Joining Forces of Bayesian and Frequentist Methodology: A Study for Inference in the Presence of Non-Identifiability

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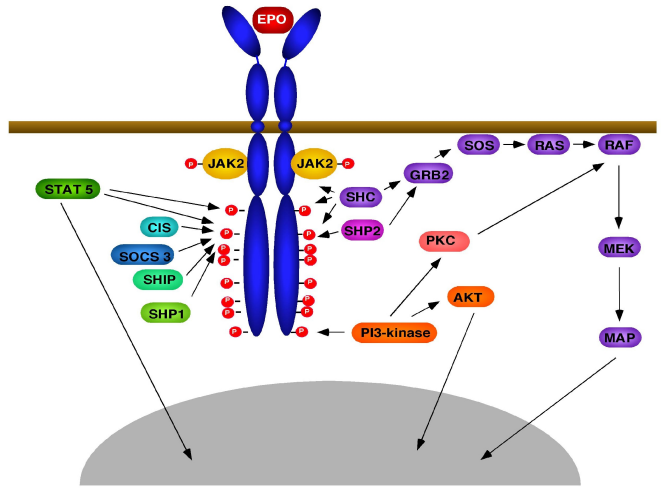
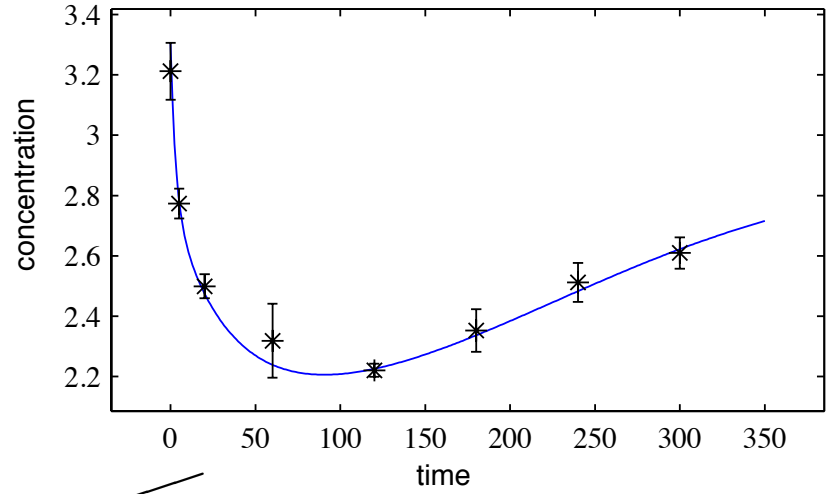
The „Systems Biology“ Approach

Signal transduction through the Erythropoietin receptor (EpoR)





$$\dot{\vec{x}} = \vec{f}(\vec{x}, \vec{p})$$

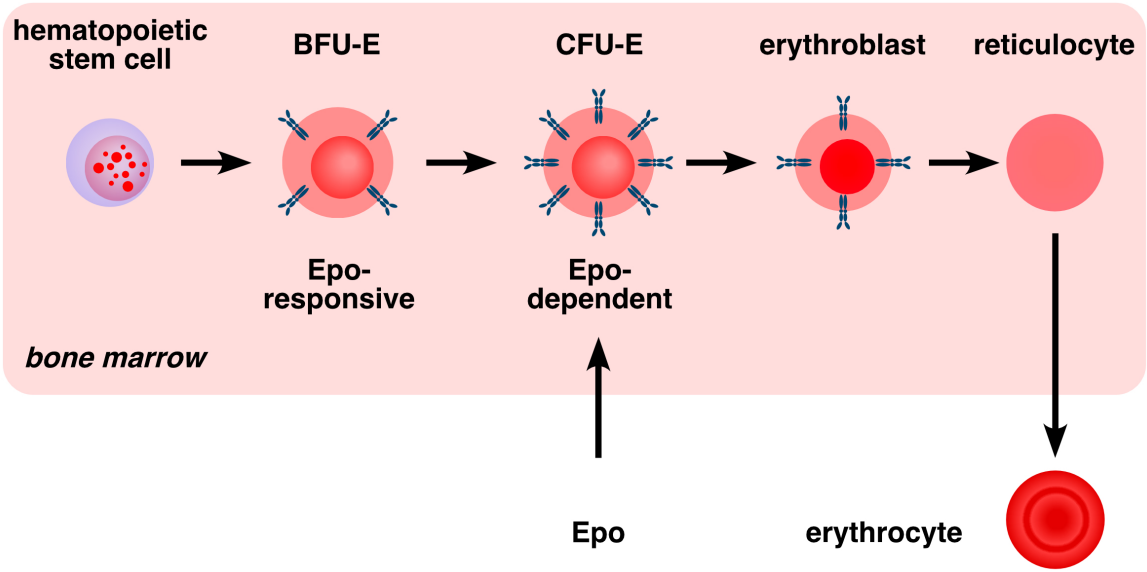
In silico biology

Test the prior knowledge

Understanding systems' properties

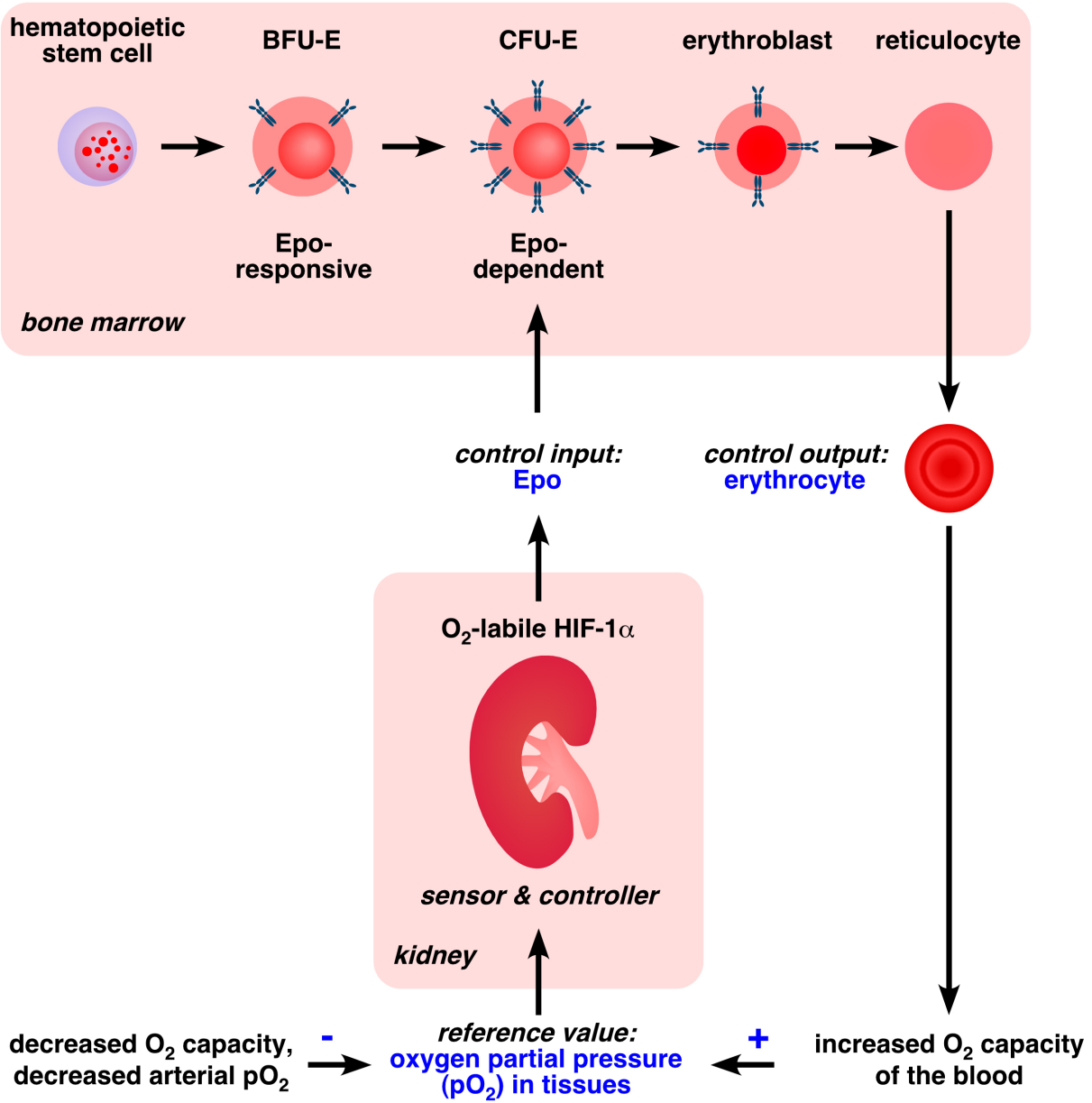
Identification of potential drug targets

