Integrating Expert ODEs into Neural ODEs: Pharmacology and Disease Progression

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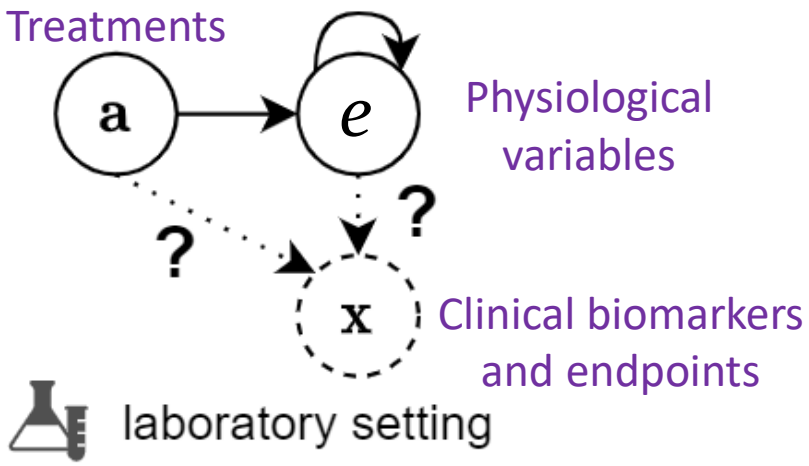
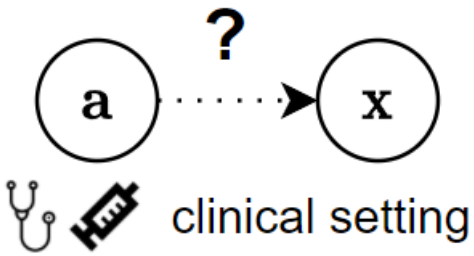
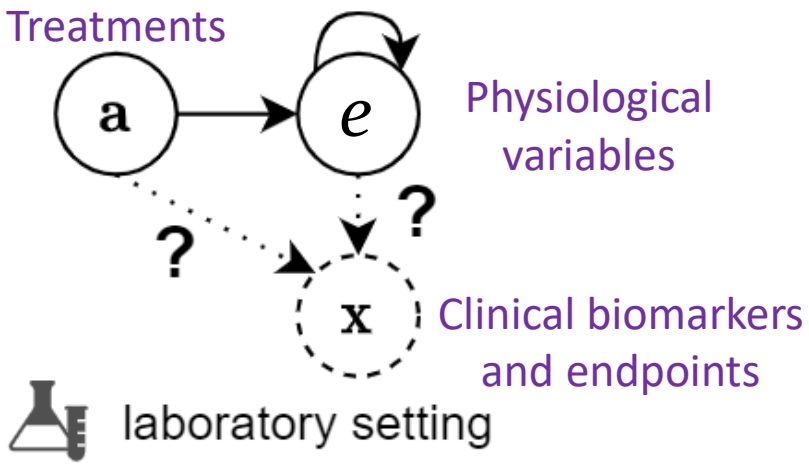
Motivation: bridging the gap between the lab and the clinic



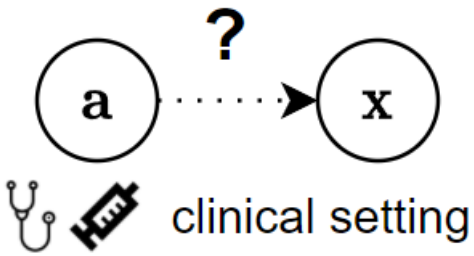


- **PKPD models** developed in **the lab settings**
- **Physiological variables**
  - PK: drug concentration
  - PD: response to drug (direct, low-level)
  - Molecular or cellular level
  - Measurable in the lab but *not* in the clinic
- **Clinical biomarkers and endpoints**
  - Important for clinical decision
  - Organ or body level (high level)
  - Not modeled by PKPD due to high complexity

