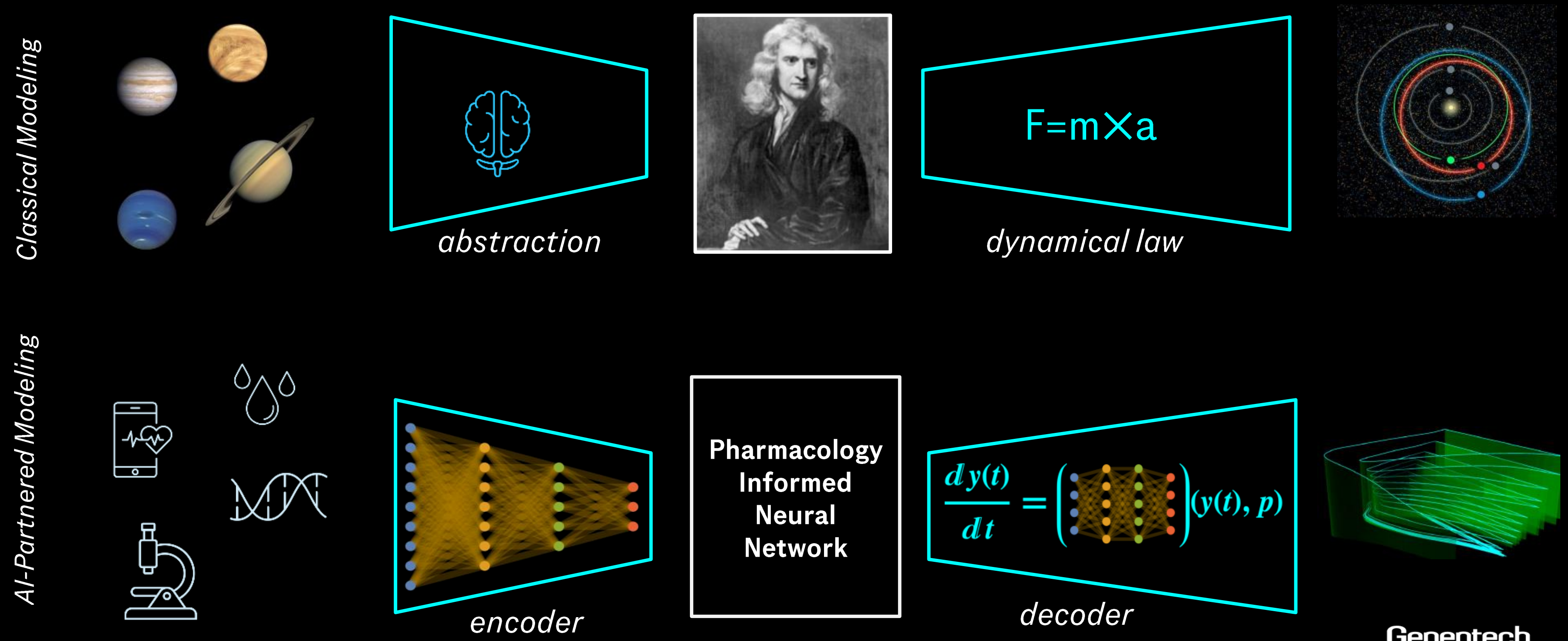
Language:
Mathematical expressions

Inductive bias:
Form of equations

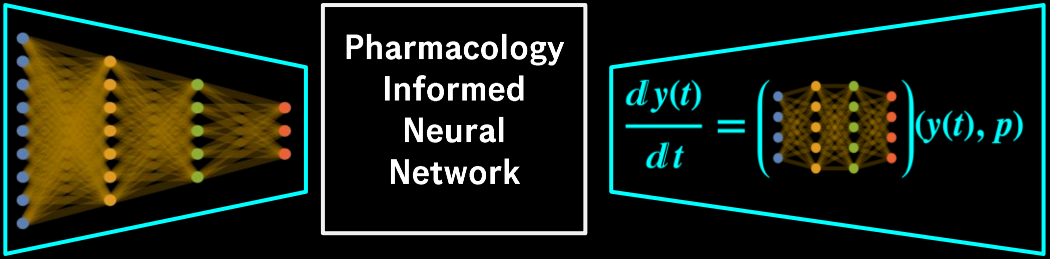
Language:
Neural networks

Inductive bias:
Network architecture

AI as Partner in Dynamical Model Discovery



Hallmarks of *Pharmacology-Informed* Neural Network Architectures



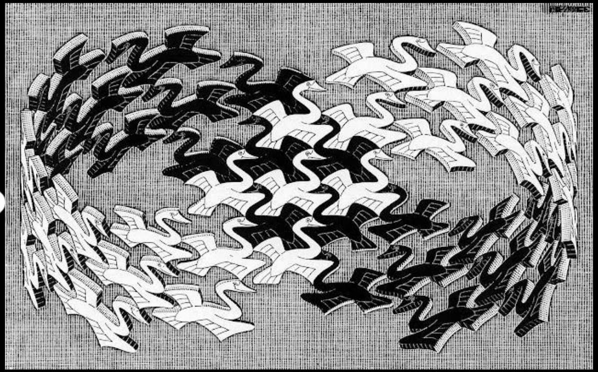
Pharmacology Concepts

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

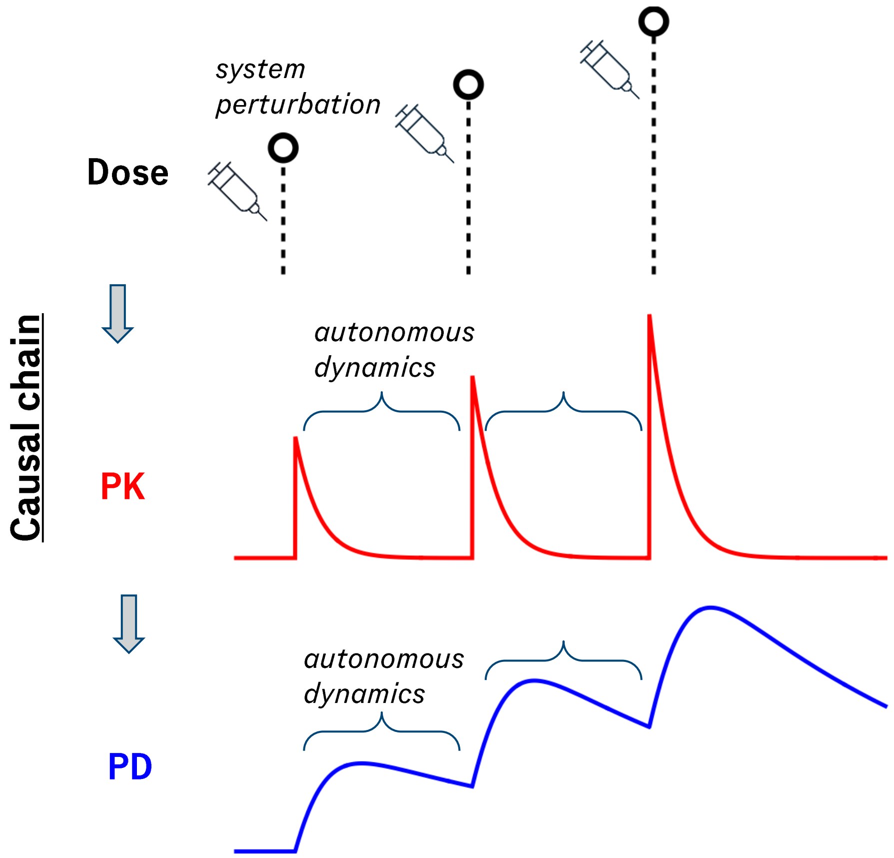
Neural Networks

- Learn to obtain useful abstractions of patient data
- Learn to improve model as the amount of data increases

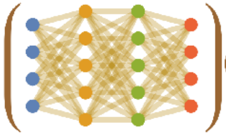
Interwining complementary concepts

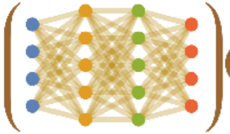


Pharmacology-Informed: Expressing Causal Relationships within Neural Network



Dosing input

$\frac{d\, y_{PK}(t)}{d\, t} =$  $(y_{PK}(t), p_{PK})$ +

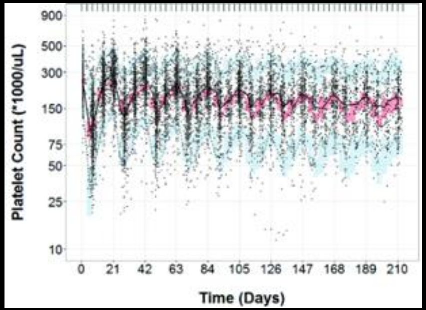
$\frac{d\, y_{PD}(t)}{d\, t} =$  $(y_{PD}(t), y_{PK}(t), p_{PD})$

