



Universität
Zürich^{UZH}

Model-Based Analysis Of Time-Resolved Comet Assay – A Prototype For Evaluating Dynamics In Scattering Data?

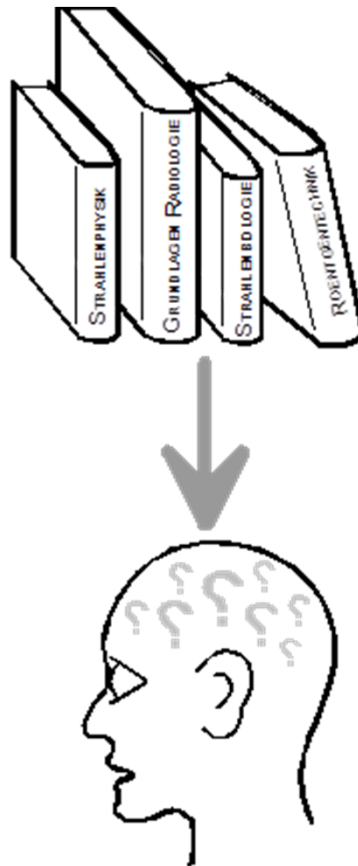
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«Real-world» data and models

Digital health – data Analysis

Example: Analysis of time-resolved Comet data

Conclusions

Systems Biophysics – Systems Medicine – a Landscape

Concepts:
Illness, disease
Body as mechanism
Compartments
Life as process
emergence

Theory:
Physiology,
Pathophysiology
Systems theory of
- *Cancer*
- *Immune system*
- ...

Math. Models:
Events, MC
Statistic mechanical
Compartmental
(neuronal) networks
Spatio-temporal

Data

← «real world»