Erythropoiesis - A Closed-Loop Control System



- **Epo: key regulator of erythropoiesis**

Erythropoiesis - A Closed-Loop Control System

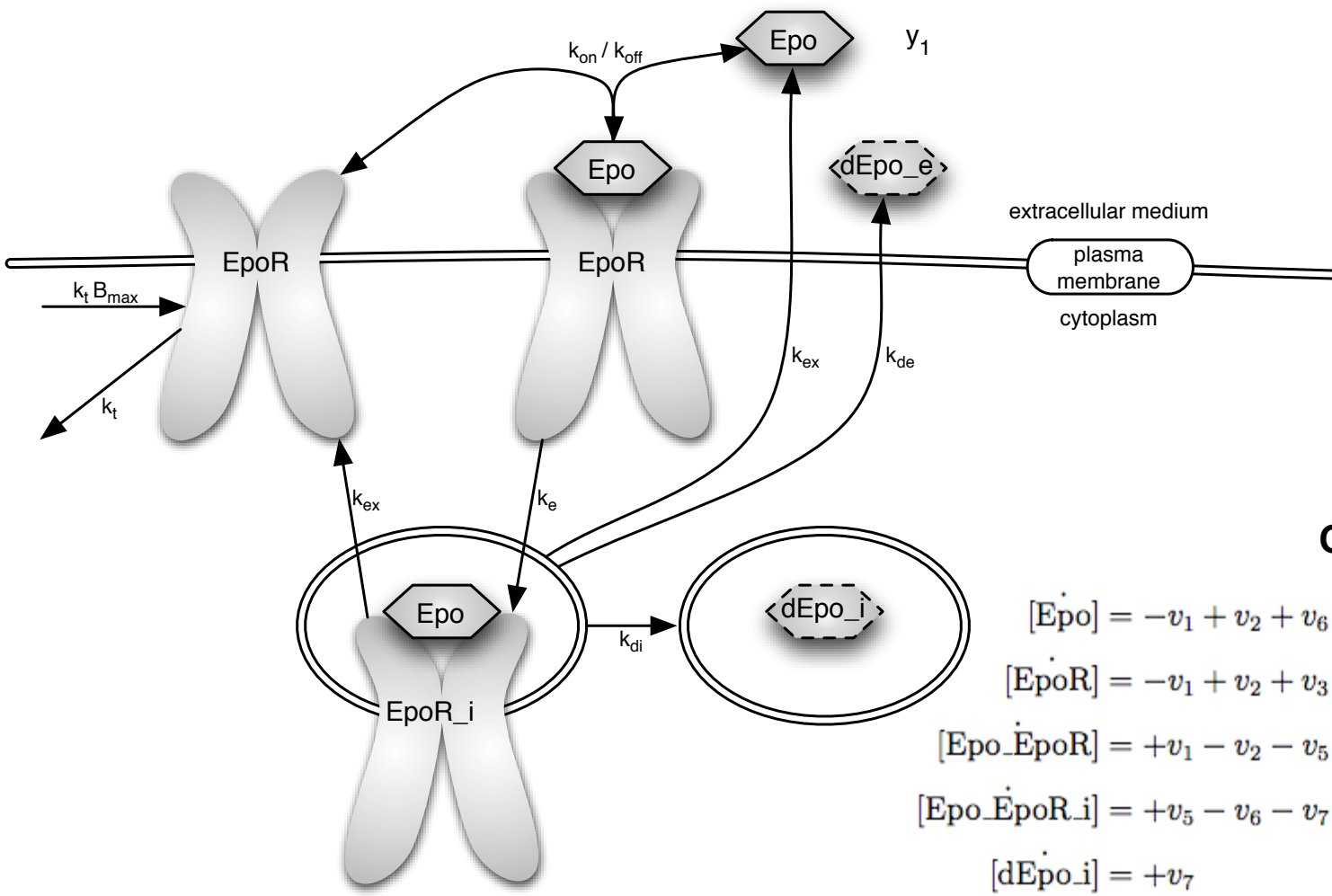


- **Epo:** key regulator of erythropoiesis
- **feedback via red blood cell mass:** establishing a closed-loop control circuit
- **normal conditions:** low levels of plasma Epo