AI-Partnered Dynamical Modeling for Personalized PK/PD Prediction

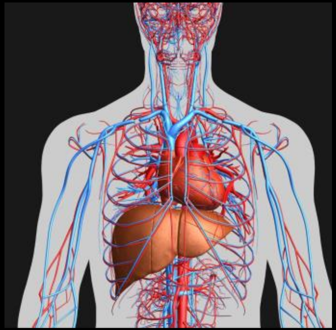
ARTICLES
https://doi.org/10.1038/s42256-021-00357-4
nature machine intelligence
Check for updates

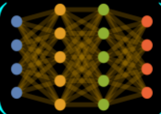
Deep learning prediction of patient response time course from early data via neural-pharmacokinetic/ pharmacodynamic modelling

James Lu[1]✉, Brendan Bender[1], Jin Y. Jin[1]✉ and Yuanfang Guan[2]



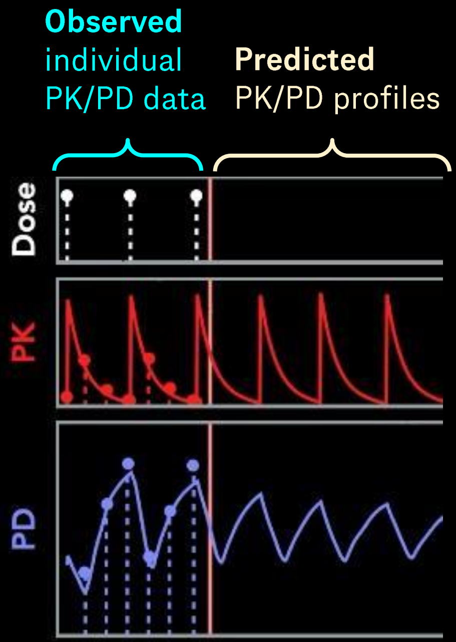
Longitudinal clinical data





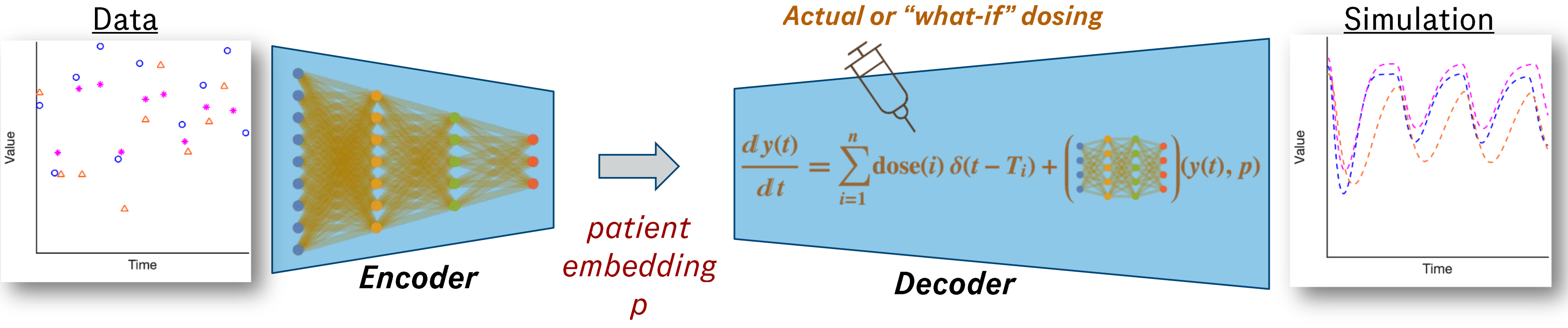
$$\frac{dy(t)}{dt} = \Big(\quad\Big)(y(t), p)$$