Clinical observations

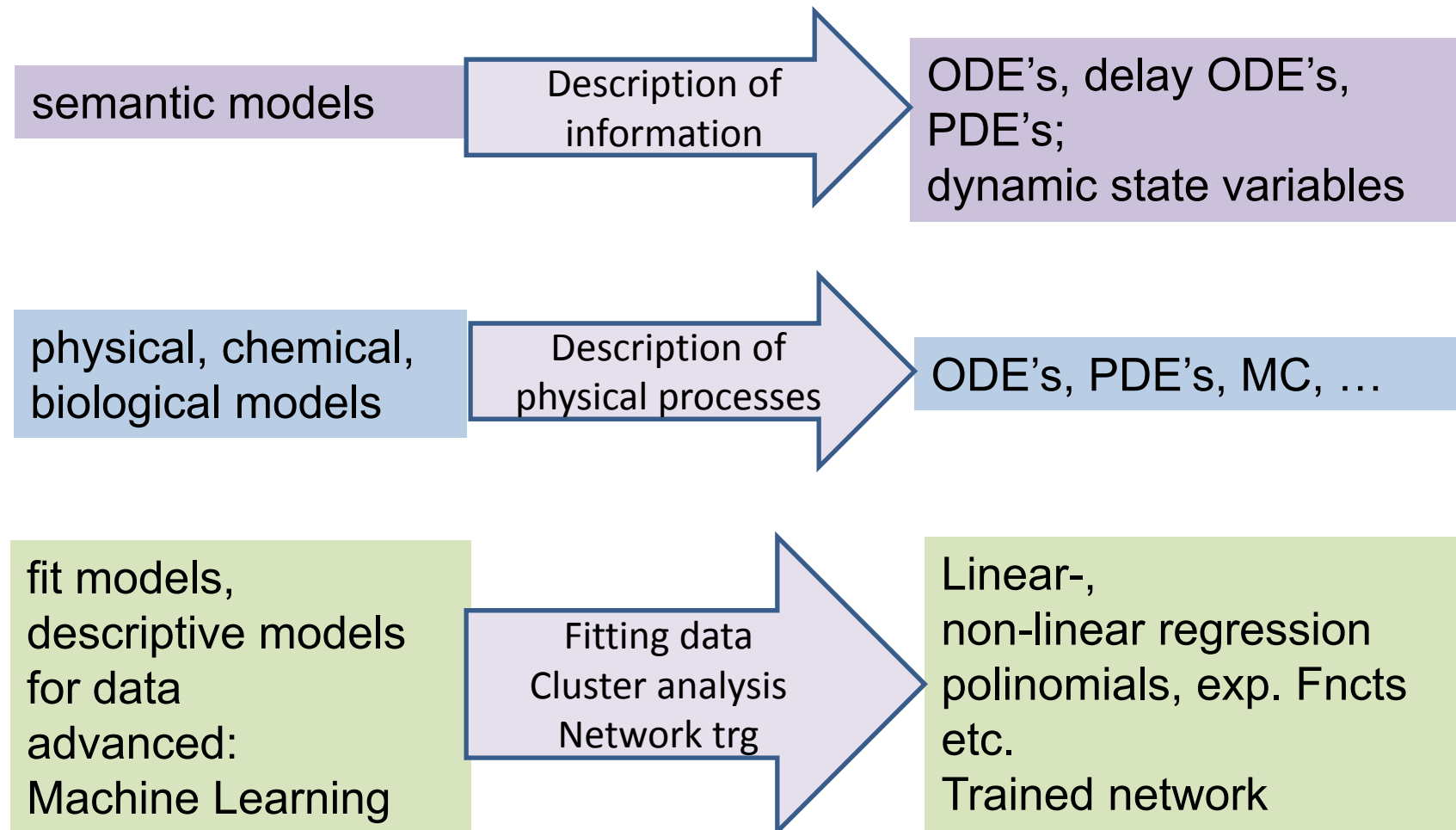
clinical trials

Experiments
In vivo

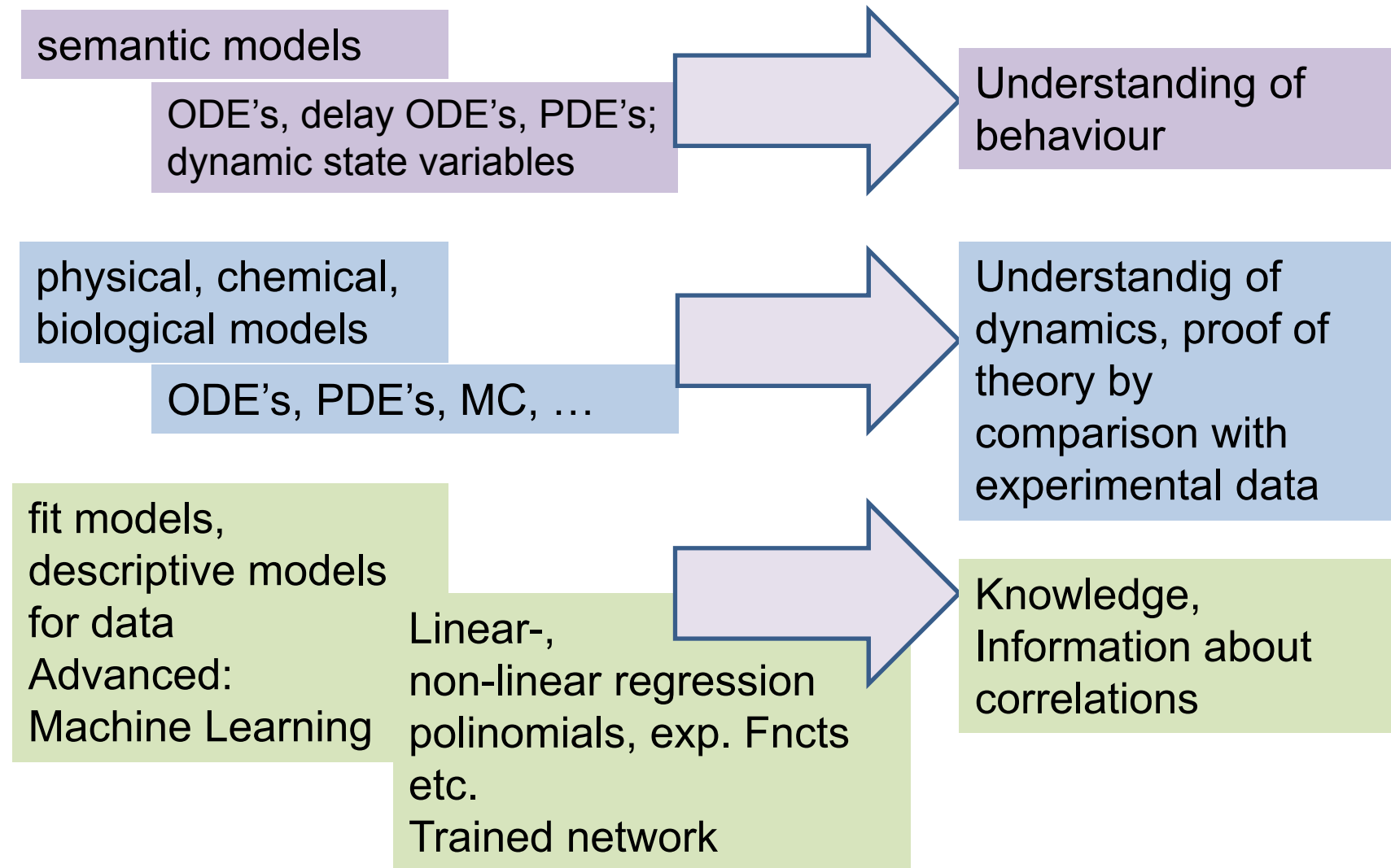
Experiments
In vitro

Experiments
In silico

Models and «Reality»



What we get out from models?



Smart sensors enabling monitoring of a population → acquisition of a large amount of time-resolved data

How to extract information? Machine learning helps to get knowledge, but does not lead directly to a deeper understanding e.g. of dynamics of the system!

