Physiologically based pharmacokinetic models may be inherently, practically unidentifiable

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PBPK models are used routinely in pharma industry

What are Physiologically Based Pharmacokinetic (PBPK) models?
• Descriptions of physiology
• Encoding of kinetics (what the body does to a drug/cell of interest)
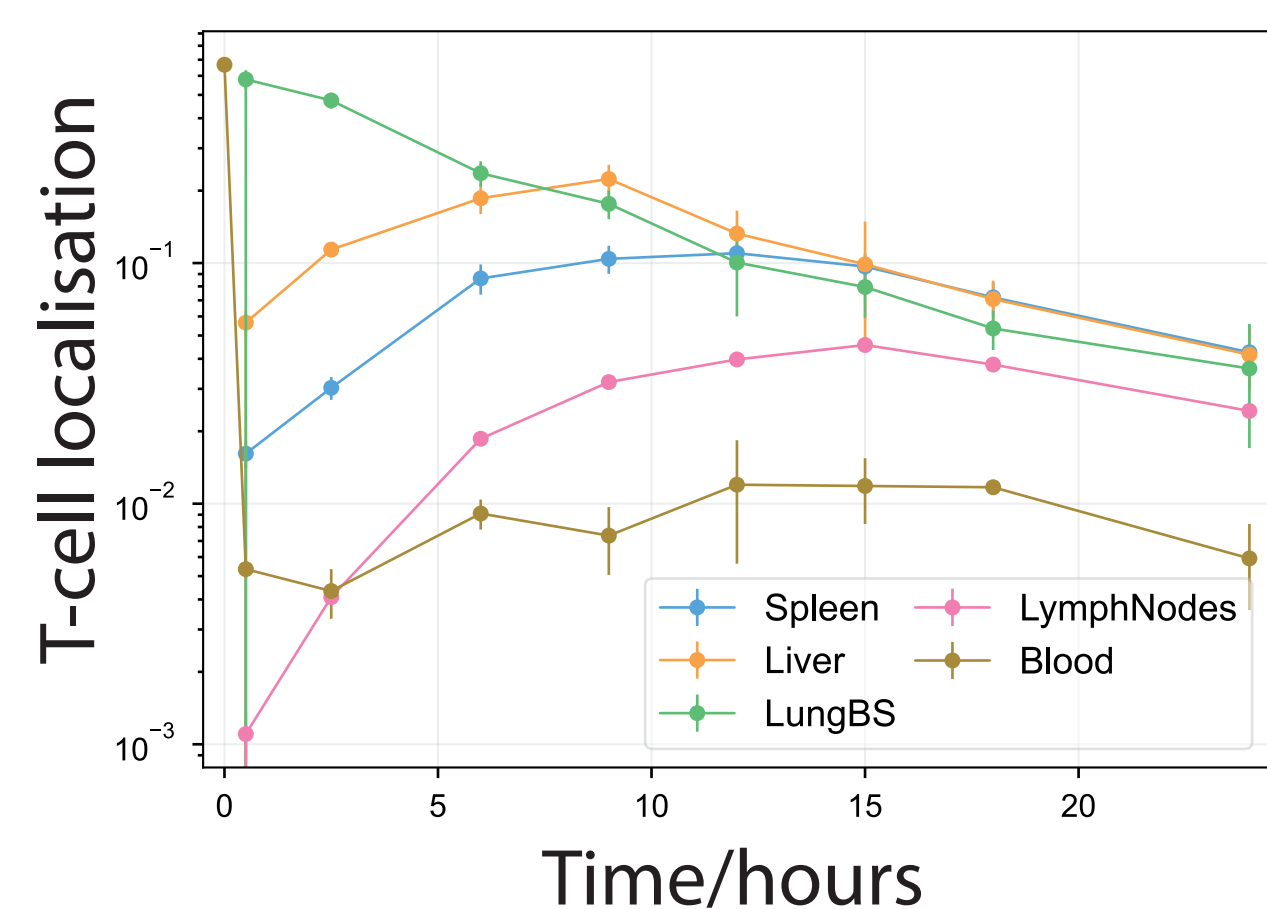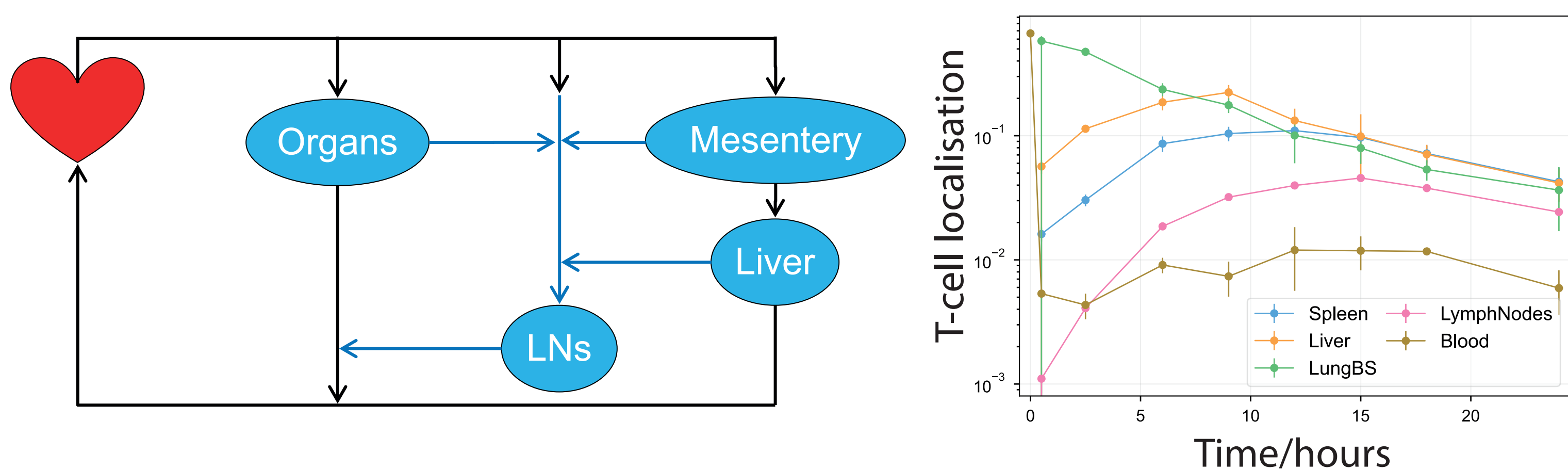
What are PBPK models used for?
• To fit to data and calculate quantities of interest
• To understand biological mechanisms of action
• To estimate rates of biological processes
• To compare subjects or interventions