Neural-PK/PD Model

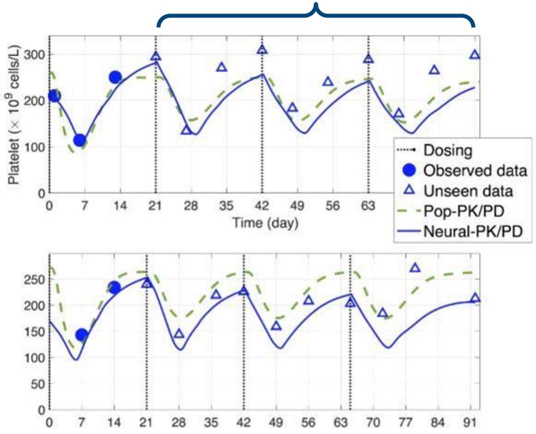


Personalized PK/PD Predictions

Enabling Improved Personalized Predictions from Early Data



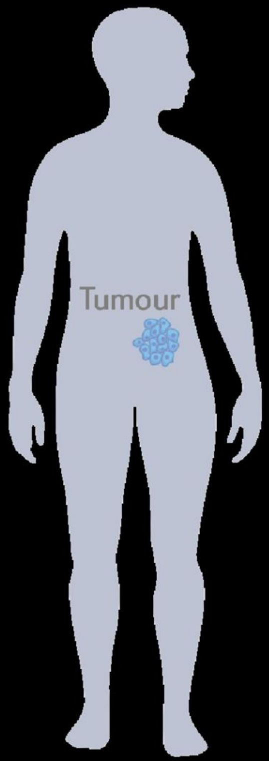
Individual patient predictions

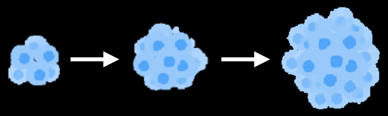


Comparison of Predictivity

	Observation window	Prediction window	Population PK/PD	Neural-PK/PD
R2	t<42 day	t≥42 day	0.39±0.02	**0.52±0.01**
R2	t<21 day	t≥42 day	-	**0.45±0.02**

Precision Medicine in Oncology: the Emergence of Multimodal Data





Tumor Dynamics

Clinical

Radiological

Pathological

Genomic

Liquid Biopsy


nature medicine

REVIEW ARTICLE

https://doi.org/10.1038/s41591-022-01981-2

Check for updates

Multimodal biomedical AI

Julián N. Acosta[1], Guido J. Falcone[1], Pranav Rajpurkar[2,4] and Eric J. Topol[3,4]

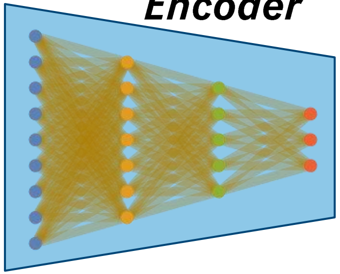
Adapted from: Boehm *et al*, Nature Reviews Cancer (2022)

AI-Partnered Tumor Dynamics Neural-ODE Model for Personalized Predictions

Data

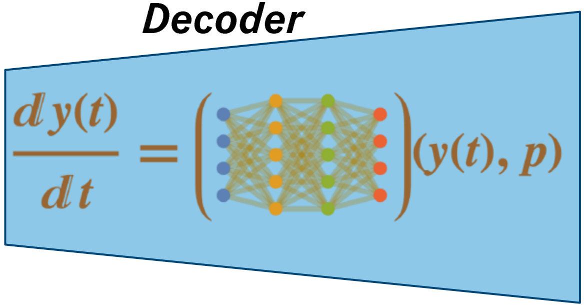
Sum-of-Longest Diameters (SLD)

Encoder

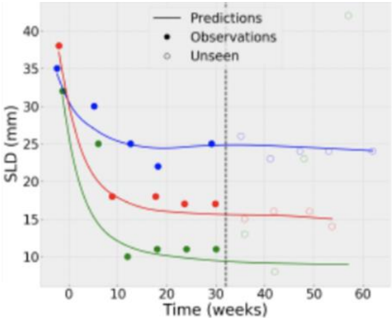


patient embedding p

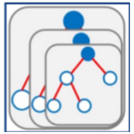
Decoder



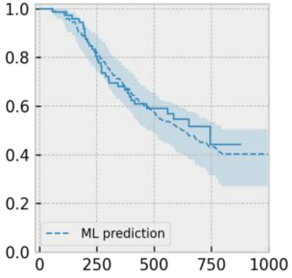
Prediction



XGBoost



Overall Survival



Benefits:

- Unbiased tumor dynamic predictions from early data
- Improved patient survival prediction at individual level (metric: c-index)
- Potential to link up with **AI models for multimodal data** in an explainable manner