Model-based data analysis may help to understand dynamics by identification of dynamic patterns, but has to be adapted to «real-world» biological or clinical data

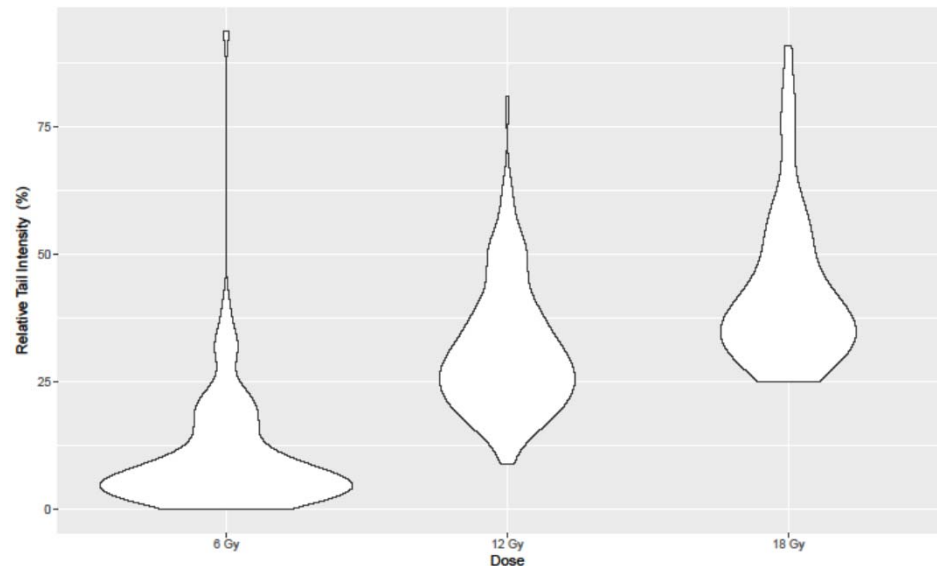
Digital Health – Data – Data Analysis

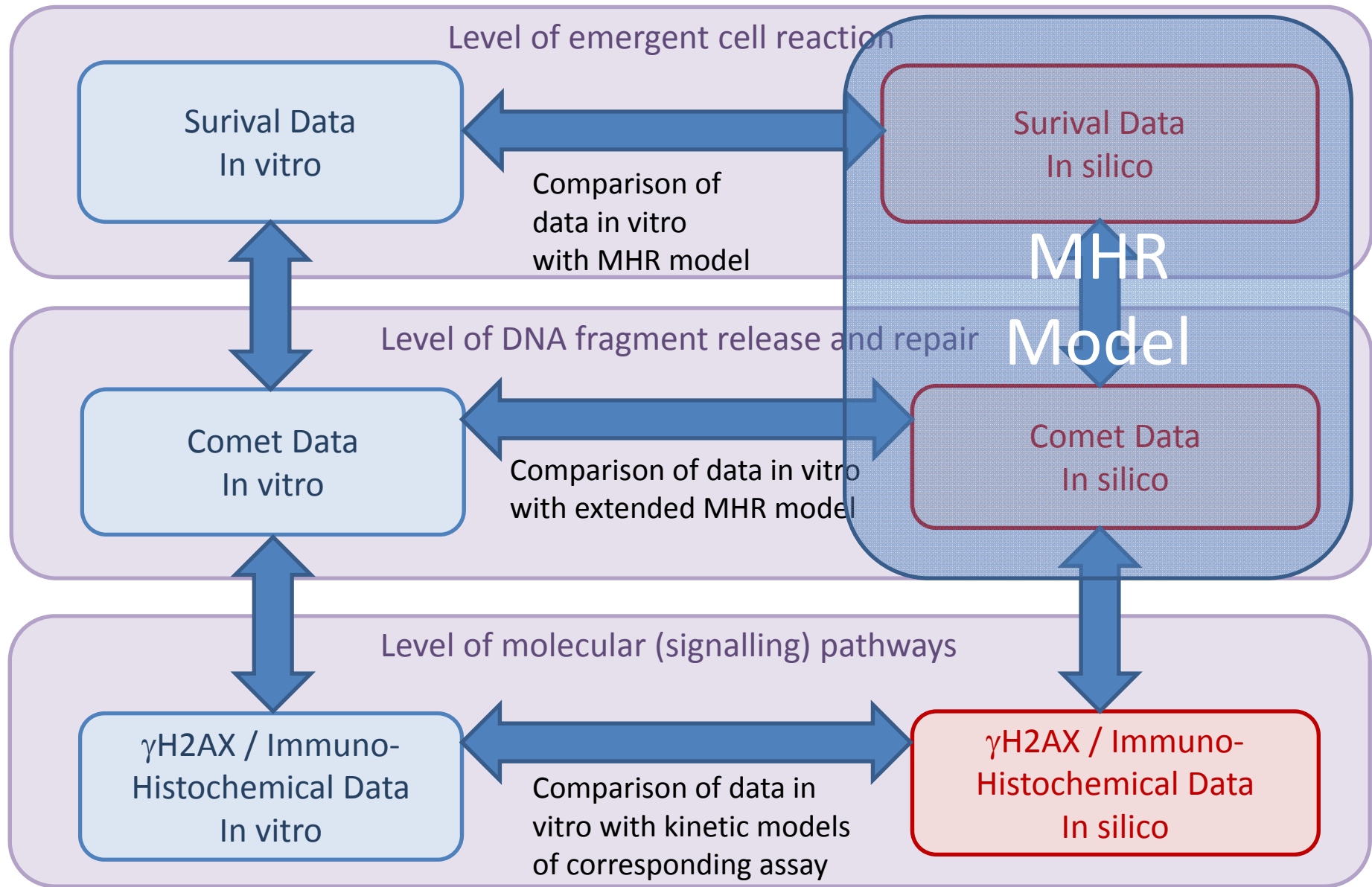
«real-world» biological or clinical data:

Populations are diverse, data are spreaded → distributions, not simple functions

Even in unclustered data, distributions may contain informations beyond means and standard deviations

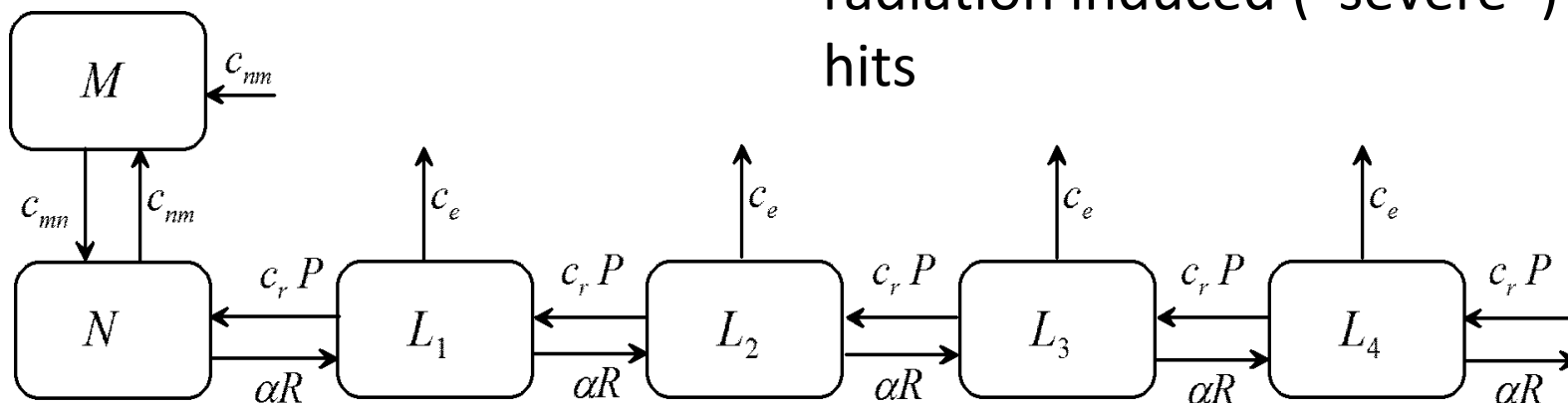
→ Example: Analysis of Comet assay data





MHR Model: Repair Probability

- N, M : No. of tumour cells in the mitotic cycle
- L_i : No. Of tumour cells with i radiation induced ("severe") hits