Parameters can't always be recovered from "good" fits to noisy synthetic data

Testing parameter estimation:
• Generate "data" by running a model with known parameters
• Fit the model to your synthetic data with noise added
• Compare fit parameters to the originals
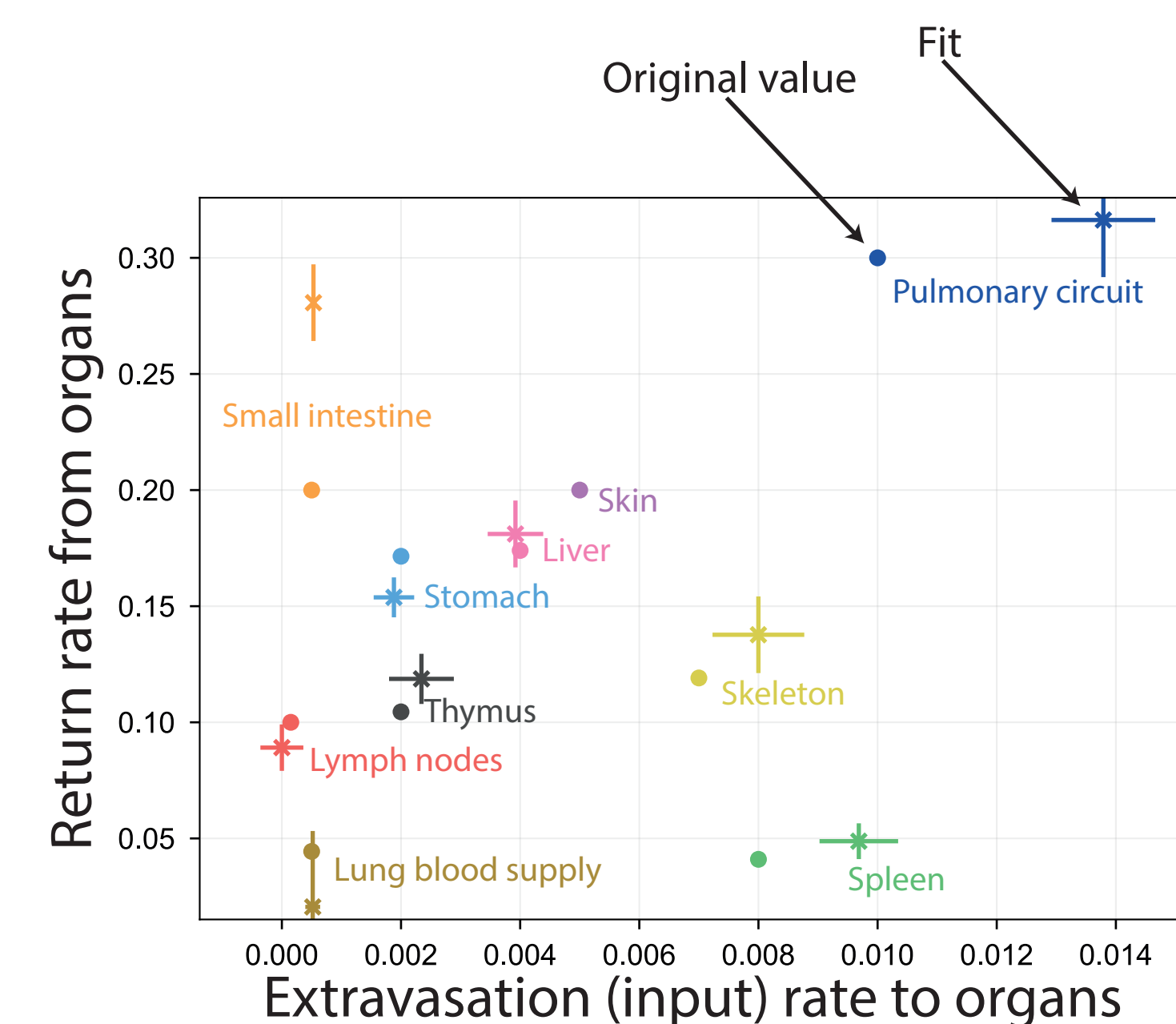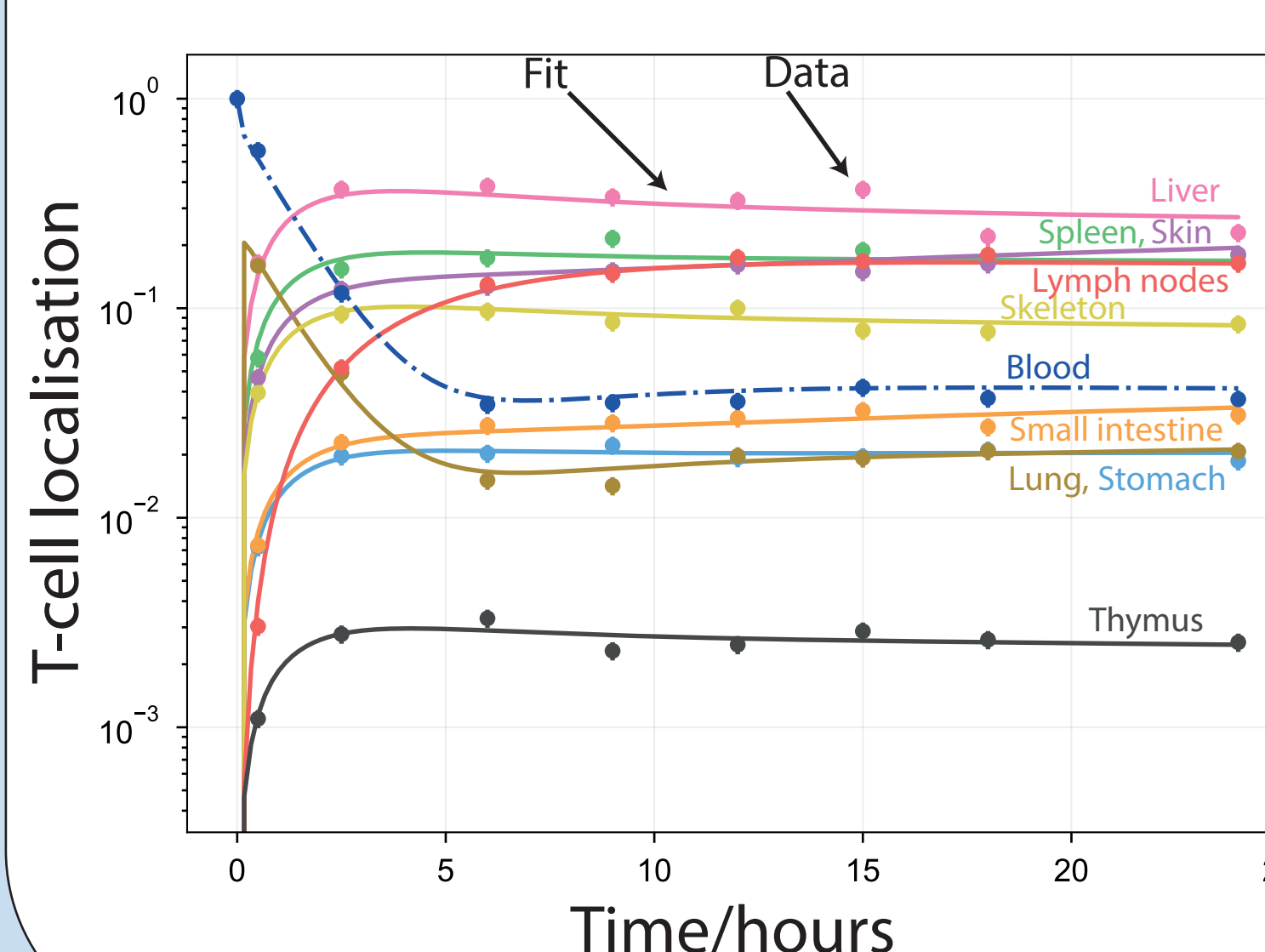
Parameters aren't identifiable & there is no easy fix