  15 mU/ml
- **hypoxic conditions:** increased Epo levels

  up to 10000 mU/ml

Epo and Epo receptor interaction and trafficking



ODE model

$$\dot{[\text{Epo}]} = -v_1 + v_2 + v_6$$

$$\dot{[\text{EpoR}]} = -v_1 + v_2 + v_3 - v_4 + v_6$$

$$\dot{[\text{Epo\_EpoR}]} = +v_1 - v_2 - v_5$$

$$\dot{[\text{Epo\_EpoR\_i}]} = +v_5 - v_6 - v_7 - v_8$$

$$\dot{[\text{dEpo\_i}]} = +v_7$$

$$\dot{[\text{dEpo\_e}]} = +v_8$$

$$v_1 = k_{on} \cdot [\text{Epo}] \cdot [\text{EpoR}]$$

$$v_2 = k_{on} \cdot k_D \cdot [\text{Epo\_EpoR}]$$

$$v_3 = k_t \cdot B_{max}$$

$$v_4 = k_t \cdot [\text{EpoR}]$$

$$v_5 = k_e \cdot [\text{Epo\_EpoR}]$$

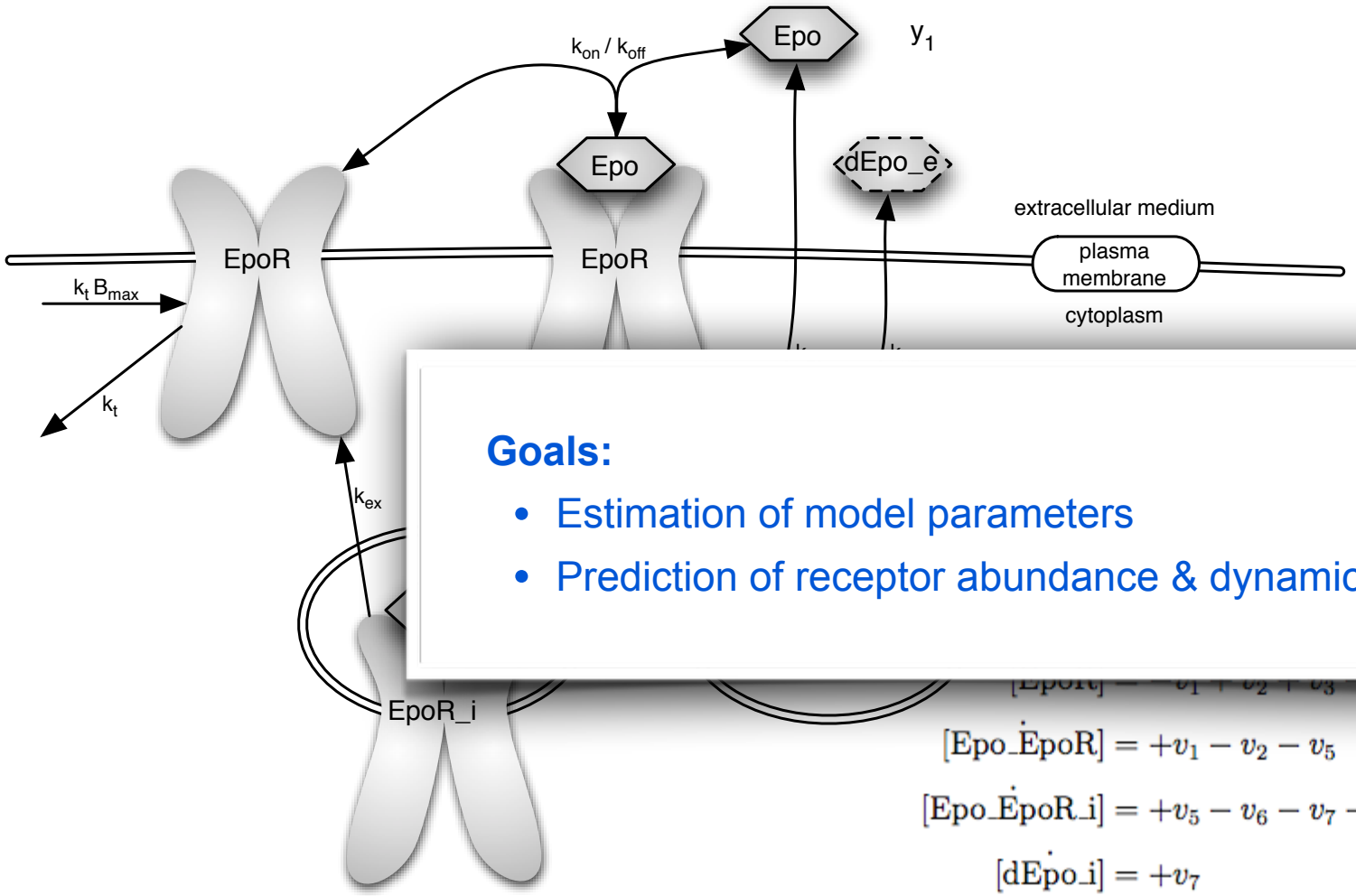
$$v_6 = k_{ex} \cdot [\text{Epo\_EpoR\_i}]$$

$$v_7 = k_{di} \cdot [\text{Epo\_EpoR\_i}]$$

$$v_8 = k_{de} \cdot [\text{Epo\_EpoR\_i}]$$

Raue *et al.* Chaos 2010

Epo and Epo receptor interaction and trafficking



Goals:

- Estimation of model parameters
- Prediction of receptor abundance & dynamics

odel

$$[\dot{\text{Epo\_EpoR}}] = +v_1 - v_2 - v_5$$

$$[\dot{\text{Epo\_EpoR\_i}}] = +v_5 - v_6 - v_7 - v_8$$

$$[\dot{\text{dEpo\_i}}] = +v_7$$

$$[\dot{\text{dEpo\_e}}] = +v_8$$

$$v_1 = k_{on} \cdot [\text{Epo}] \cdot [\text{EpoR}]$$

$$v_2 = k_{on} \cdot k_D \cdot [\text{Epo\_EpoR}]$$

$$v_3 = k_t \cdot B_{max}$$

$$v_4 = k_t \cdot [\text{EpoR}]$$

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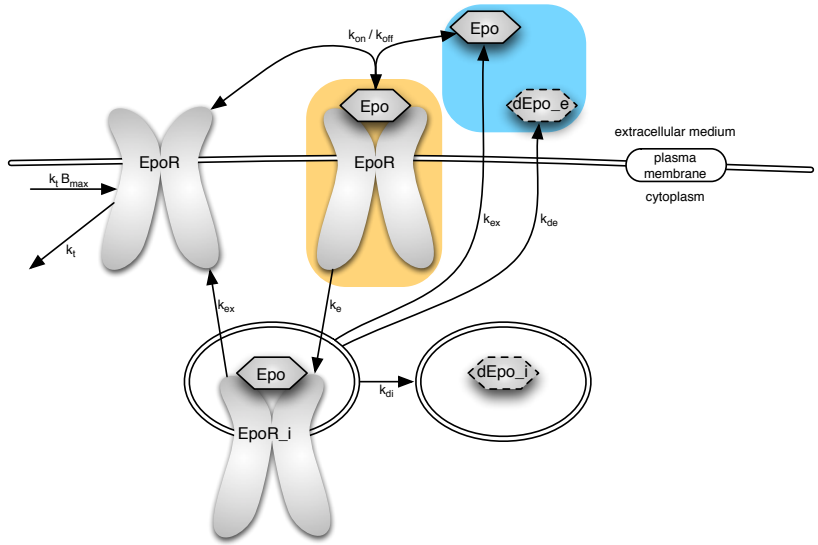
Raue *et al.* Chaos 2010