Motivation: bridging the gap between the lab and the clinic



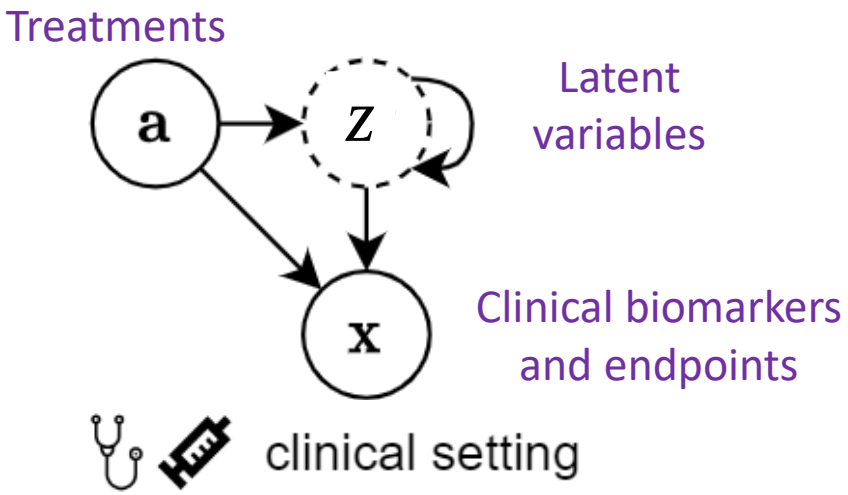
	Lab	Clinic
Physiological variables	Observed	Not observed
Clinical biomarkers and endpoints	Not modelled	Need to model



Two sides of the same goal:

1. Use ML to bridge the gap between the lab and the clinic
2. Use prior knowledge on PKPD to inform ML

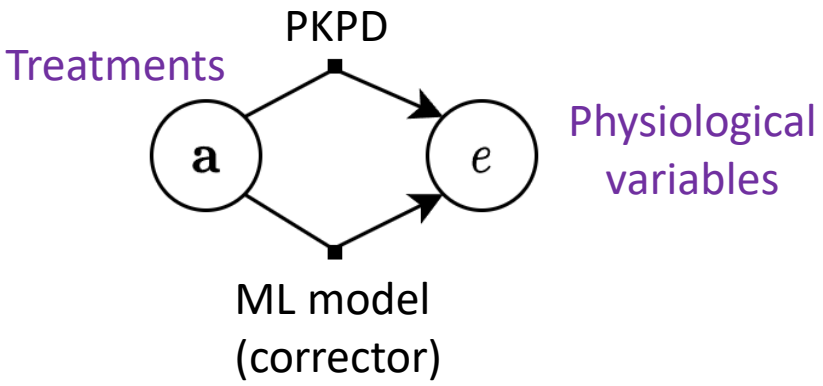
Existing approach: latent variable models (Pure ML)



- **Latent variables / representations**
  - Introduced to model the complex (often high dimensional) clinical bio-markers and endpoints
  - Fully data driven

- **Limitations**
  - Z does not correspond to known entities / variables
  - Ignores existing scientific knowledge (PKPD)
  - Poor sample efficiency

Challenge: naïve hybridization fails (unobserved variables)



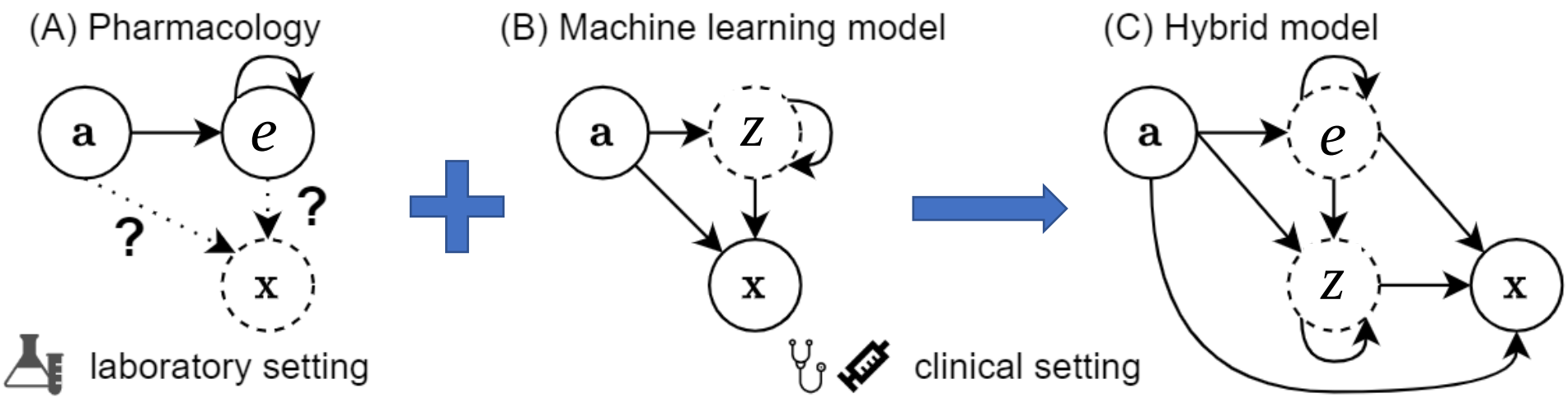
Naïve hybridization (residual model)