Mark Laurie

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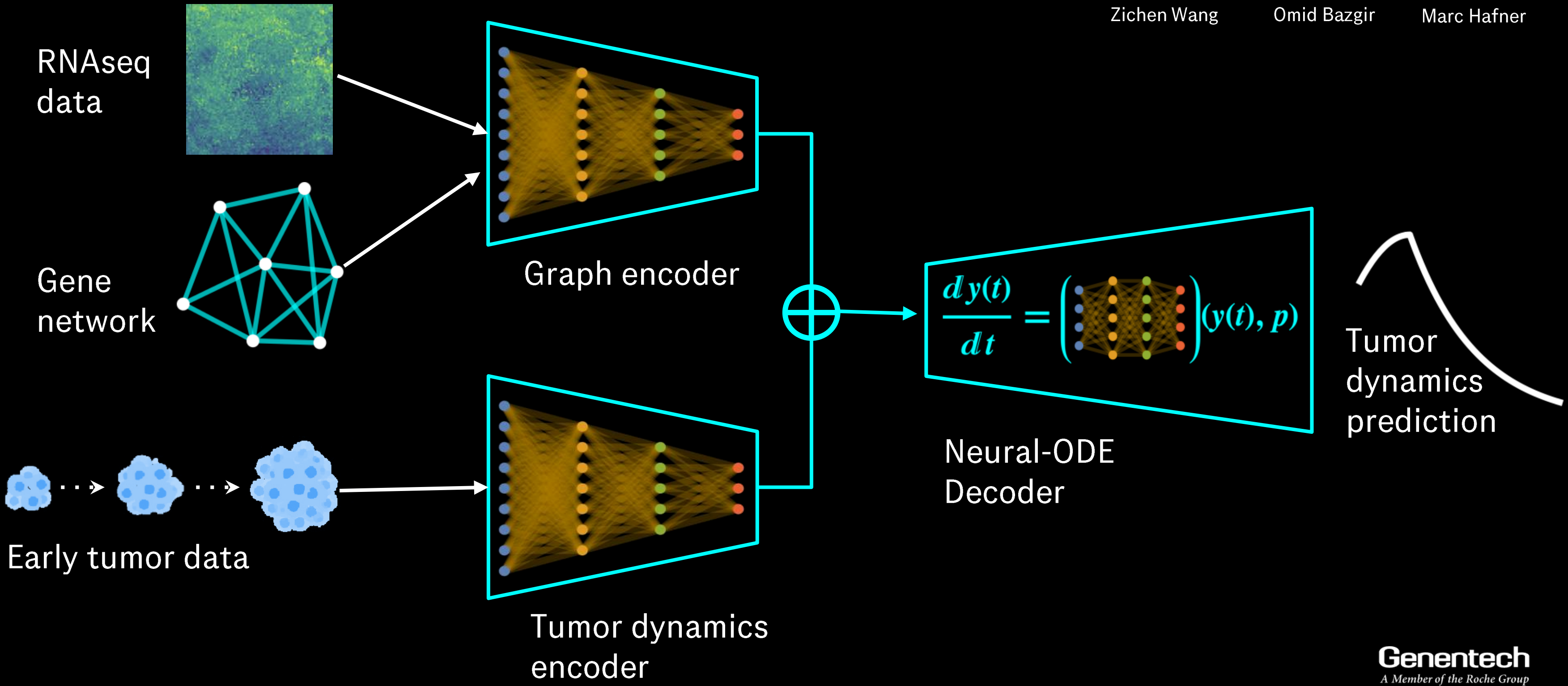
Enhancing Tumor Dynamics Predictions by Incorporating High Dimensional Data

Zichen Wang

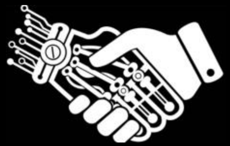
Omid Bazgir

Marc Hafner

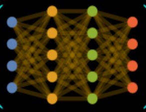


Summary

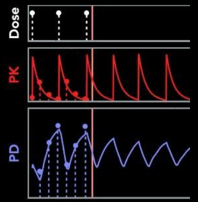
- Dynamical modeling of modern high volume data calls for partnership with AI



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

$$\frac{dy(t)}{dt} = \Big($$  $$\Big)(y(t), p)$$

- 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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Right Dose for Every Patient

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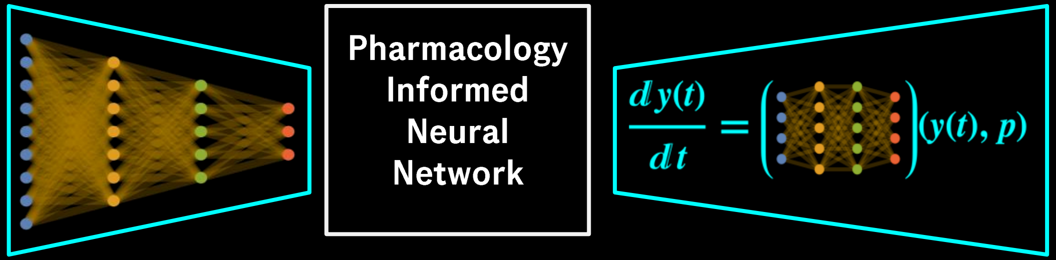
Zichen Wang

University of Michigan

Yuanfang Guan
Kaiwen Deng



THANK YOU!

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