From Physiologically Based Pharmacokinetic Modeling toward System Biology

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Overview

What is a PBPK model?

Main goals of PBPK modelling

Classical PK Data

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Examples

Current work on cellular stochasticity

- Stochasticity at low exposures
- Analysis at steady state
- Consequences for dose-response curves
- Dynamics

What is missing

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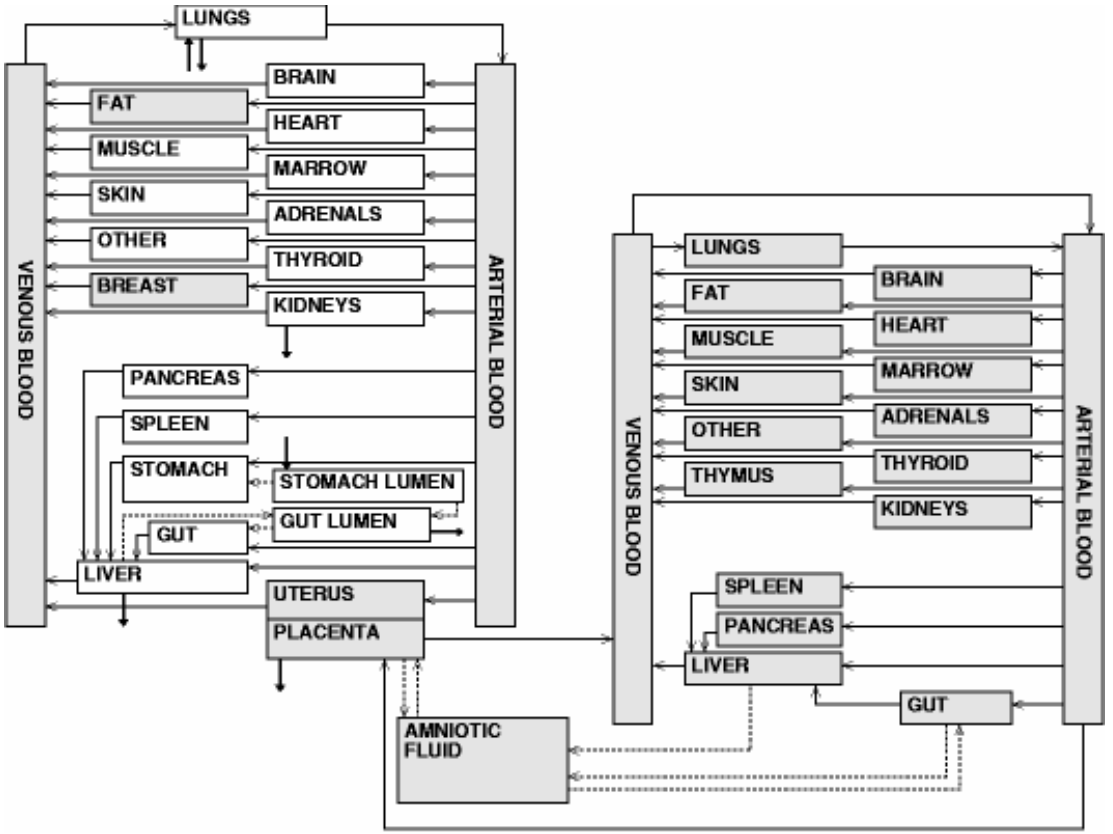
What is a PBPK model?

Physiologically-Based Pharmacokinetic model: The body is described as a set of compartments corresponding to organs or tissues where substances can be transported, metabolised, etc.