- **Assumption 1**: expert (PKPD) and ML models predict the same variables
- **Assumption 2**: the prediction target is observable

Limitations

- Variable mismatch: Clinical biomarkers and endpoints vs Physiological variables
- Unobserved variable: Physiological variables in PKPK not observed in clinical setting

Proposed solution: latent hybridization model

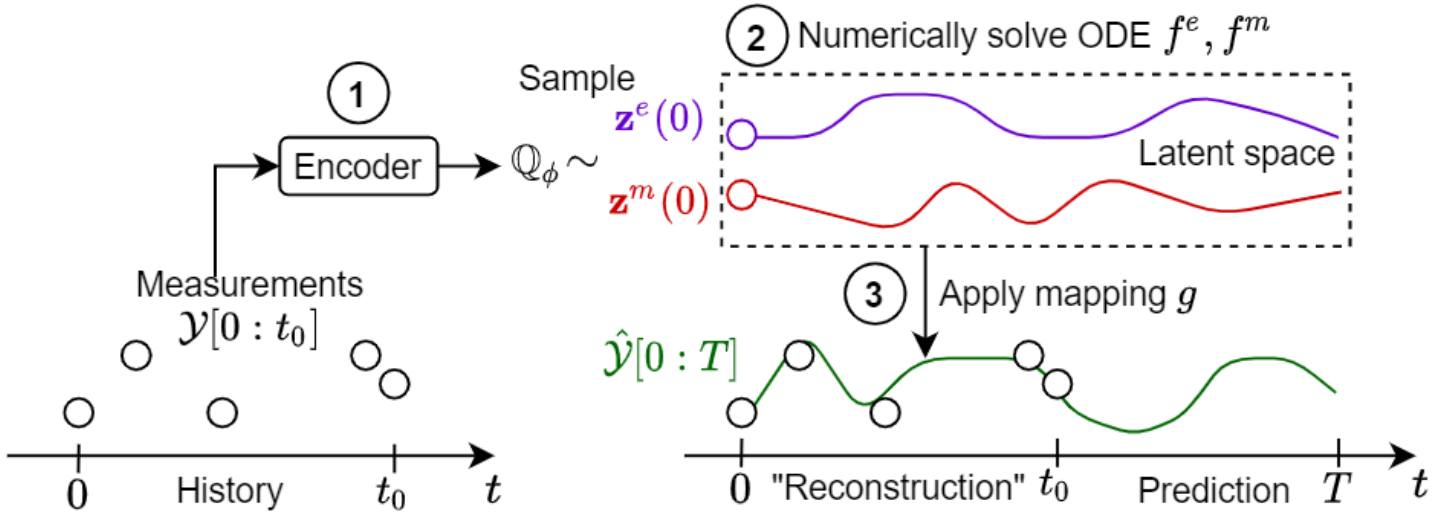


- Latent hybridization model
  - **Physiological variables** driven by **PKPD**
  - **Latent variables** learned by **ML**
  - Influence **clinical endpoints** nonlinearly

$$\dot{\mathbf{z}}^e(t) = f^e(\mathbf{z}^e(t), \mathbf{a}(t); \theta^e)$$
$$\dot{\mathbf{z}}^m(t) = f^m(\mathbf{z}^m(t), \mathbf{z}^e(t), \mathbf{a}(t);\ \theta^m)$$
$$\mathbf{x}(t) = g(\mathbf{z}^e(t), \mathbf{z}^m(t), \mathbf{a}(t);\ \gamma)$$

- Temporal patterns modeled by ordinary differential equations

Proposed solution: latent hybridization model



Training and prediction via Bayesian variational inference

- Encoder network: infer the latent variables and physiological variables
- Decoder: numerical ODE solver (RK4)
- End-to-end training: adjoint sensitivity method