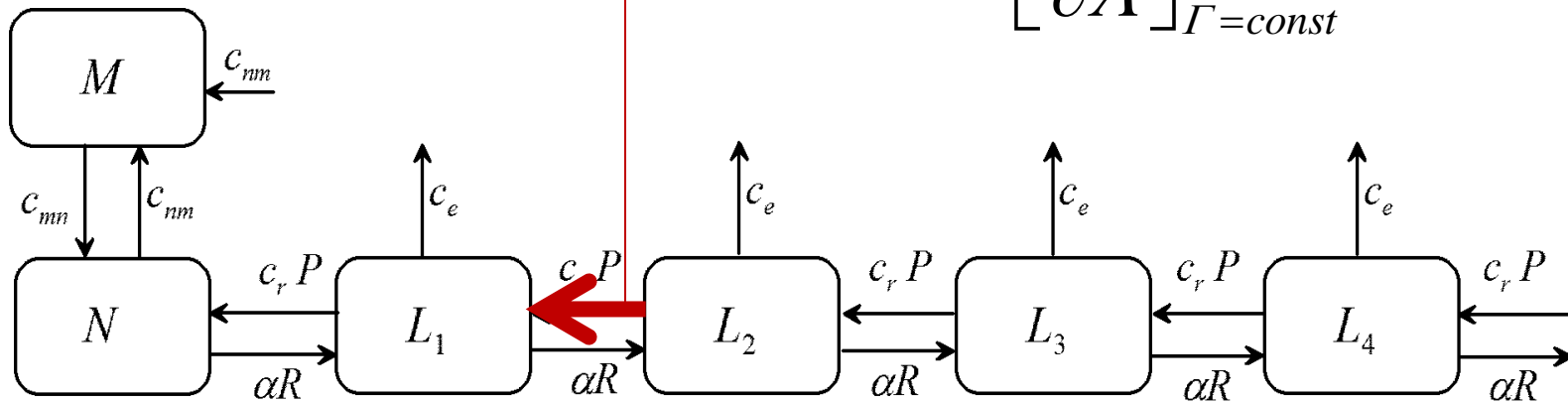


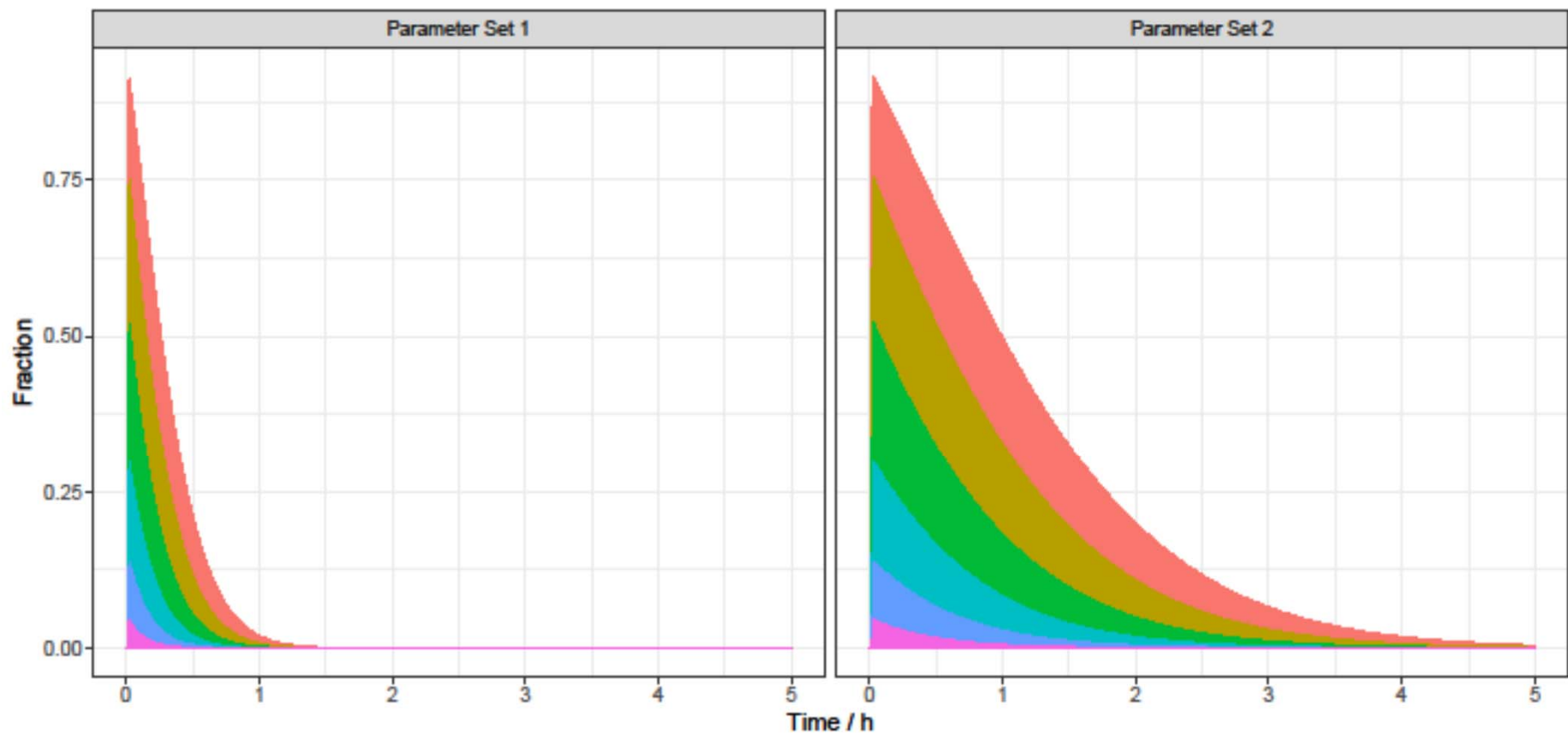
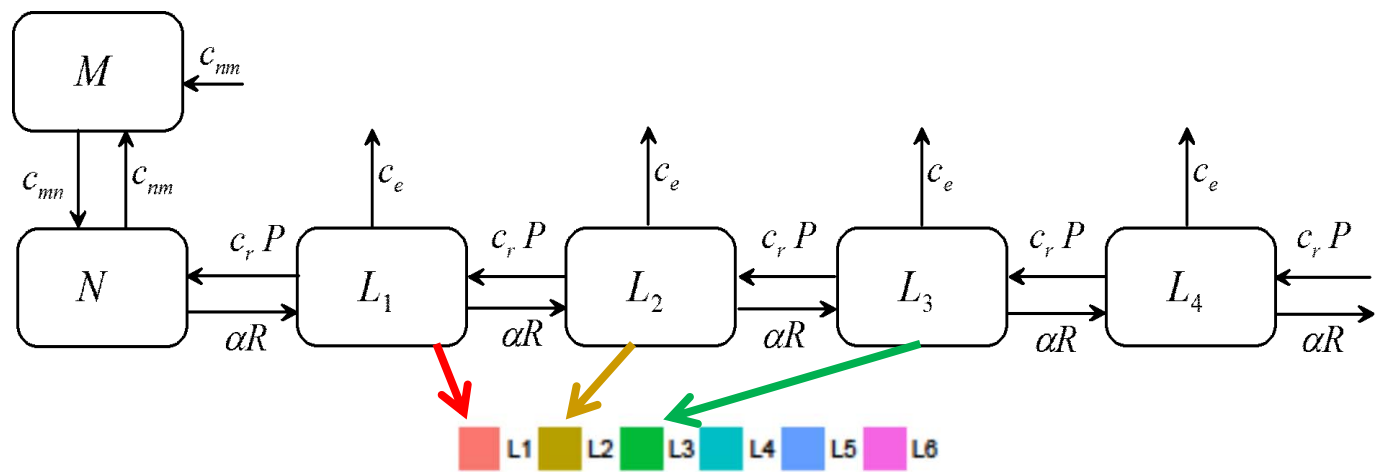
MHR Model: Repair Probability