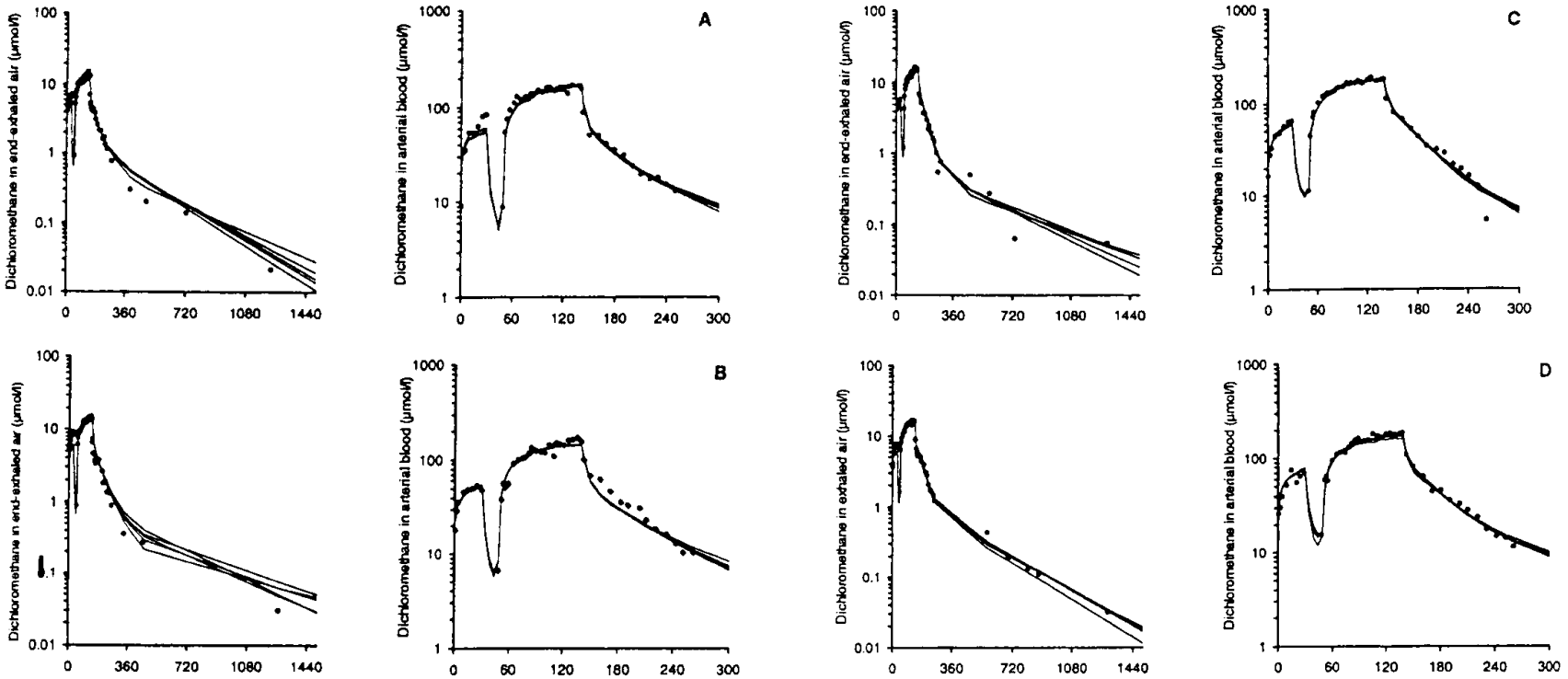


Main goals of PBPK modelling

- Data integration (QSAR, *in vitro*, *in vivo,* medical imaging)
- Checking complex hypotheses
- Internal dose predictions, exposure dose reconstruction
- Extrapolations
  - Dose
  - Time
  - Administration routes
  - Inter-species
  - Inter-individuals

Classical PK Data

- Times series data, with multilevel structure



Inference

- Inference on parameter values can be made via MCMC in a multilevel Bayesian framework (Gelman *et al*., JASA, 1996)
- We use Metropolis within Gibbs, Metropolis on the full set of parameters, Metropolis with tempering, Particle algorithms, for :
  - inference
  - posterior predictions, model checking, sensitivity analysis on the structural model
  - optimal design (Amzal *et al.*, JASA, 2006)

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Inference

- Inference on parameter values can be made via MCMC in a multilevel Bayesian framework (Gelman *et al*., JASA, 1996)
- There are typically from 10 to 100 parameters per subject, with 5 to several hundred subjects (Mezzetti *et al.*, JRSS C, 2003)
- Software available
  - PK BUGS
  - MCSim
  - R
  - ACSL

