

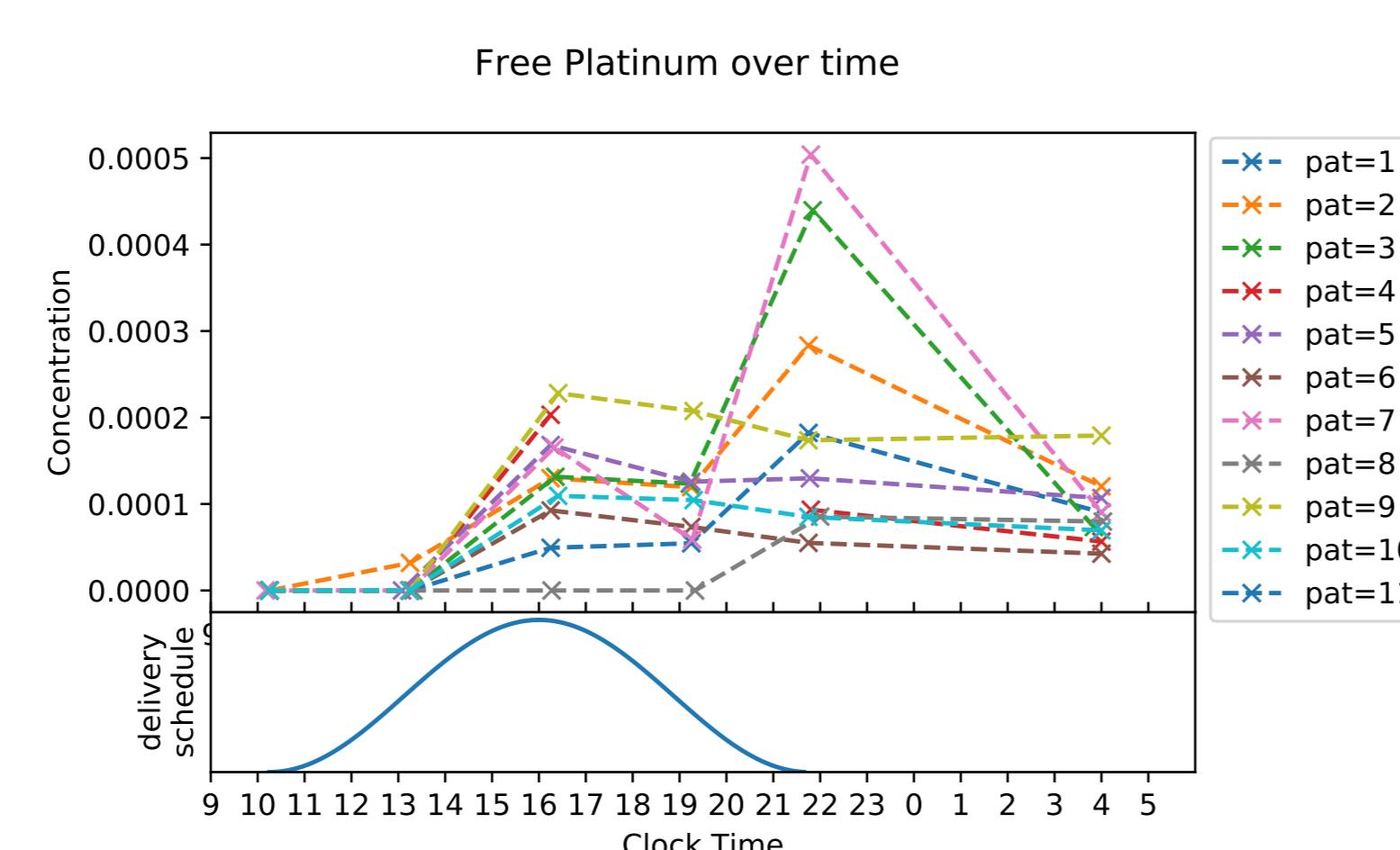
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## Background

This project aimed to improve the understanding and optimise the delivery of colorectal cancer treatment by using mathematical techniques.

## Motivation/Data

- Data from OPTILIV hepatic arterial infusion trial<sup>a</sup> of FOLFOX treatment regime.
- Three drugs delivered according circadian timings: irinotecan (CPT11), 5-fluorouracil (5-FU) and oxaliplatin (LOHP).
- Data showed anomalies in delivery times and plasma concentration.
- The need to understand and quantify inter-patient variability.