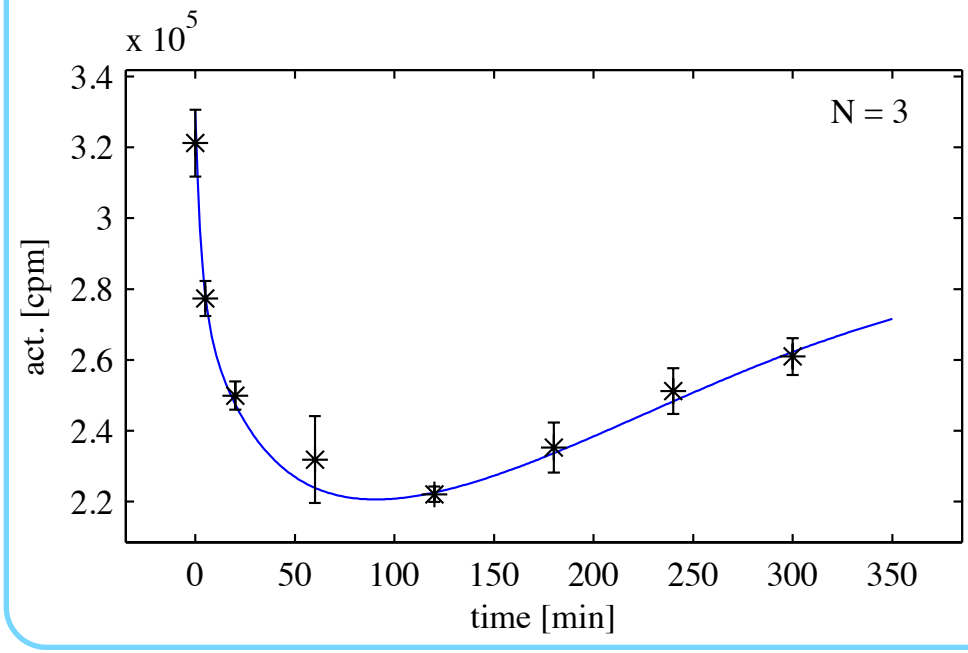
Initial Experimental Setup



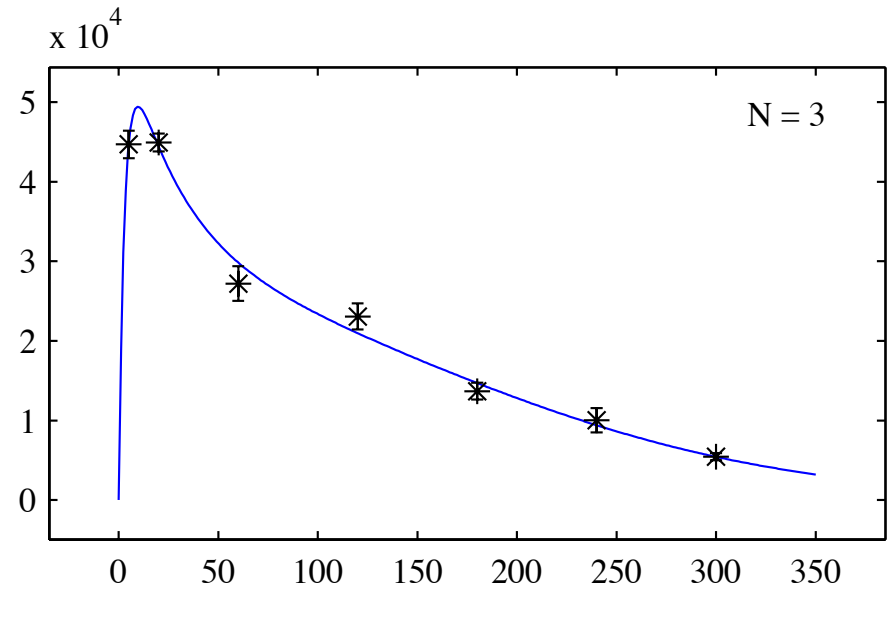
Maximum Likelihood Estimation

$$L(y|\theta) = \prod_{k=1}^{m} \prod_{l=1}^{d_k} \frac{1}{\sqrt{2\pi\sigma_{kl}^2}} \exp\left(-\frac{1}{2}\left(\frac{y_{kl} - y_k(t_l, \theta)}{\sigma_{kl}}\right)^2\right)$$