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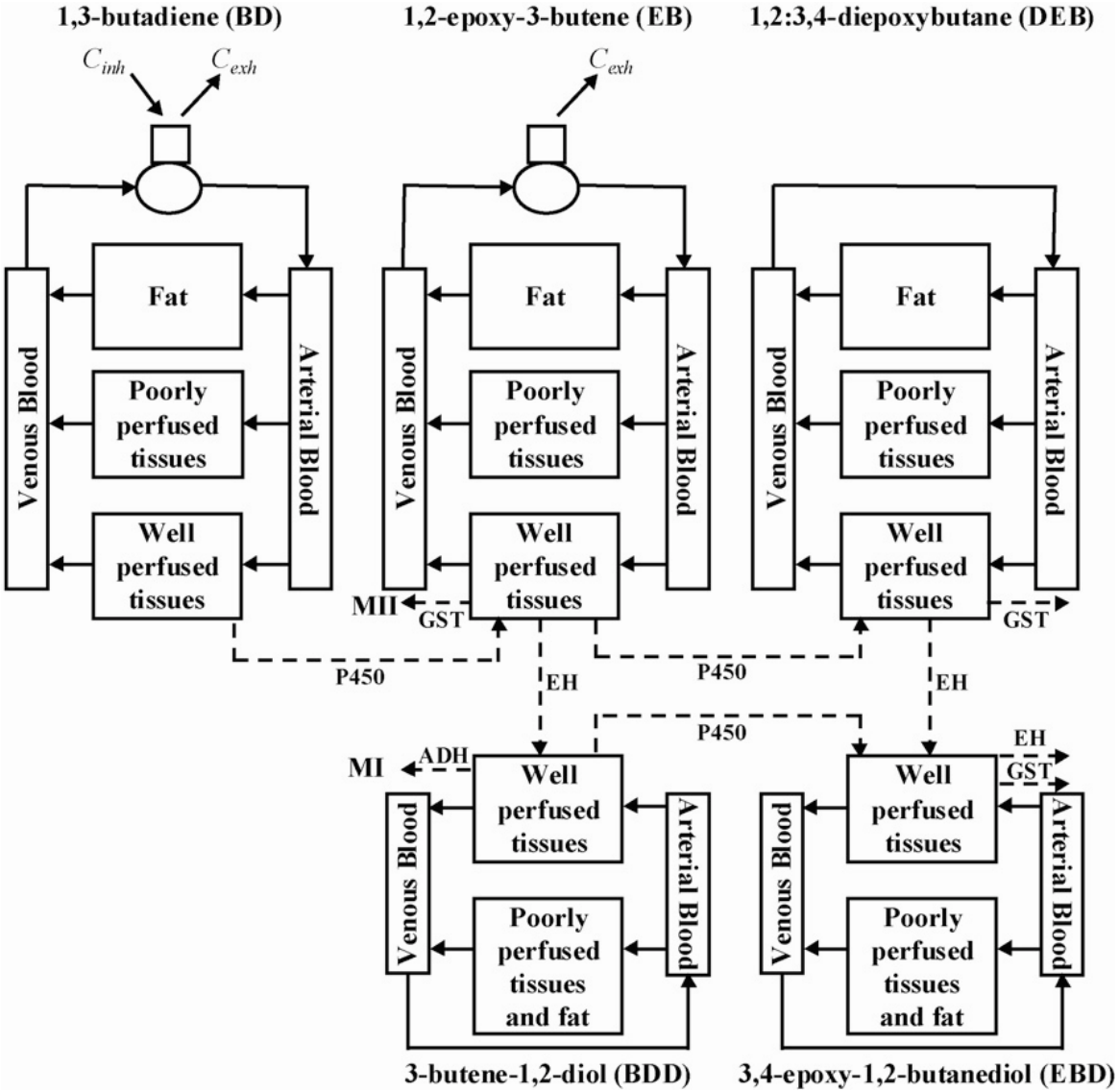
Links to Systems Biology