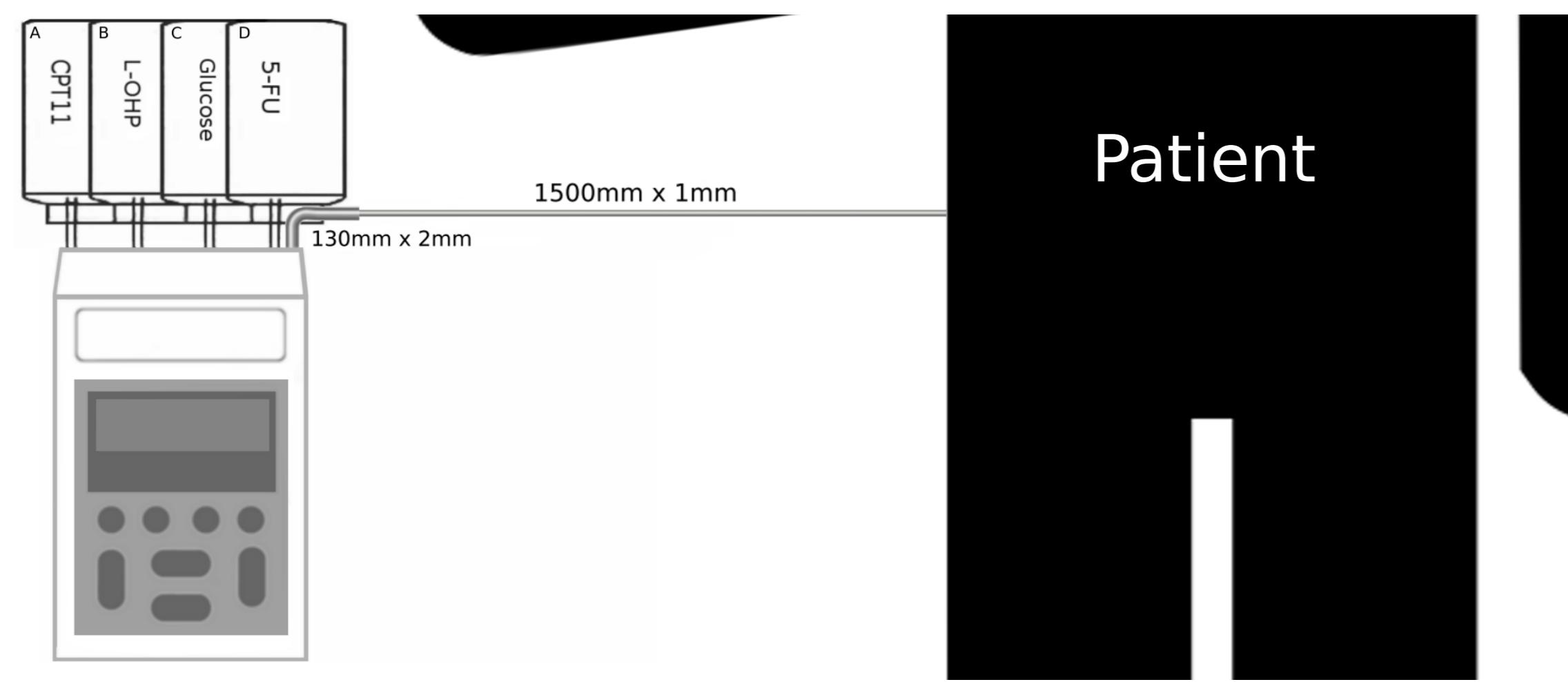


Data from the OPTILIV trial, showing delay in PK concentration and peak in delivery when delivery should have stopped.

## Project Outline

- Create a PDE pump-to-patient model to predict actual drug delivery.
- Use this to fit PK model for each drug.
- Use PK parameters to assess inter-patient variability.