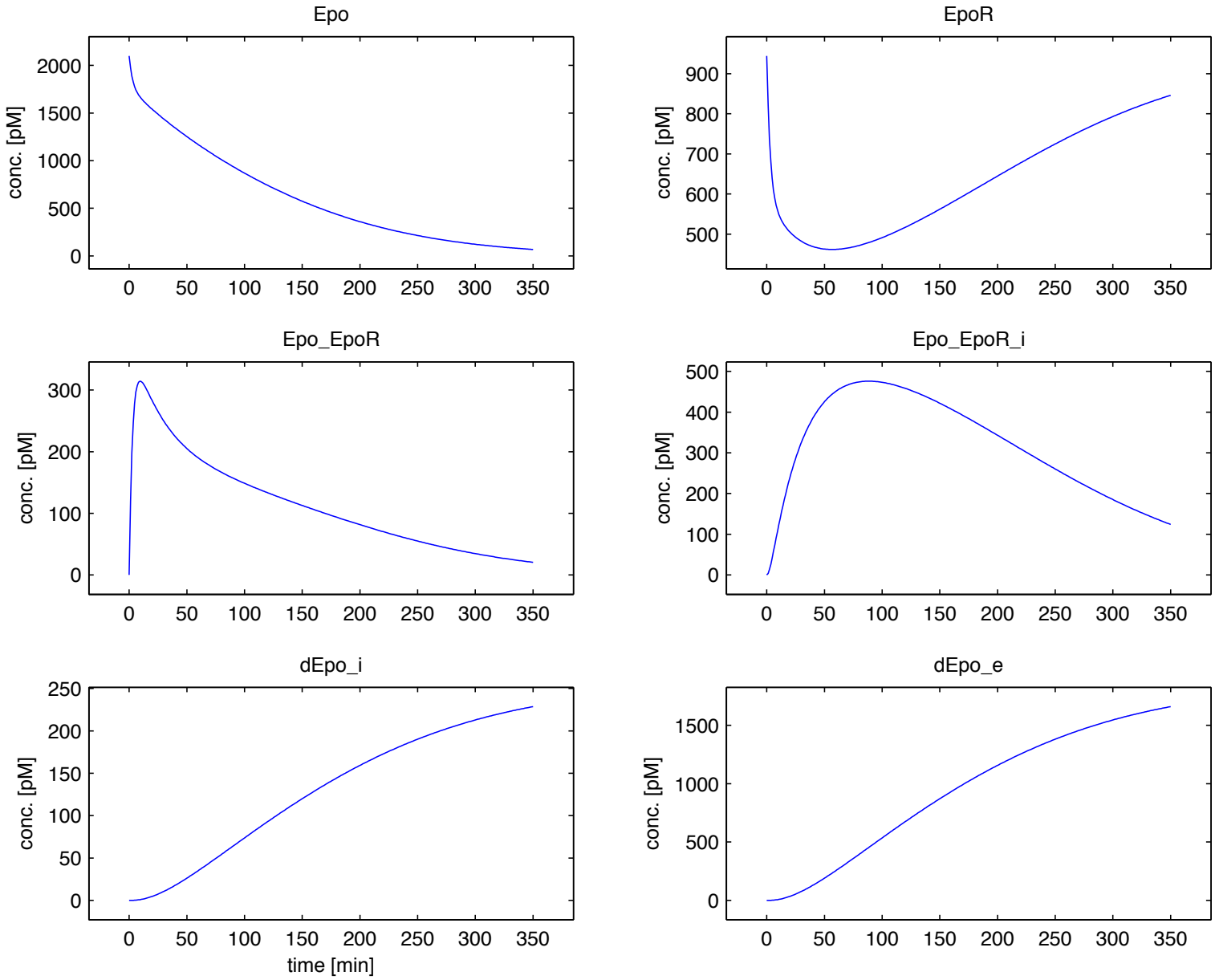
Epo in extracellular medium



Epo bound to receptor on membrane



Predicted Model Dynamics

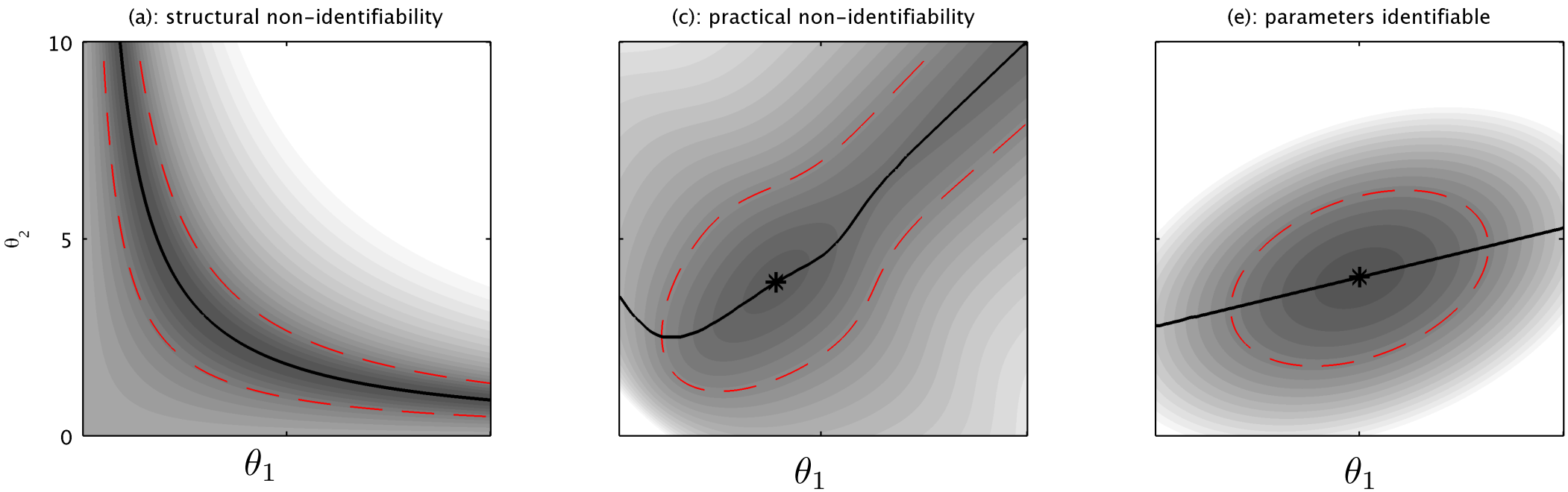


Are the model parameters well identified?

Are the predictions reliable?

Parameter Identifiability

Identifiability is a matter of flatness of the likelihood ...



ODE $\quad \dot{\vec{x}}(t) = f(\vec{x}(t), \vec{u}(t), \vec{p}, t)$

Observables $\quad \vec{y}(t) = g(\vec{x}(t), \vec{s}) + \vec{\epsilon}(t)$

Likelihood $\quad L(y|\theta) = \prod_{k=1}^{m} \prod_{l=1}^{d_k} \frac{1}{\sqrt{2\pi\sigma_{kl}^2}} \exp\left(-\frac{1}{2}\left(\frac{y_{kl} - y_k(t_l, \theta)}{\sigma_{kl}}\right)^2\right)$

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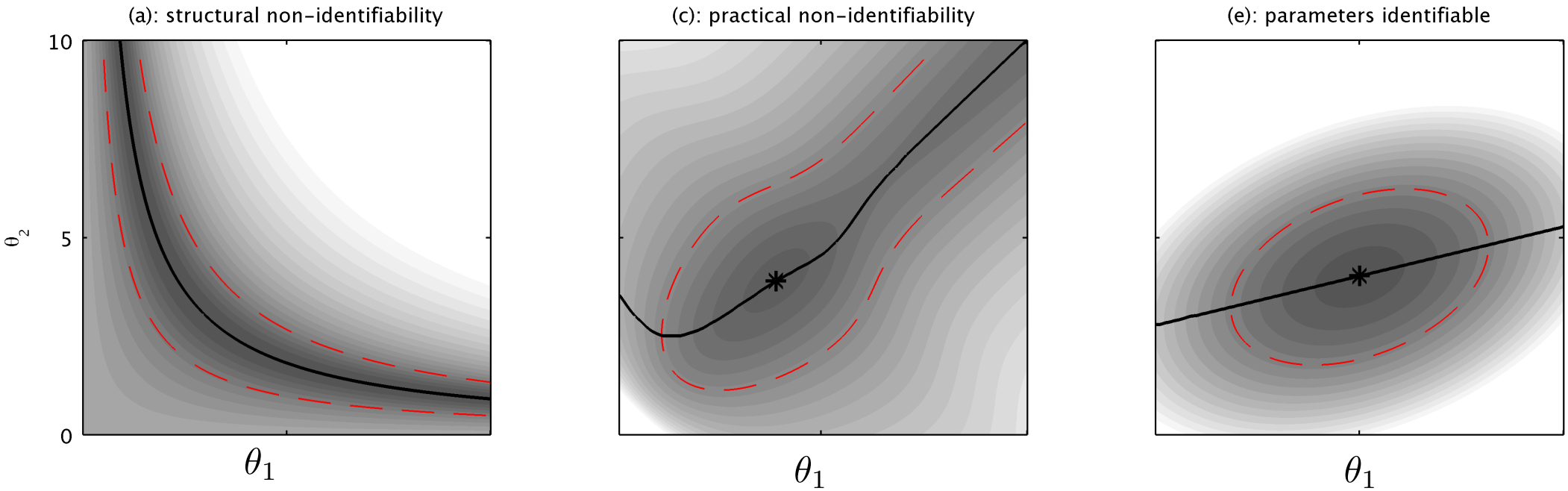


➔ **Profile Likelihood Approach**

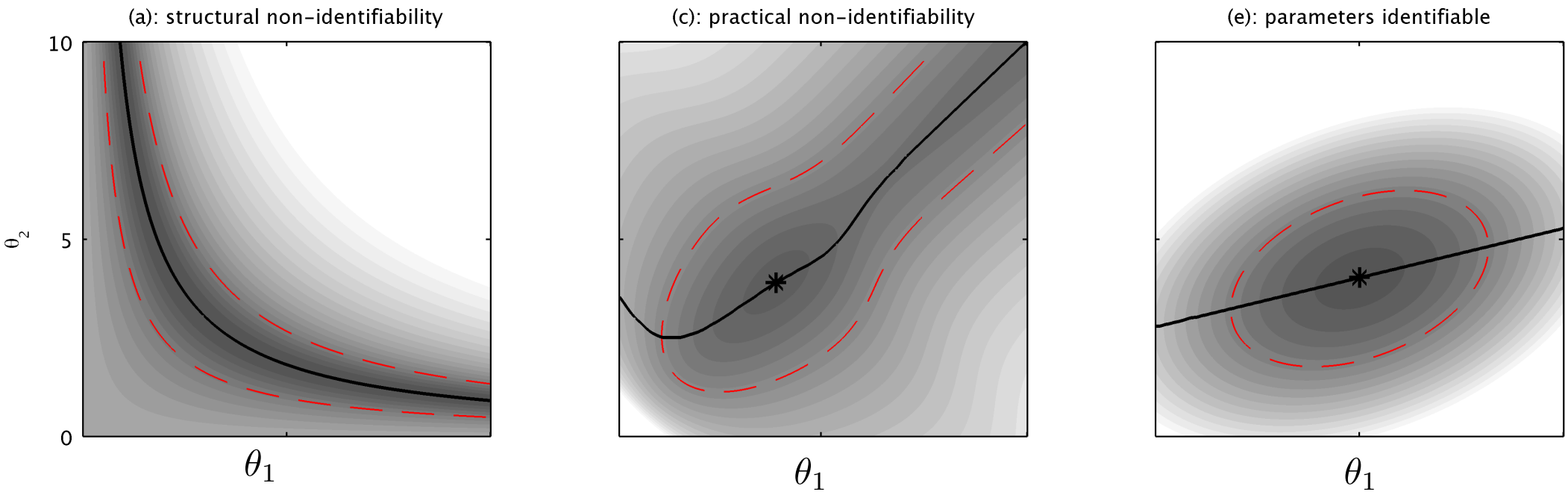
Raue *et al.* Bioinformatics 2009

Likelihood $$L(y|\theta) = \prod_{k=1}^{m} \prod_{l=1}^{d_k} \frac{1}{\sqrt{2\pi\sigma_{kl}^2}} \exp\left(-\frac{1}{2}\left(\frac{y_{kl} - y_k(t_l, \theta)}{\sigma_{kl}}\right)^2\right)$$

Profile Likelihood $$PL(y|\theta_i) = \max_{\theta_{j\neq i}}[L(y|\theta)]$$

Parameter Identifiability

Identifiability is a matter of flatness of the likelihood ...