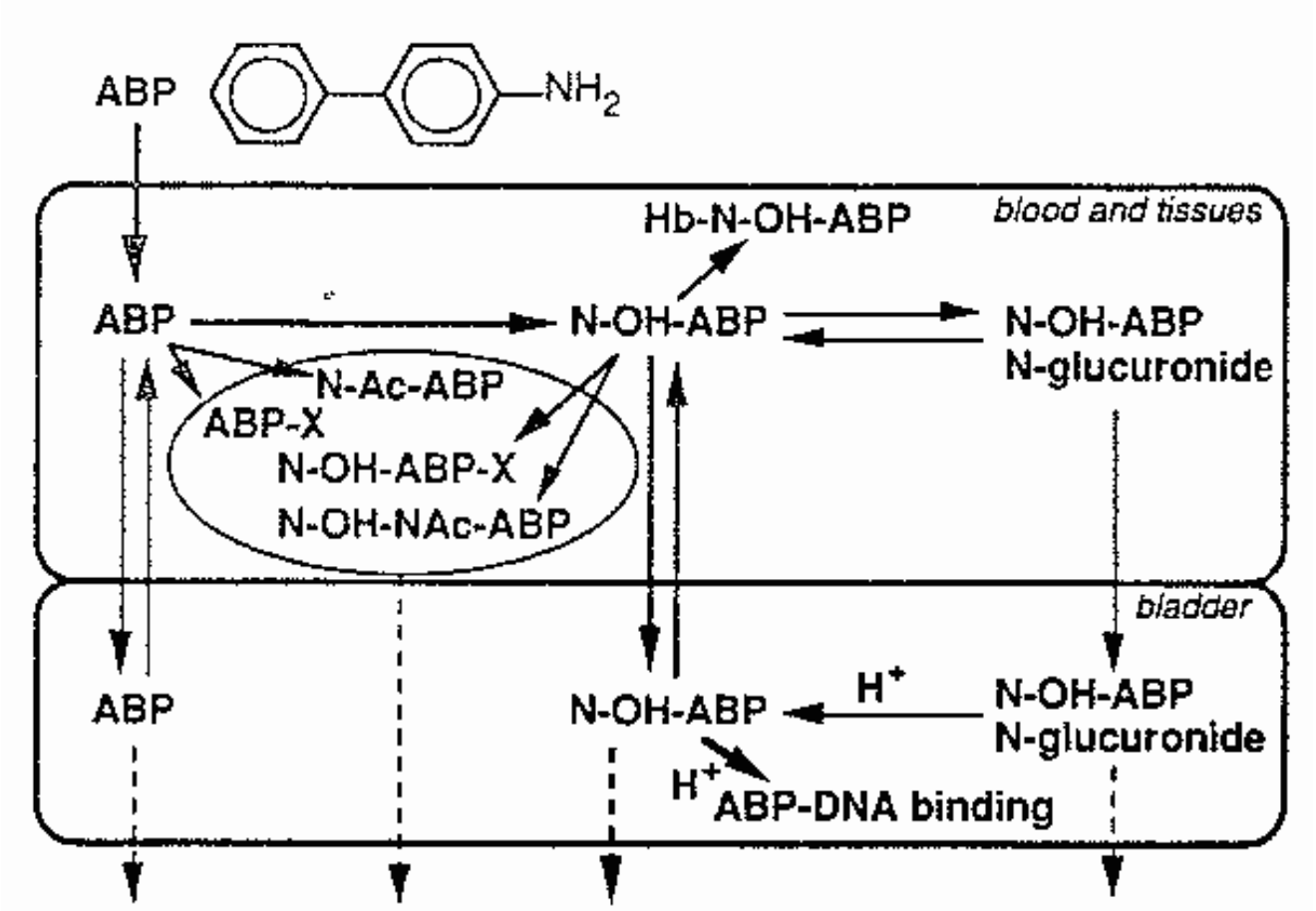
Links are obvious, as PBPK modelling starts at an upper level of the body hierarchy and progresses downward :

- Metabolic networks (for interactions between multiple chemicals)
- Mechanistic link to effects (perturbation of regulations, signalling,...)
- Impact of stochasticity on activity or damage at the cellular level