$$\frac{dL_2}{dt} = -c_r P \cdot L_2$$

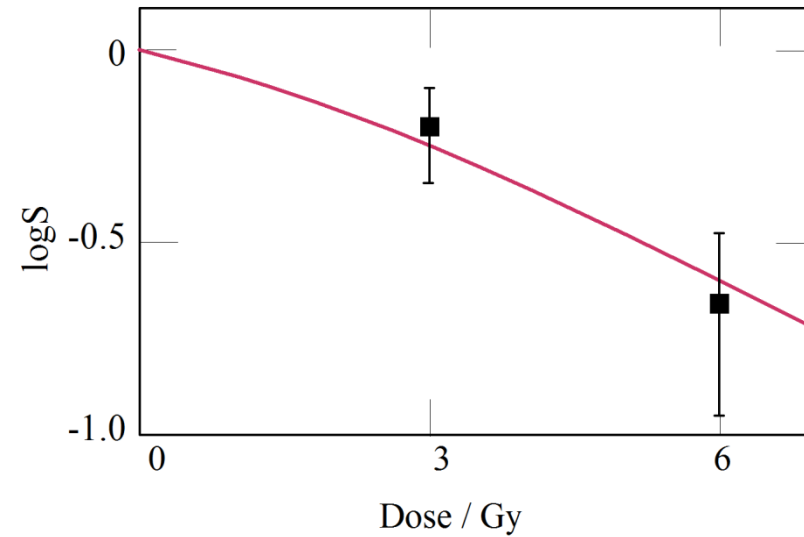
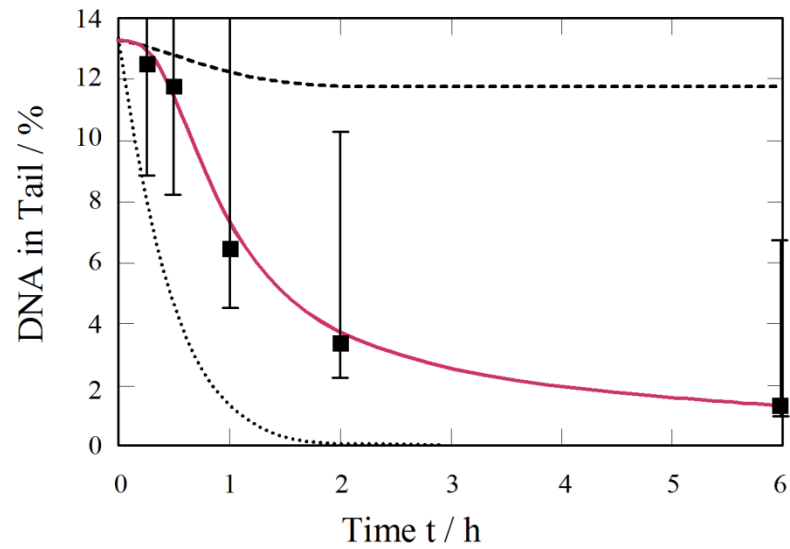
P : Repair probability

$$\left[\frac{\partial P}{\partial \Lambda} \right]_{\Gamma = \text{const}} = -\mu_A P$$



