



Deep Compartment Models and NeuralODEs

Leverage machine learning to gain insights for pharmacometric modeling

Alexander Janssen, PhD
Research fellow and University Lecturer
AmsterdamUMC and ErasmusMC

ISoP AI/ML in Pharmacometrics: Hands-on Workshop and Regulatory Panel
34th PAGE Meeting, Dubrovnik, Croatia
June 2, 2026

Why AI/ML in Pharmacometrics?

- Classical model development involves several manual (*subjective*) decisions.
- Some of these decisions are informed by **prior knowledge**.
- Design decisions are evaluated on data (e.g. through significance testing).
- Open problems:
 - How do we find the optimal model?
 - How do we prevent biases from creeping into our process?
 - How do we prevent overfitting?

Why AI/ML in Pharmacometrics?

- Goals:
 1. Find the optimal model without worrying (too much) about model architecture.
 2. Reduce time spend on model development.

Use-case: tobramycin for the treatment of sepsis

- Tobramycin is an aminoglycoside antibiotic used to treat life-threatening infections.
- Prevents bacterial mRNA transcription.
- Primarily renally cleared (unchanged; not metabolised).
- Narrow therapeutic index: risks of nephrotoxicity.
- Critically-ill have high risk of organ dysfunction → highly individual disease trajectories.
- Precision dosing generally complicated.

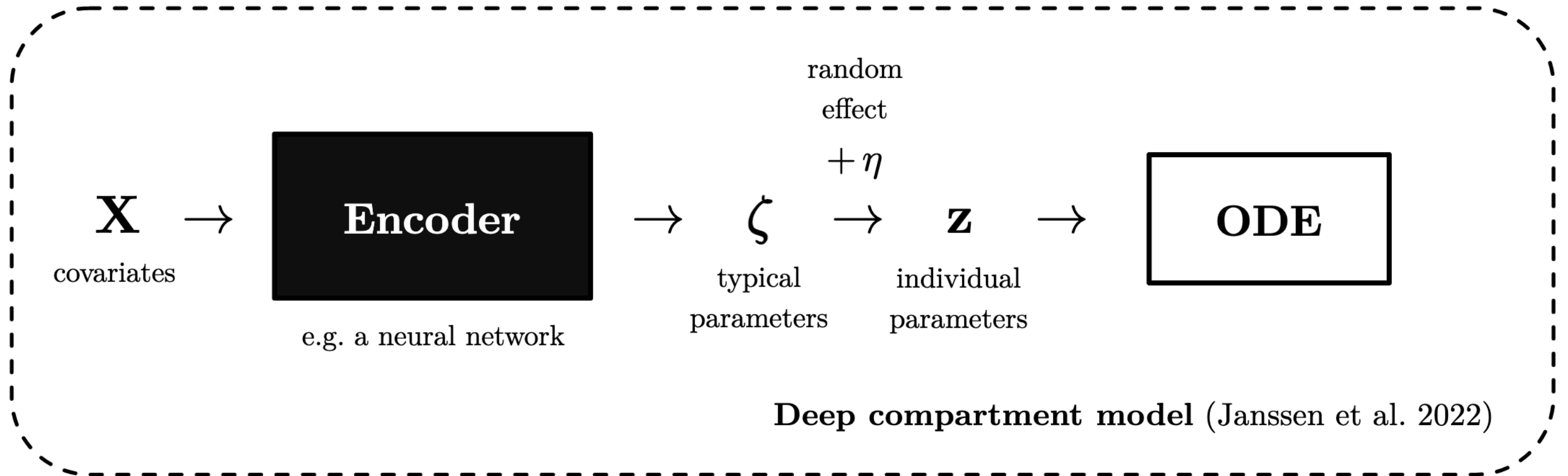
Classical pharmacometric modeling

- Focussed around two key components:
 1. Structural model: dynamical system governing model output.
 2. Covariate model: “explanation” of inter-individual variability.
- How can we leverage ML for building these components?
 1. Structural model: learn unknown components of the dynamical system.
 2. Covariate model: Learn optimal relationship between covariates and parameters.

Covariate / fixed-effect model

- Examples of design decisions:
 - What covariates do we consider for inclusion?
 - What functional relationship do/should we use?
 - Does the learned effect represent noise or actual signal?
 - What does “statistical significance” in this context actually mean?

Deep compartment models



Deep compartment models

- Benefits:

- Directly learn covariate relationships from data.
- Encoder can learn more complex relationships, potentially improving predictive accuracy.
- Use specialised models for different data modalities (e.g. images)

→ We'll use this model to learn covariate effects on PK parameters.

- Limitations:

- Encoder is a black-box model, how do we control its behaviour?
- How do we identify what the model has learned?

→ Use explainable AI method to understand model behaviour.

DeepCompartmentModels.jl

Julia package for defining and training differential equation based ML models.