Two fits in the figure are indistinguishable:
One set of lines: output using true params
2nd set of lines: output using best fit
Difference between fits is less than noise
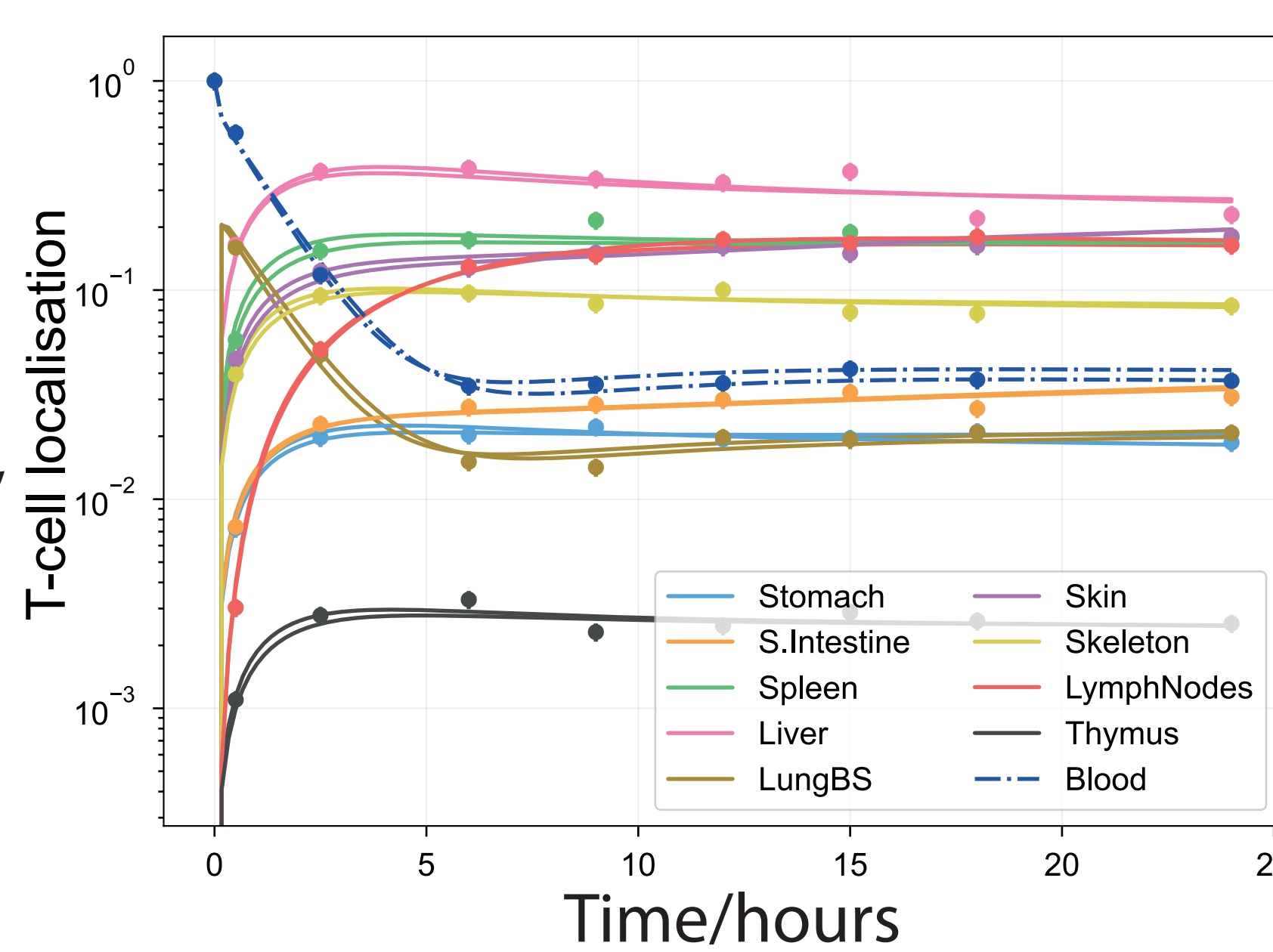
Structural identifiability
For parameters to be structurally identifiable, there is some output y such that