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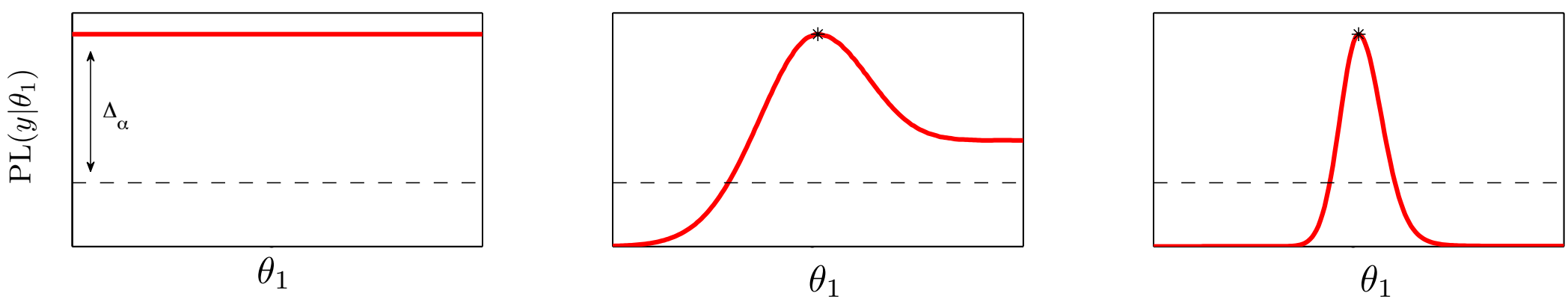
Raue *et al.* Bioinformatics 2009



MCMC Sampling

Likelihood Prior

Posterior $P(\theta|y) = c \cdot L(y|\theta) \cdot P(\theta)$

normalisation factor

Markov process with transitions $\theta \rightarrow \theta'$

Metropolis-Hastings algorithm

Proposal function $q(\theta'|\theta) \sim \mathrm{N}(0, s \cdot \mathbb{I})$

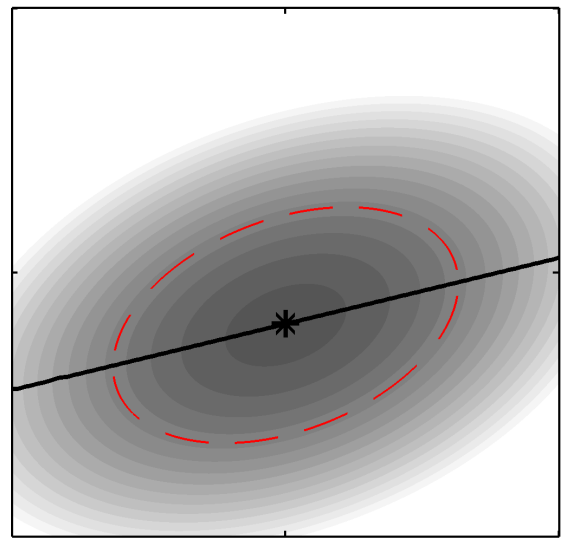
Acceptance probability

$$\alpha(\theta'|\theta) = \min[1, (L(y|\theta')/L(y|\theta)) \cdot (q(\theta|\theta')/q(\theta'|\theta))]$$