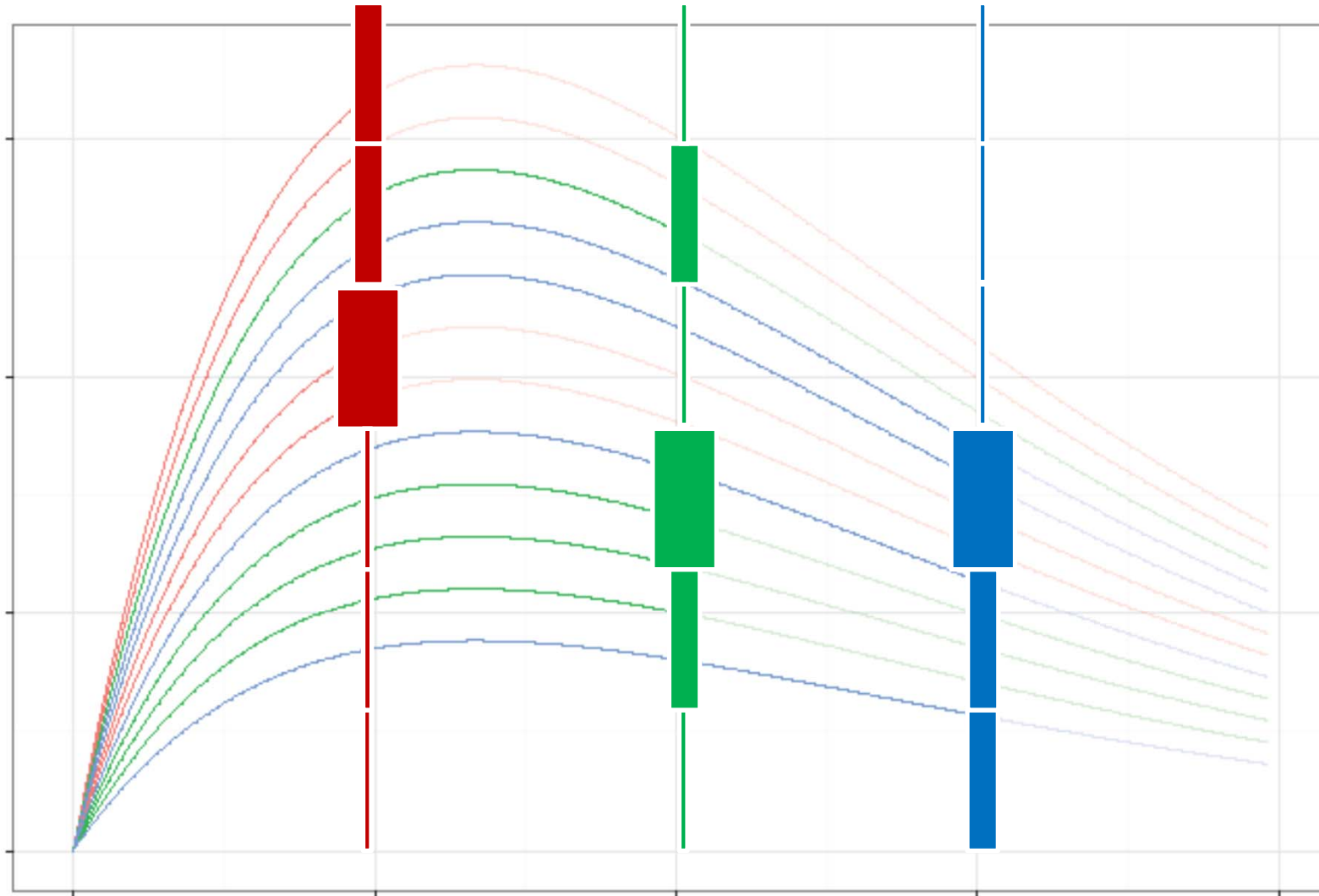


MHR Model: Looking at the DNA Damage

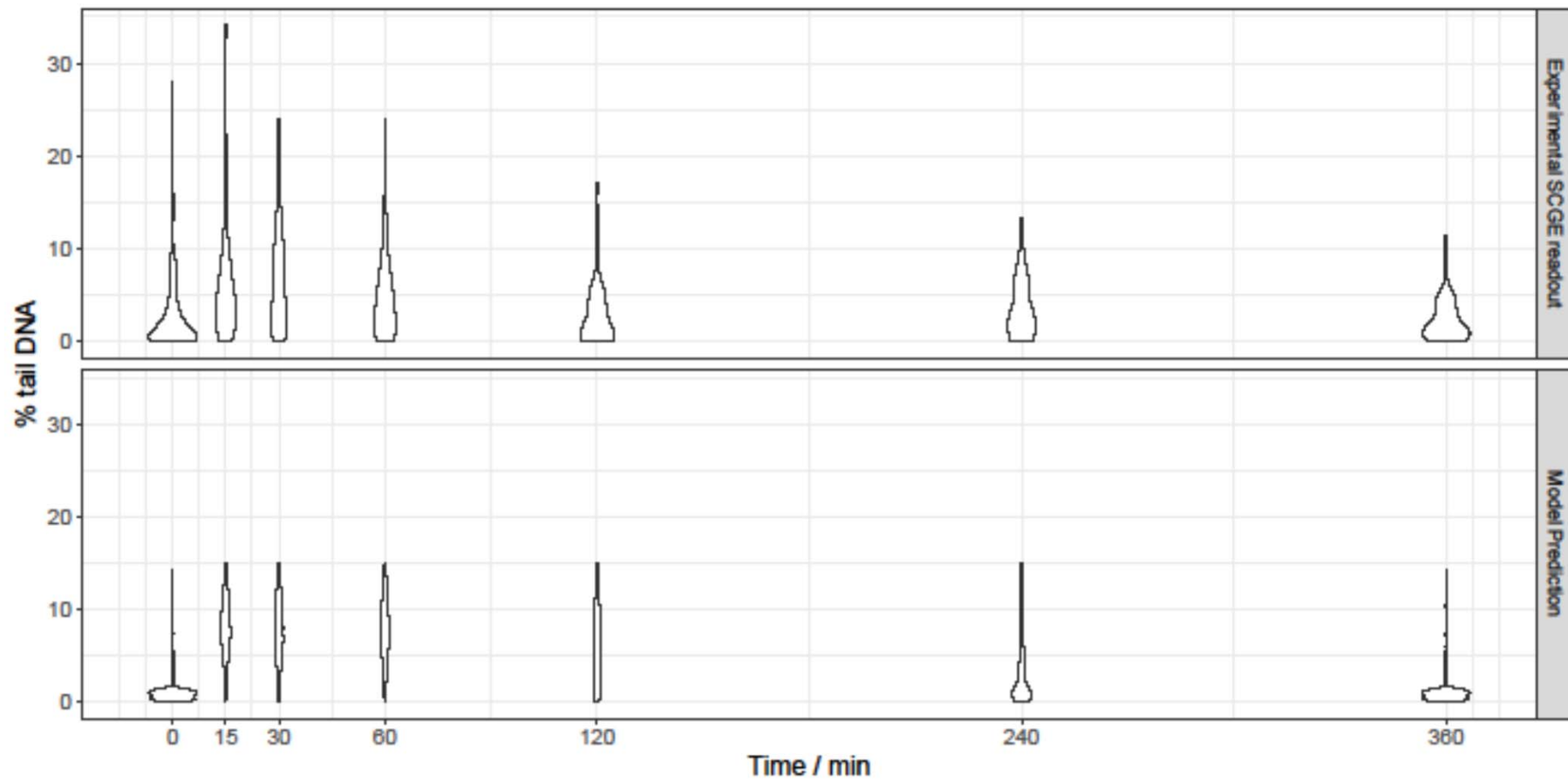


COMET: DNA Damage \longleftrightarrow Survival of Sarcoma Cells

Comet Assay: Looking at the DNA Damage



Experiment & Model: Looking at the DNA Damage

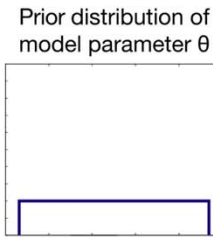
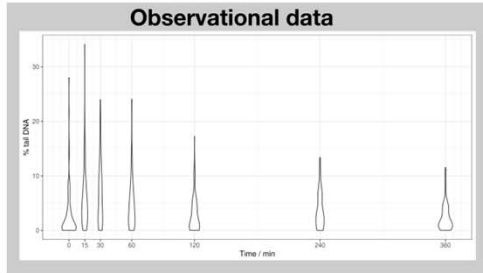


Monte Carlo ABC in a nutshell

1. **Seeding:** Find initial parameter sets with low cost-function.
2. **Evolution:** Perturb each parameter set, re-evaluate cost-function, reject sets where cost has increased.
3. **Evaluation:** Build parameter histograms from evolved parameter sets and evaluate.

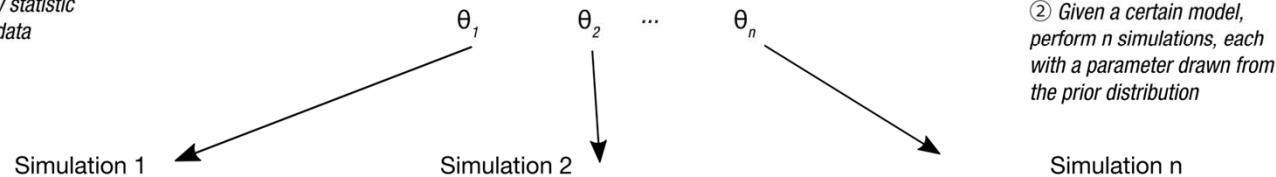
This method yields distributions of parameters as a result, which can be evaluated with respect to moments, number of modes etc.

Approximate Bayesian Computation (ABC)

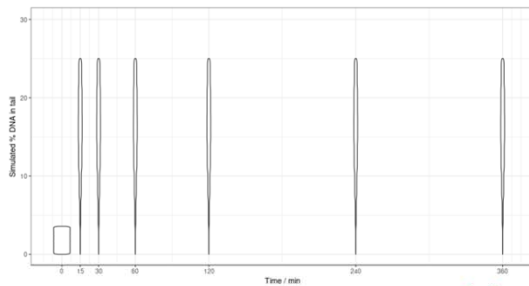


① Compute summary statistic μ from observational data

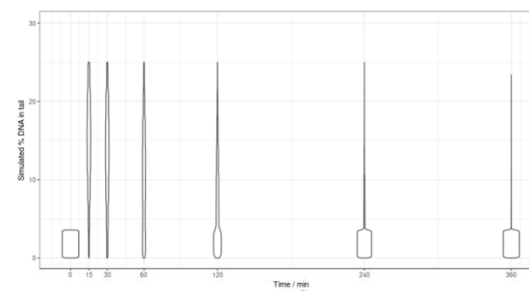
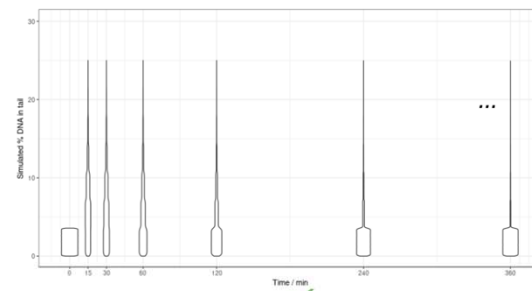
③ Compute summary statistic μ_i for each simulation



② Given a certain model, perform n simulations, each with a parameter drawn from the prior distribution

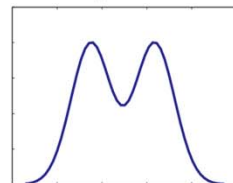


$$\rho(\mu_i, \mu) \stackrel{?}{\leq} \epsilon$$



④ Based on a distance $\rho(\cdot, \cdot)$ and a tolerance ϵ , decide for each simulation whether its summary statistic is sufficiently close to that of the observed data.

Posterior distribution of model parameter θ



⑤ Approximate the posterior distribution of θ from the distribution of parameter values θ_i associated with accepted simulations.

Conclusions

Method potentially has a large field of applications.
The essential ingredients for this are:

- (time-resolved) distributions of measurements (data)
- a dynamic model delivering distributions of simulation results as function of time which can be compared to the experimental data
- algorithm allowing fitting of the simulated distribution to the experimentally observed distribution.

Thanks to the audience ...
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