$$y(t, p) = y(t, p') \rightarrow p = p'$$

This model is structurally identifiable, but

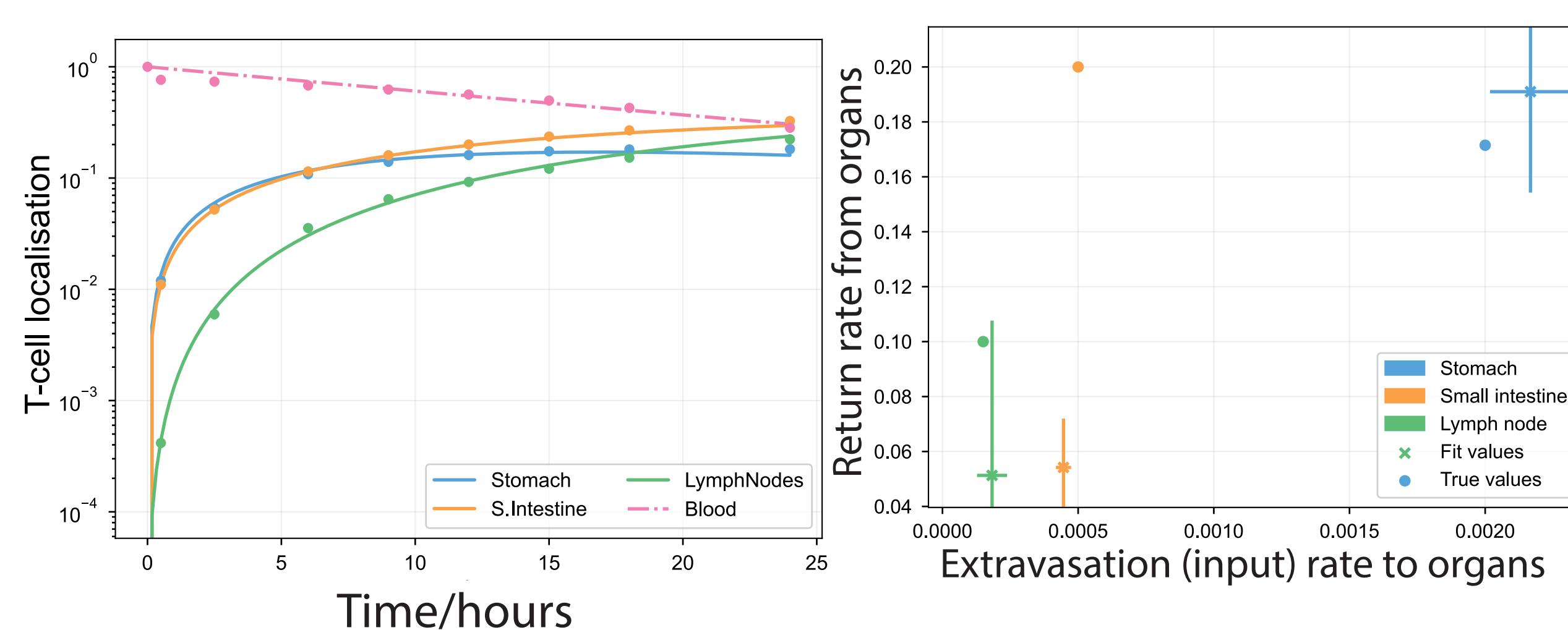$$y(t, p) \approx y(t, p'); \quad p \neq p'$$