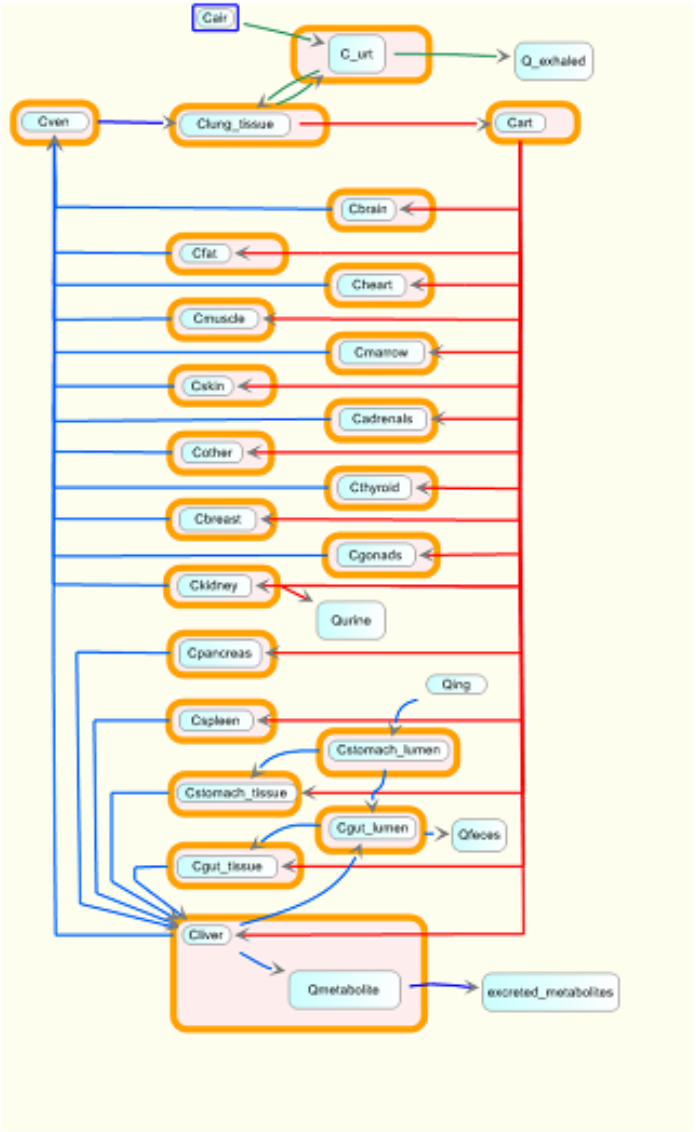
Example of PBPK metabolic network



Example of a semi-PBPK detailed reaction path



Current work on cellular stochasticity

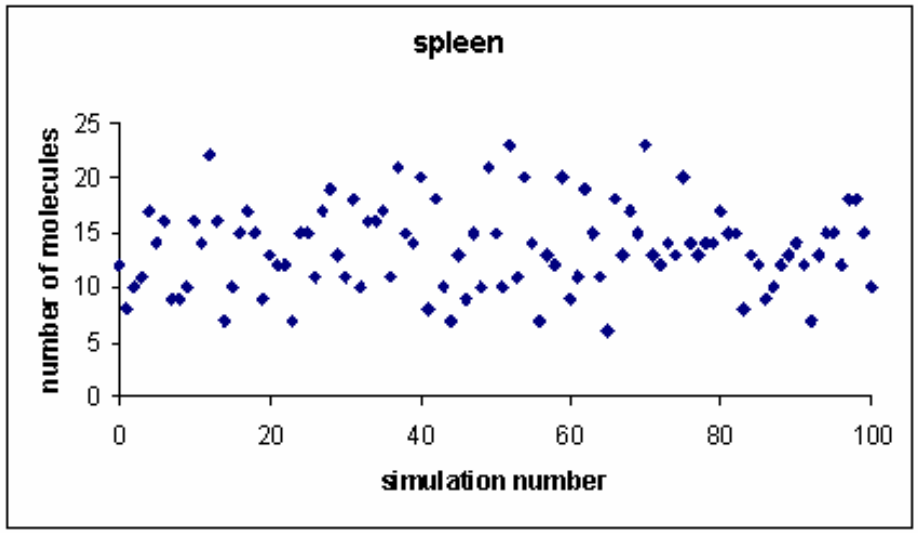


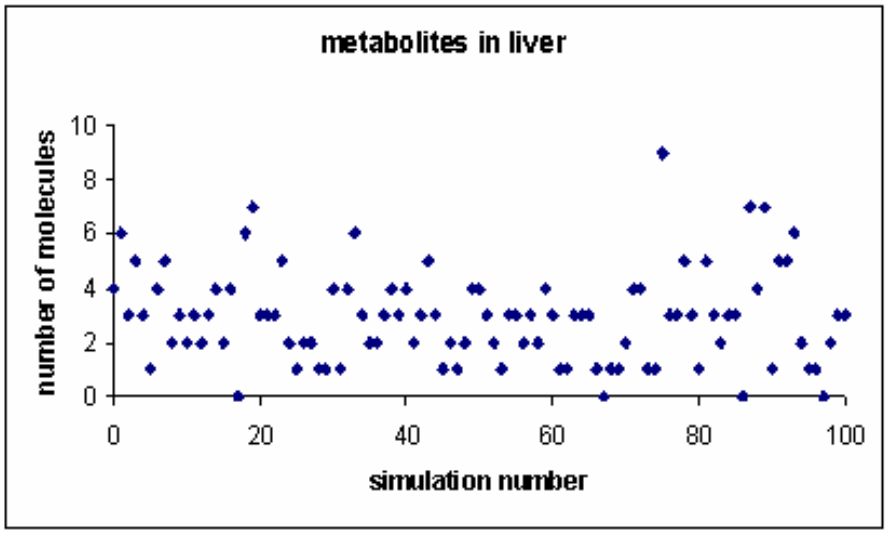
- Our PBPK model was implemented in JDesigner 2.0.39 and MCSim 5.0.0. It is parameterised for a human male.
- It has 23 physiological compartments linked through kinetic or transport equations.
- 1,3 butadiene can be eliminated either through expiration or metabolism in the liver (as a 1st order approximation).