In pseudo-code:

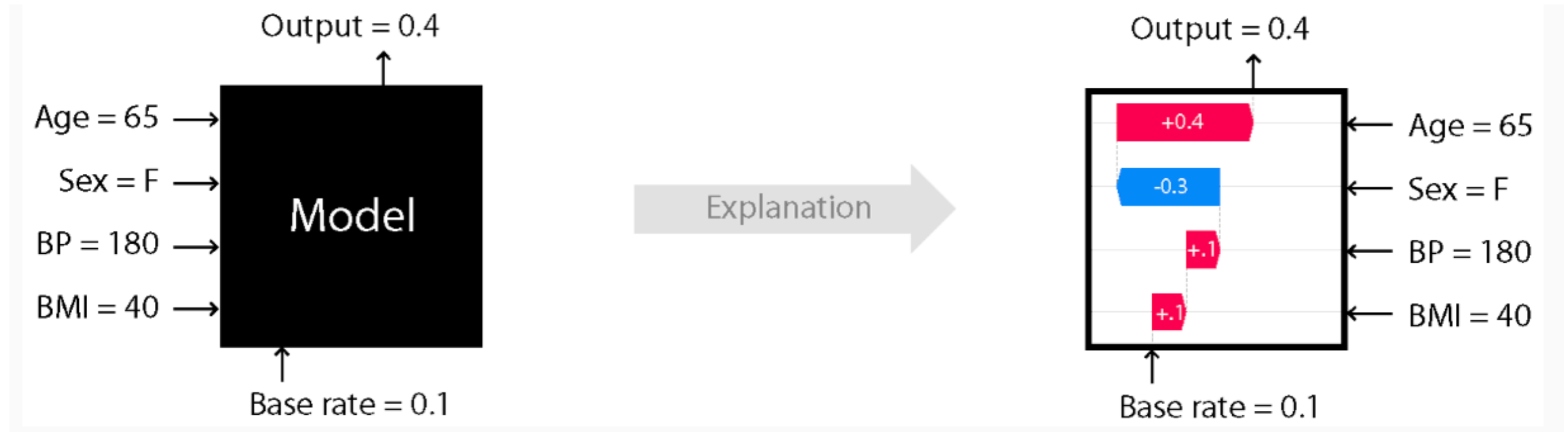
```
1 # Select ODE function:
2 ode_fn = two_comp!
3 # Define neural network using Lux.jl:
4 ann = Lux.Chain(
5     Lux.Dense(num_covariates, 12, relu),
6     Lux.Dense(12, num_params, relu),
7 )
8 # Build Deep Compartment Model:
9 dcm = DeepCompartmentModel(ode_fn, ann, AdditiveError())
```

In this workshop, we'll train basic deep compartment models to predict tobramycin PK, quickly iterating on different models.

Explainable and interpretable AI

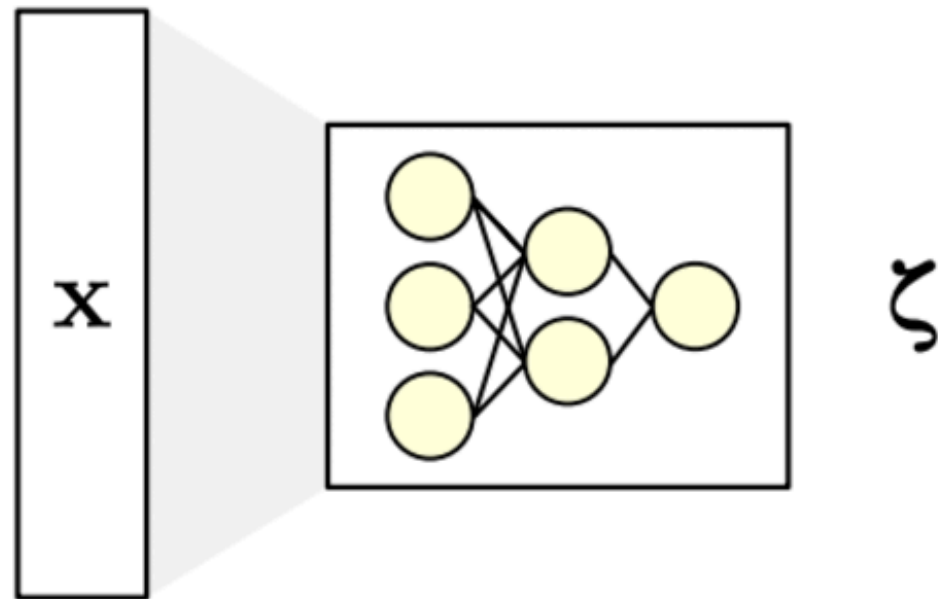
- After training different models, we want to understand how these models come to their predictions.
- There are two related but distinct concepts to understand:
 - **Explainability:** Understanding how to model came to its output.
 - **Interpretability:** Understanding how the model operates internally.