## Pump-to-Patient



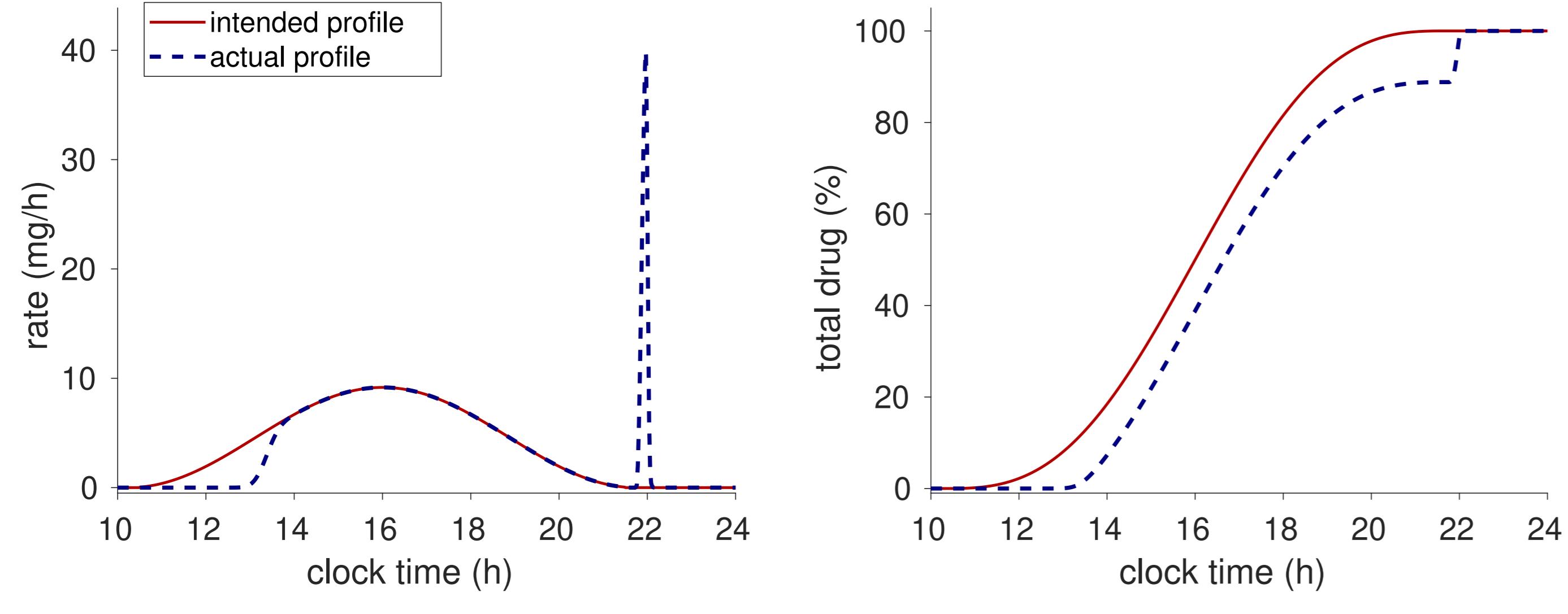
## PDE Model

$$\frac{\partial U}{\partial t} = V(t) \frac{\partial U}{\partial x} + D \frac{\partial^2 U}{\partial x^2} + \delta(x) S(t) \quad t \in [0, T], \quad x \in [0, L]$$