Stochasticity at low exposures

- If we consider that a human has typically got 10^{14} cells, the mean cell density in our PBPK model is **1.34 10^{12} cells/L**
- According to Higashino *et al*. (2007), exposure to butadiene in general environment in Japan is 0.25 µg/m^3. Lifetime excess cancer risk level is estimated at 10^{-5} for exposure concentration 1.7 µg/m^3. With a butadiene molar mass of 54.09 g/mol, 0.25 and 1.7 µg/m3 corresponds to **2.75 10^{12}** and **18.7 10^{12} molecules/L**
- So, we only expect a few molecules per cell at those levels. We adapted our JDesigner model, in terms of flows and volumes, to be able to study cell kinetics.

Analysis at steady state

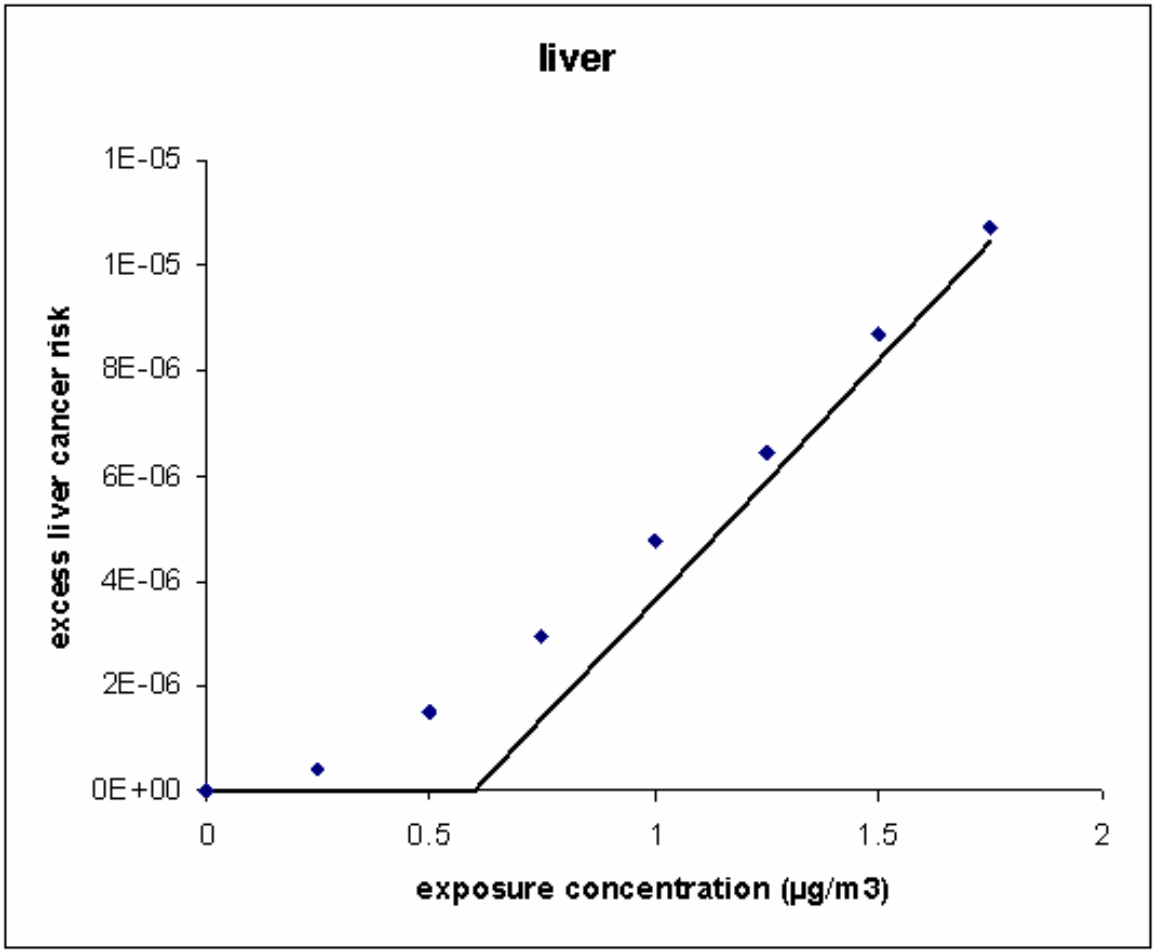




- Using Dizzy 1.11.4, we simulated for 100 cells the number of molecules per cell at a given time.
- Even at steady state for organ concentration, the concentration per cell can differ substantially between cells.

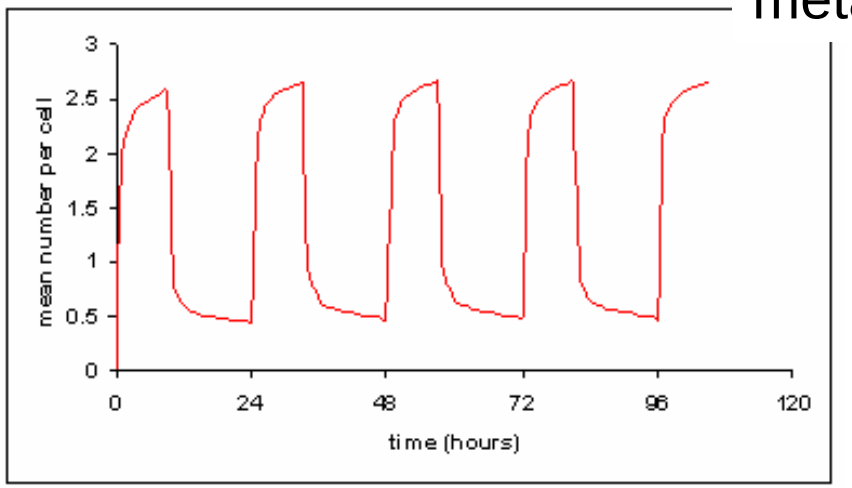
Consequences for dose-response curves