Explainable AI: SHAP

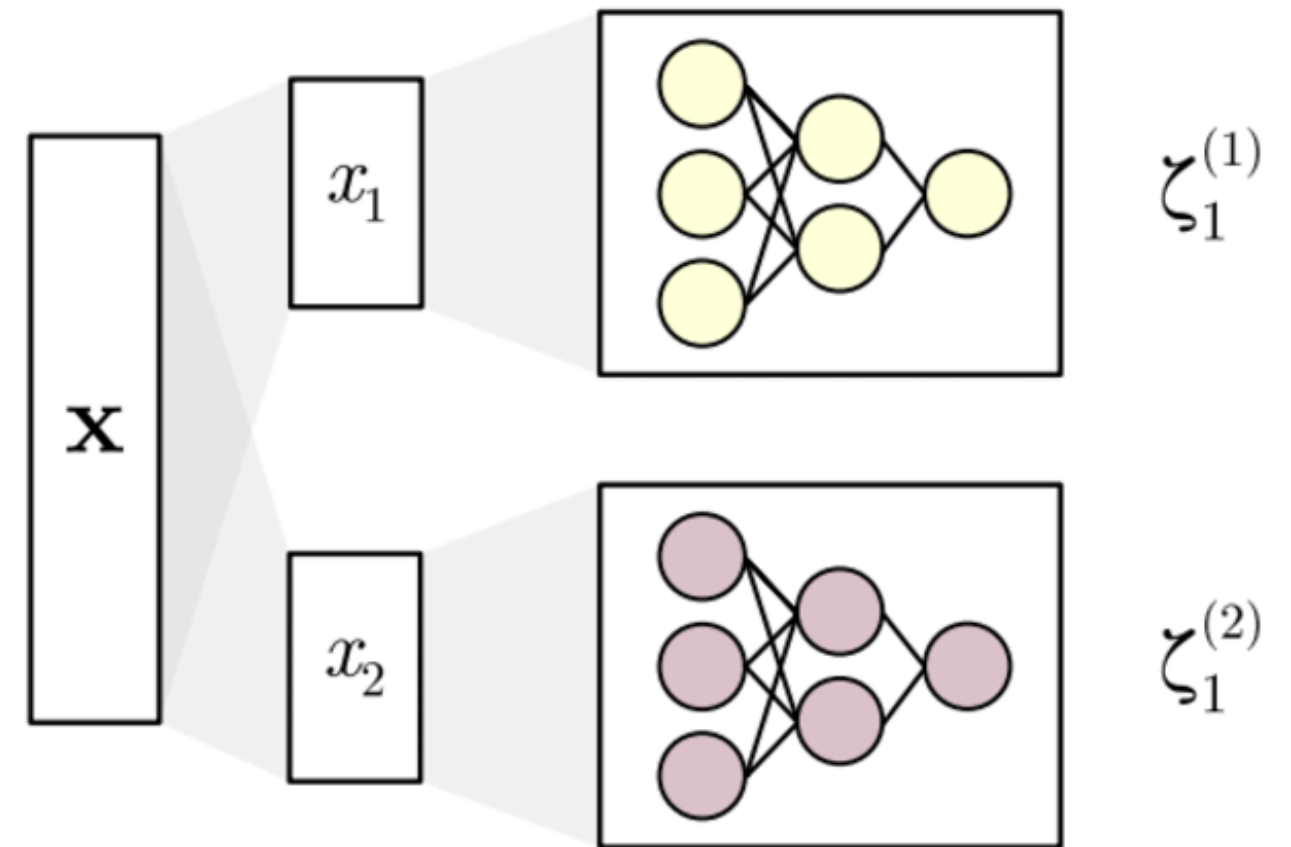


Interpretation: Multi-branch network

Fully-connected network



Multi-branch network



Use-case: tobramycin for the treatment of sepsis

- Tobramycin is an aminoglycoside antibiotic used to treat life-threatening infections.
- Prevents bacterial mRNA transcription.
- Primarily renally cleared (unchanged; not metabolised).
- Narrow therapeutic index: risks of nephrotoxicity.
- **Critically-ill have high risk of organ dysfunction → highly individual disease trajectories.**
- Precision dosing generally complicated.

Effect of kidney function on tobramycin PK

- Renal function strongly influences tobramycin clearance.
- Effect presents as **time-related variability** and is highly **subject-specific**.
- How do we model these kinds of effects? → NeuralODEs.

NeuralODE / universal differential equations

- NeuralODE: use neural networks to directly learn drug kinetics / dynamics.
 - Limitations: unstable, difficult to train.
- Universal differential equations:
 - Use a standard compartment model base \rightarrow prior knowledge.
 - Use neural networks to represent unknown dynamics.

Example:

```
1 function two_comp_with_node!(dC, C, p, t)
2   cl_0, v1, q, v2, I = p
3   # add time related change in clearance
4   cl_t = cl_0 + model(t)
5   k10 = cl / v1
6   k12 = q / v1
7   k21 = q / v2
8
9   dC[1] = I / v1 - (k10 + k12) * C[1] + k21 * C[2]
10  dC[2] = k12 * C[1] - k21 * C[2]
11 end
```

The final model architecture