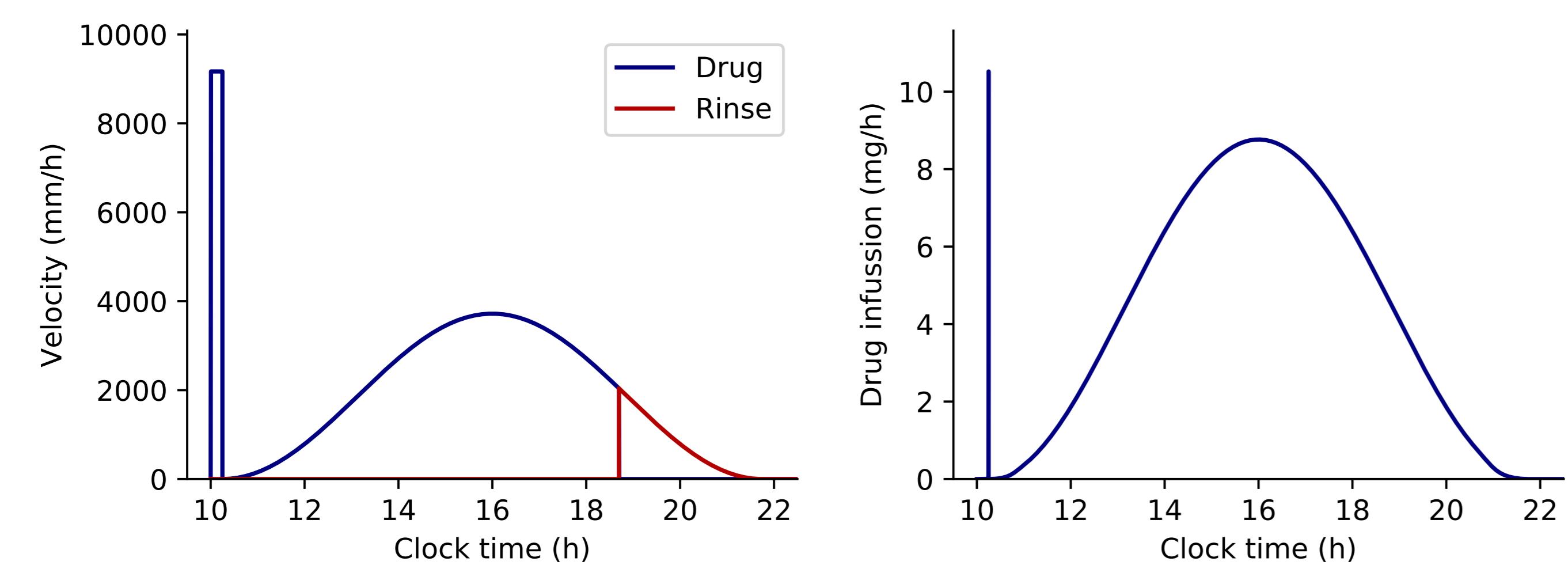
## Methods

- Transport diffusion equation.
- Solved using backwards finite difference method in Matlab