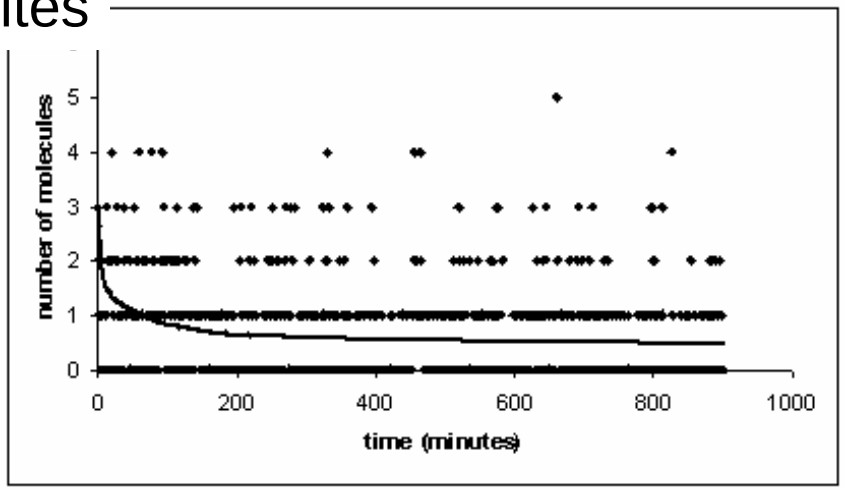
- Simulated lifetime excess risk cancer due to butadiene metabolites in the liver.
- Assuming a threshold for cellular response.
- Liver response is integrated on all its cells.
  - Plain lines : theoretical dose response with threshold.
  - Diamonds : dose-response obtained from stochastic simulation



Dynamics

metabolites





- Simulated 9h exposure to 1.7 µg/m^3 butadiene and then at 0.25 µg/m^3.
- The risk of cancer due to butadiene metabolites in the liver is significantly underestimated by a deterministic estimate of their quantity

What is missing

- We have not linked the posteriors of model parameters to stochastic simulations at the cell level. Let alone the reverse (which might be needed for correct inference
- We have not worked a lot on model structure: structure is quite obvious at the anatomic and physiologic level (huge prior), much less so at the metabolic level.

→ We have a sofware problem, which we might try to solve by adapting our *Mcsim* software