So, the model is **practically unidentifiable** in the presence of noise or an imperfect fit

Brute-force solutions
Is the model practically identifiable if we...
Have more data?   Only to an extent
Have fewer organs?   Same problem with 3 organs *(below)*
Fix parameters?   Same with organ input rates fixed
Use another model?   Same with 2 other published models

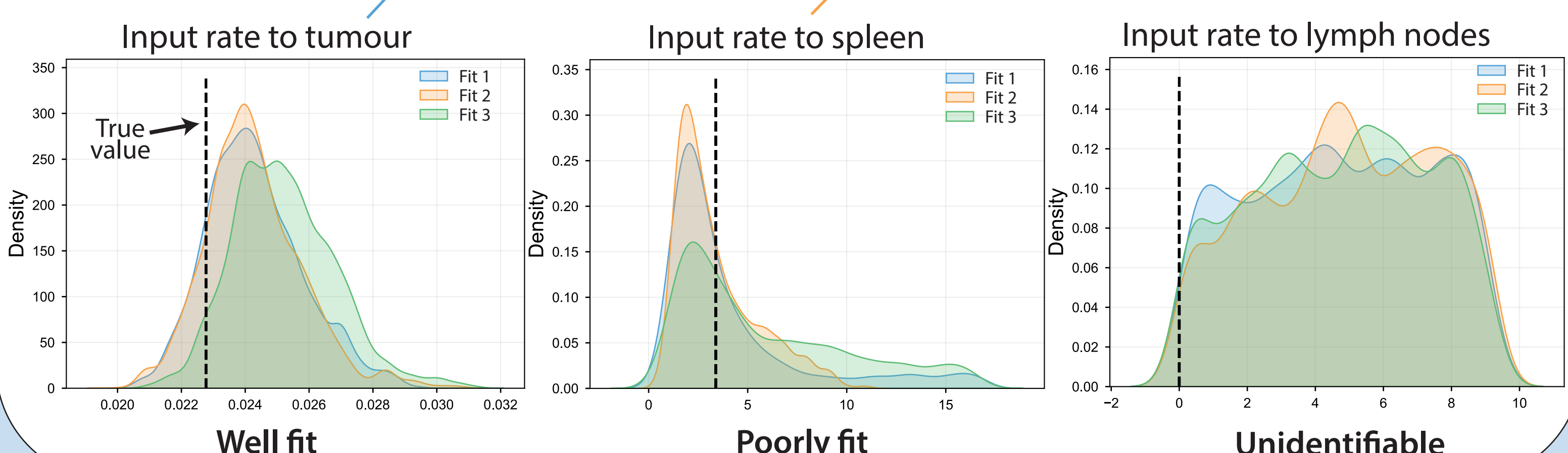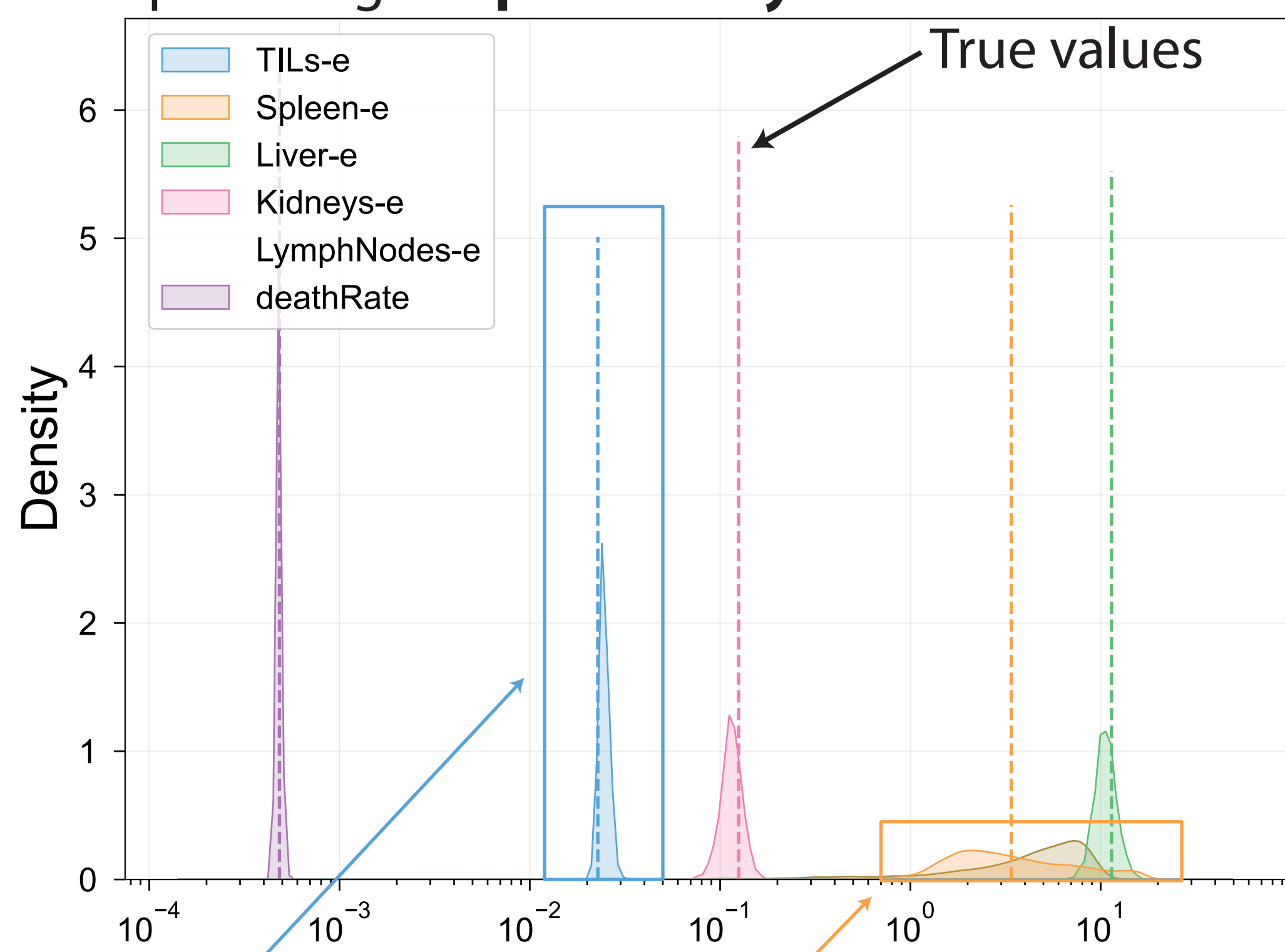## Simple identifiability analyses go a long way

Sensitivity analysis:
Do any parameters affect no outputs?
Timescale analysis (table right):
Are timescales associated with parameters on the timescale of the data?

Name	Equilibrium time / hours
Stomach	14
S.Intestine	285
Lymph Nodes	239

Better: a technique that gives **probability densities**

When are parameter values important?

• If parameters have biological meaning or analogues
• When taking parameter values from literature
• When scaling a model to other populations or species
• When interpreting differences between fits or models

If parameters are important, we need to know
• Are their values unique or could many values fit the data?
• What is the confidence interval on the parameter estimates?

• Of the top 13 cited PBPK studies since 2010, none reported parameter uncertainty or identifiability analyses

• Many biological models exhibit "sloppy" sensitivities and their parameters may have no meaning [1]

Take home messages

Most physiologically based models are likely to be practically unidentifiable

If parameters are important, test for identifiability and give confidence intervals!

Most published PBPK studies report neither

Published parameter values may not always be trustworthy in another model

Key references
1. Gutenkunst et al (2007), PLoS Comp Bio, doi:10.1371/journal.pcbi.0030189
2. Liam V Brown et al (2022), Journal of PKPD, in press