## Results

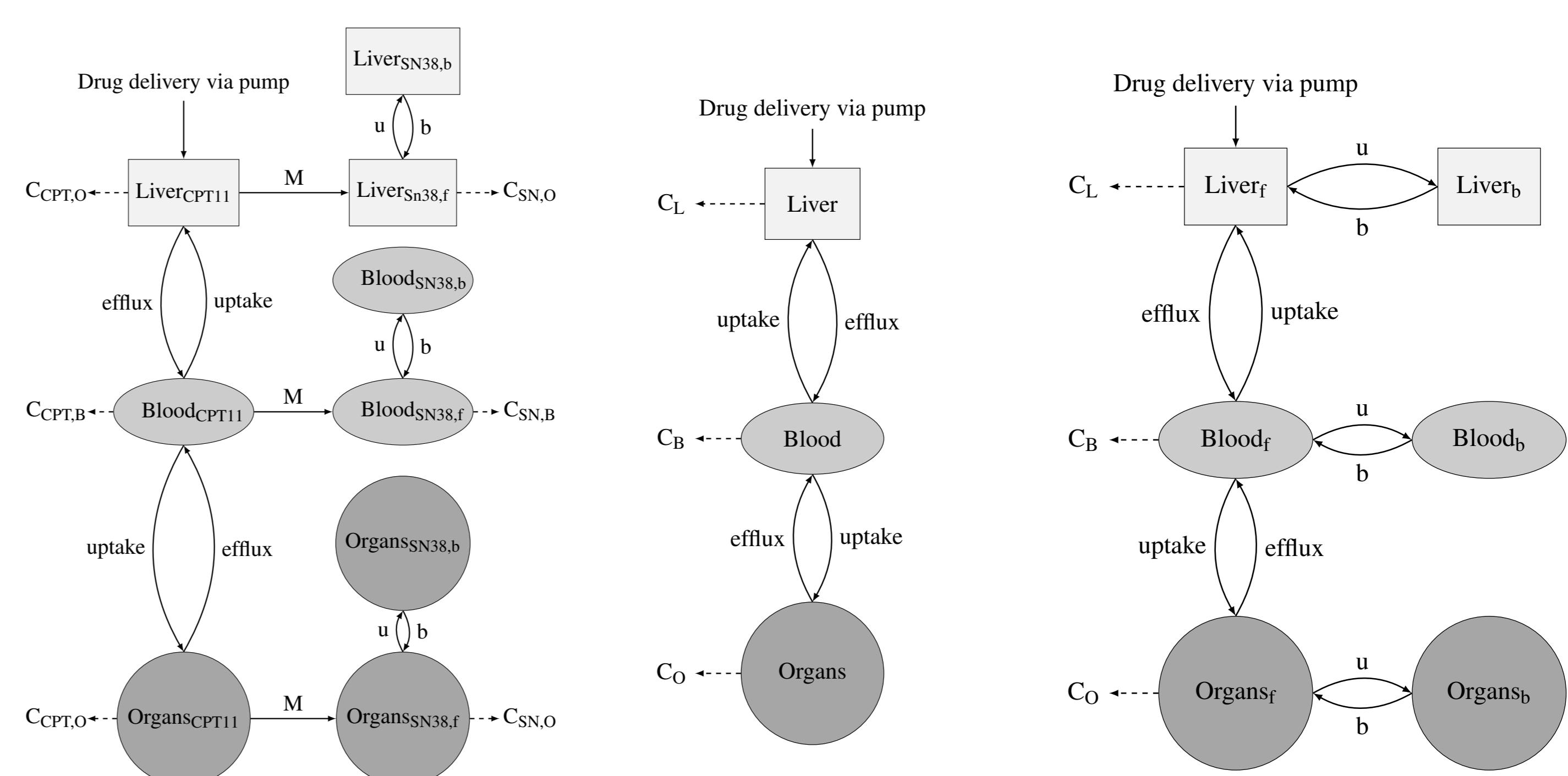


## Solution



## references

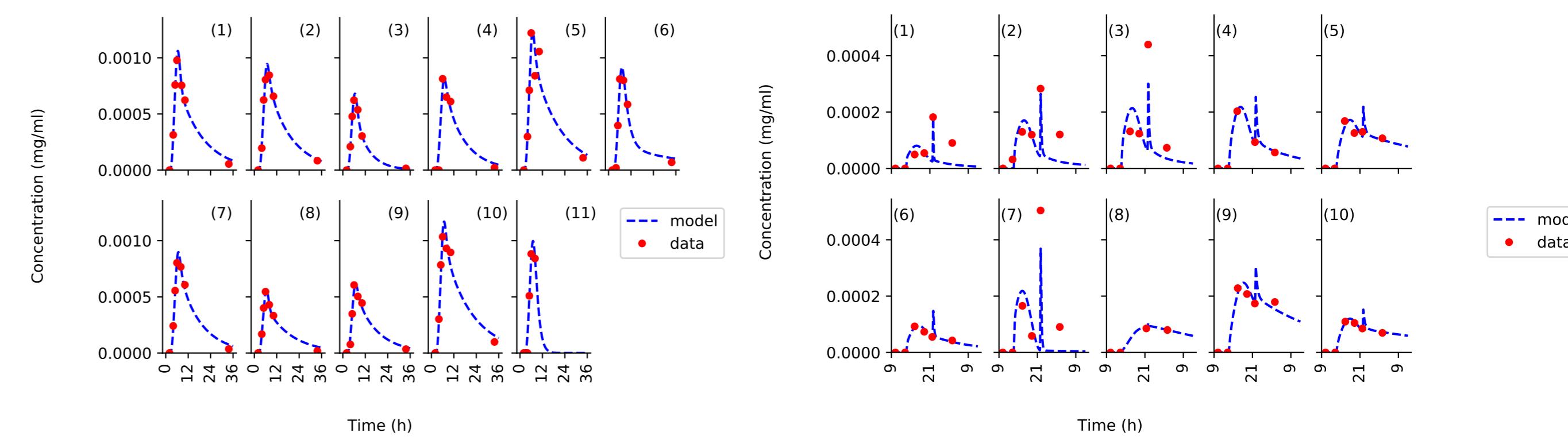
## PK Models



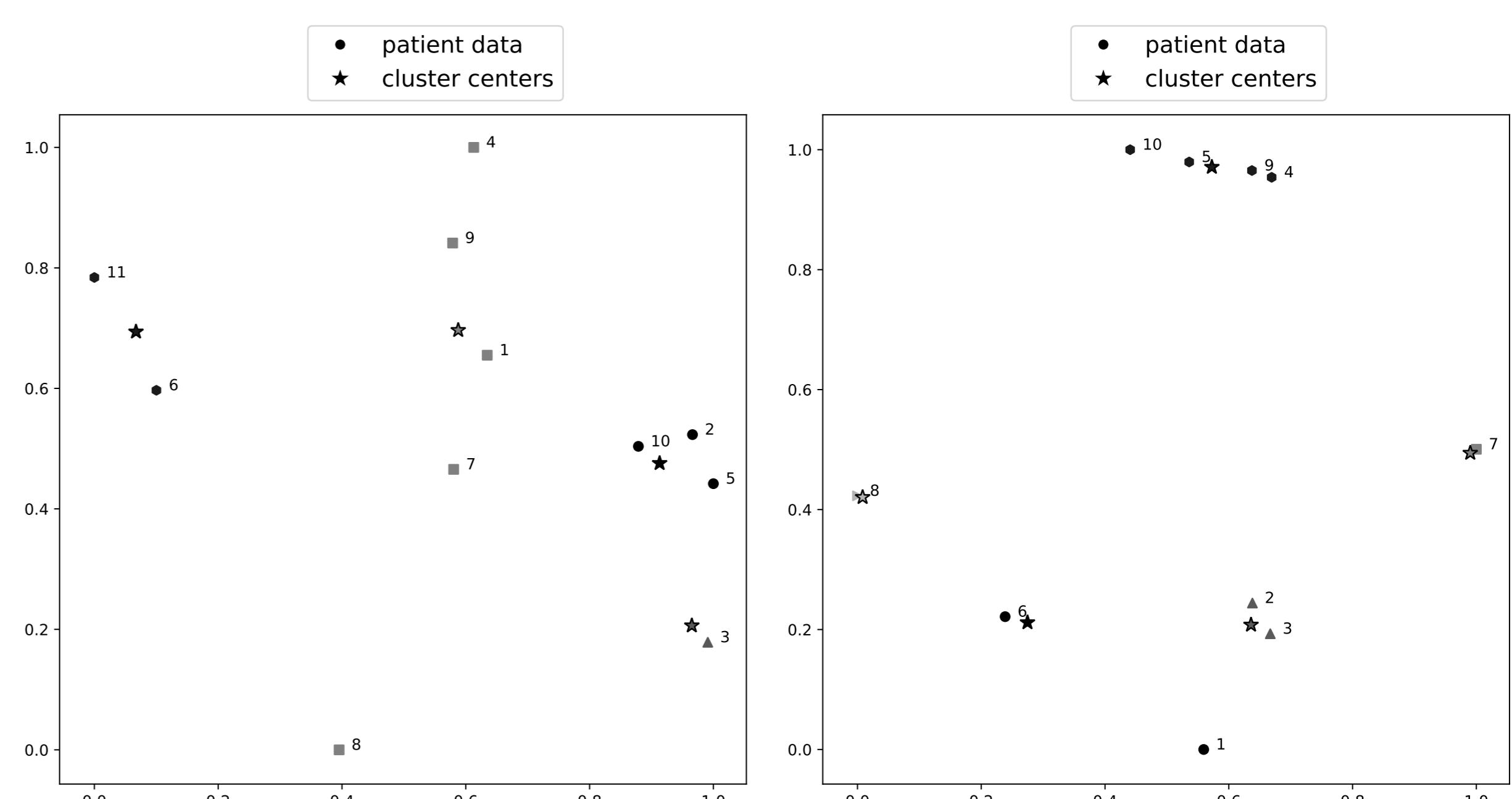
## ODE Compartment Models

- The pump-to-patient model was used to get actual delivery profiles into the PK models.
- Each model had three main compartments
- These compartments for CPT11 and LOHP were split to represent the metabolites, and bound states of the drugs.
- Number of parameters were chosen based on sensitivity analysis.
- Efflux and uptake parameters were chosen to be identical within the organ compartment and clearance was chosen to be the same as clearance in the organ.

## Model Fit



## Clustering



Multi-dimensional scaling plot of clusters for CPT11 and LOHP.

## Inter-Patient Variability

Inter-patient variability was assessed using coefficient of variation and fuzzy c-means clustering. Clustering was determined by finding highest fuzzy partition coefficient (fpc).

Drug	Mean CV (%)	CV range	# Clusters
CPT11	89.58	16.88 - 247.58	4
5-FU	125.73	64.16 - 192.5	5
LOHP	91.84	55.90 - 125.42	5

## Conclusion

- PDE model showed insights into the actual drug delivery
- PDE model showed how the inaccuracies in delivery could be overcome.
- PK model confirmed that the PDE model explained the abnormal data.
- PK model gave an indication of the inter-patient variation of each drug.
- These results can be used to target which drug to personalise.
- 5-FU is most varied, the LOHP, then CPT11. This could be an indication of the order of personalisation.