Results: accurate and actionable predictions

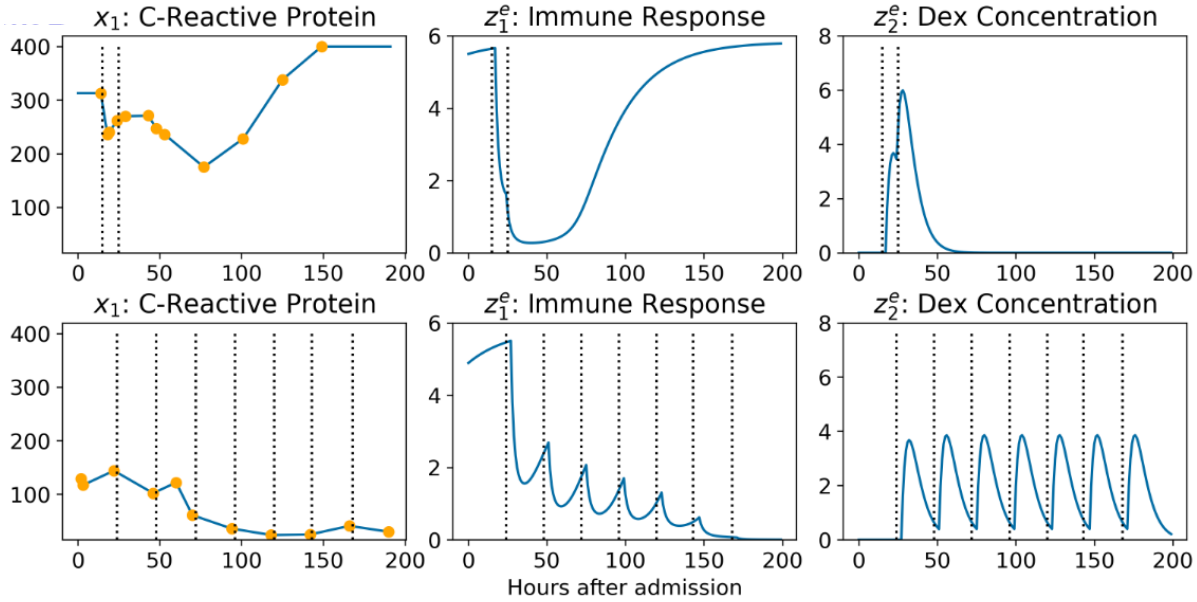


Table 1: Prediction accuracy (RMSE) on COVID-19 intensive care data under different training sample sizes N. Prediction horizon $H = 24$ hours. The standard deviations are shown in the brackets.

Method \ N_0	100	250	500	1000
Expert	0.718 (0.71)	0.704 (0.02)	0.702 (0.02)	0.713 (0.01)
Residual	0.958 (0.63)	1.003 (0.03)	0.717 (0.05)	0.635 (0.04)
Ensemble	0.707 (0.60)	0.657 (0.05)	0.628 (0.05)	0.599 (0.05)
NODE	0.662 (0.65)	0.659 (0.02)	0.644 (0.05)	0.650 (0.04)
ODE2VAE	0.674 (0.62)	0.666 (0.02)	0.643 (0.02)	0.619 (0.02)
GRU-ODE	0.722 (0.60)	0.673 (0.05)	0.623 (0.05)	0.601 (0.05)
Time LSTM	0.706 (0.63)	0.649 (0.03)	0.600 (0.03)	0.631 (0.02)
LHM	**0.633 (0.51)**	**0.605 (0.02)**	**0.529 (0.02)**	**0.511 (0.02)**

Case study on dexamethasone treatment for COVID-19 patients in the ICU

- **PKPD of dexamethasone**: well-studied immunosuppression effect
  - However, the level of immune response is not routinely measured in the clinic
- **Observable clinical variables**: e.g., C-Reactive protein (marker for inflammation)

Reference:

Z. Qian, W. R. Zame, L. M. Fleuren, P. Elbers, M. van der Schaar, Integrating Expert ODEs into Neural ODEs: Pharmacology and Disease Progression, Neurips 2021

Code: https://github.com/ZhaozhiQIAN/Hybrid-ODE-NeurIPS-2021

Lab website: https://www.vanderschaar-lab.com/

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