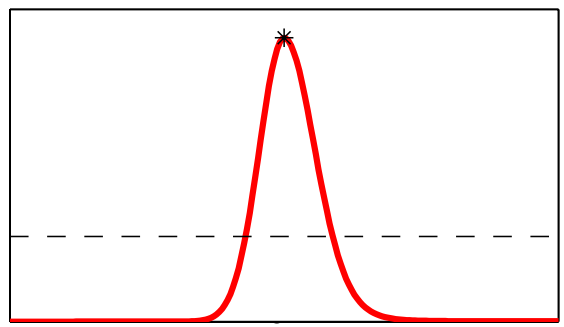
→ simplified MMALA algorithm

Girolami *et al.* J. R. Statist. Soc. B 2011

(e): parameters identifiable

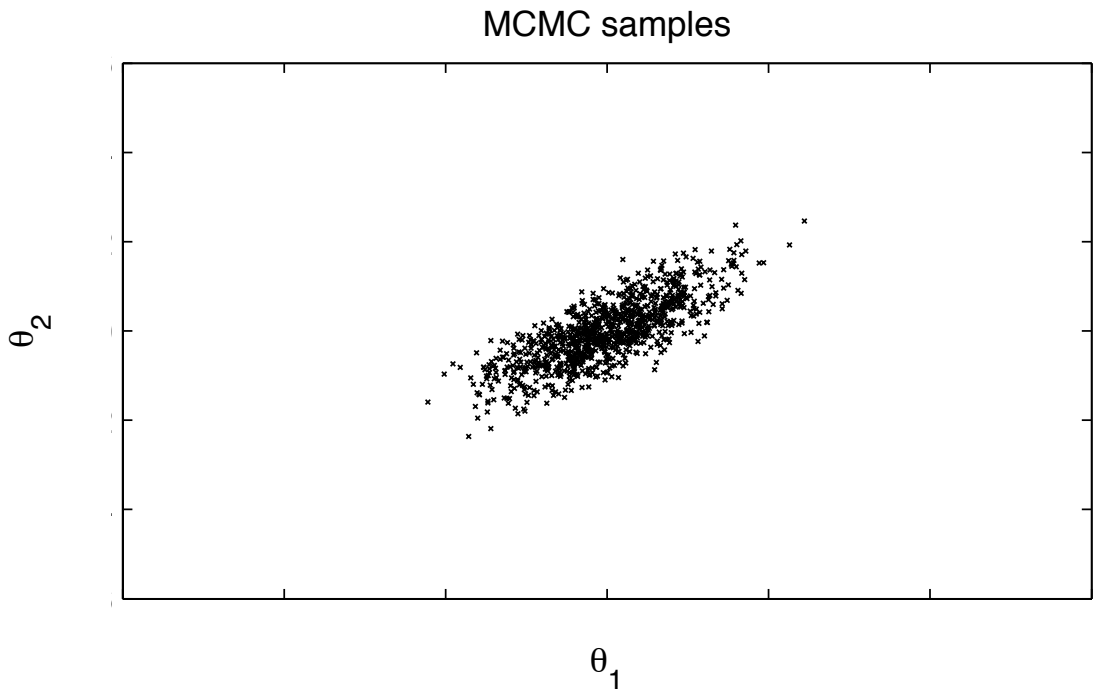


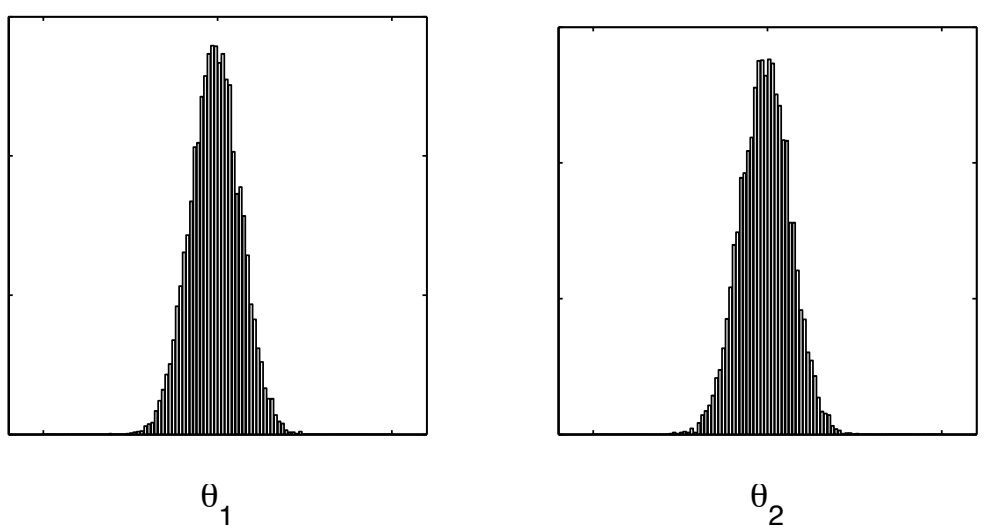
θ_1

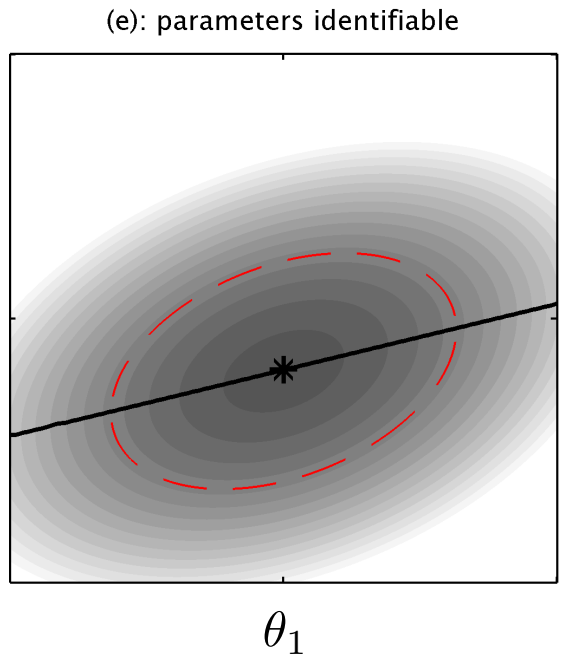


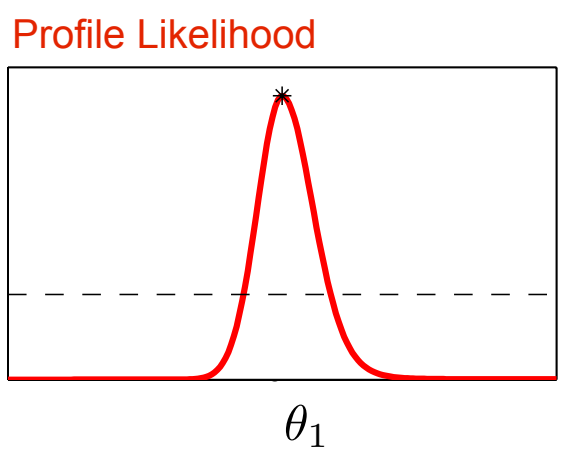
θ_1

MCMC Sampling

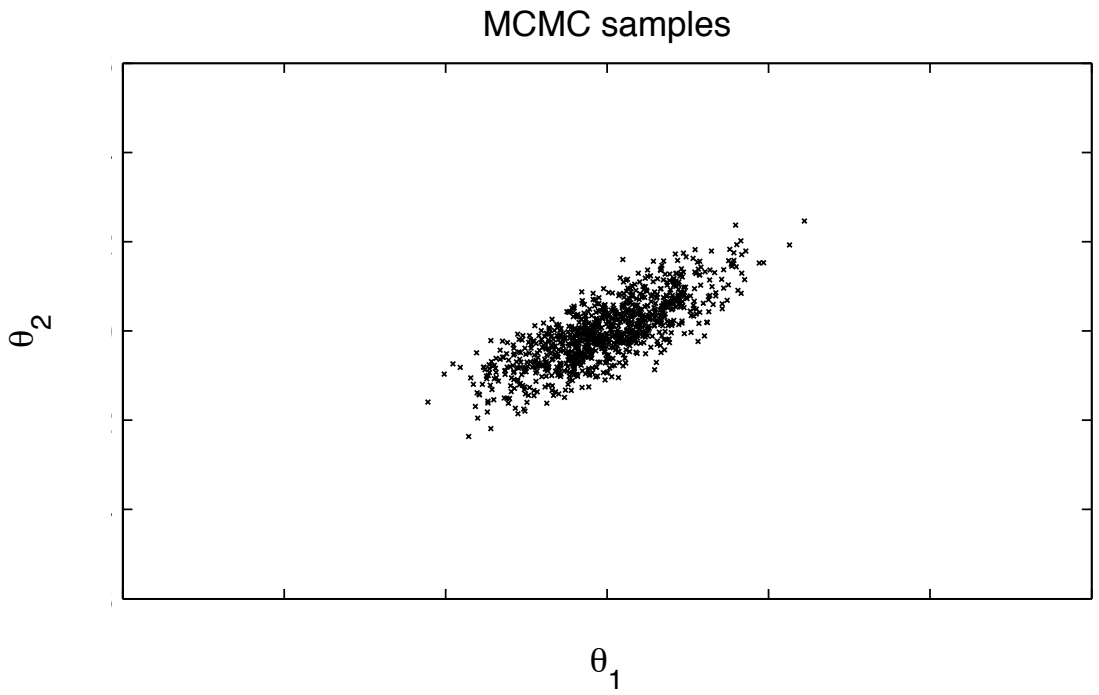


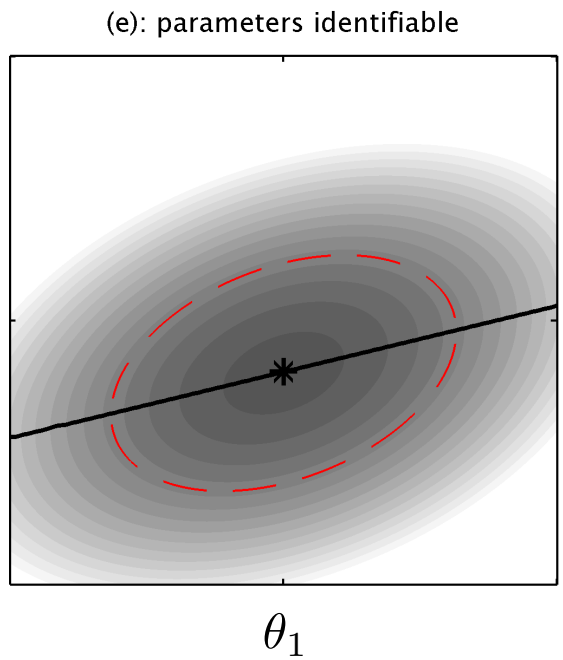


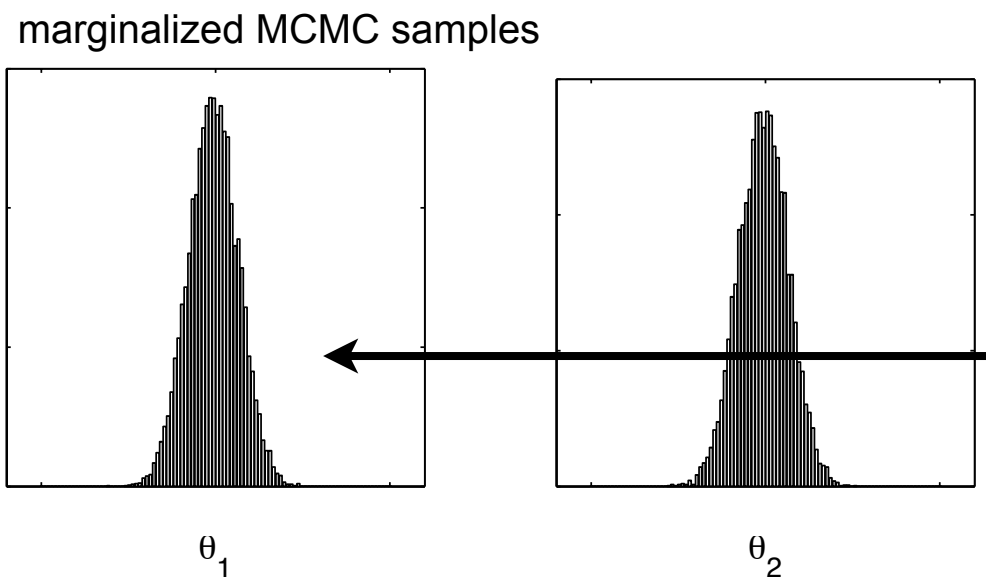


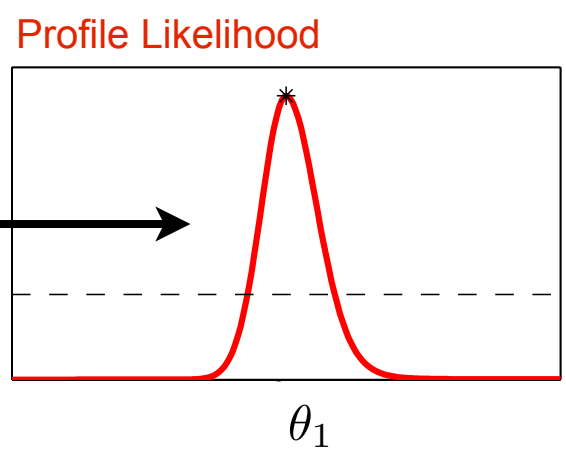


MCMC Sampling

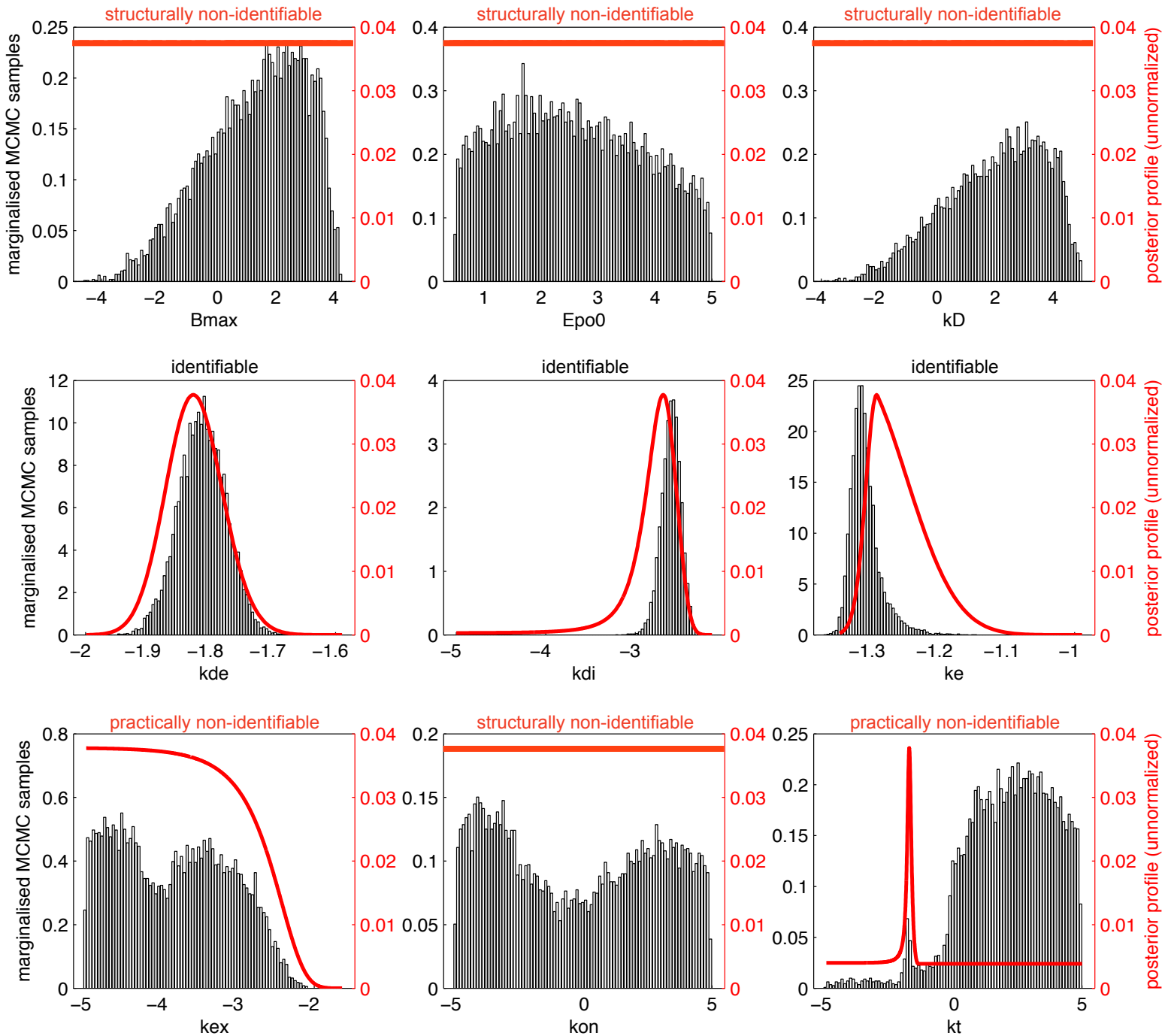




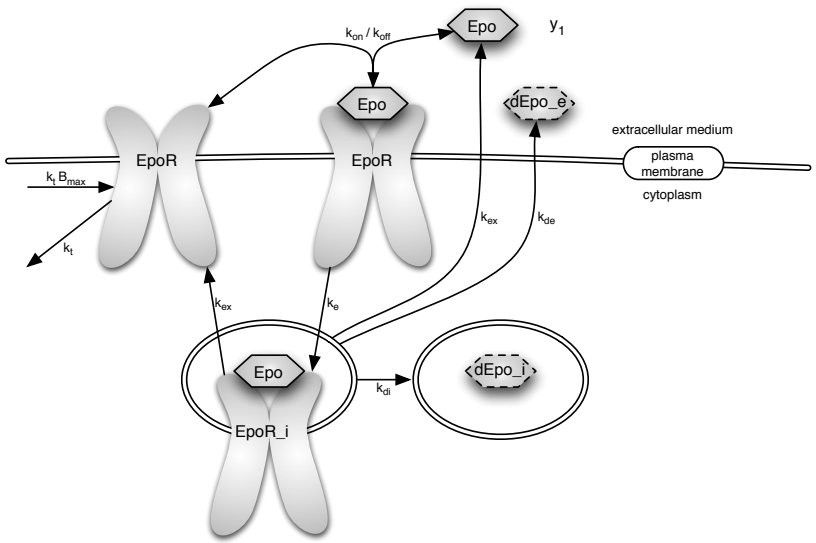


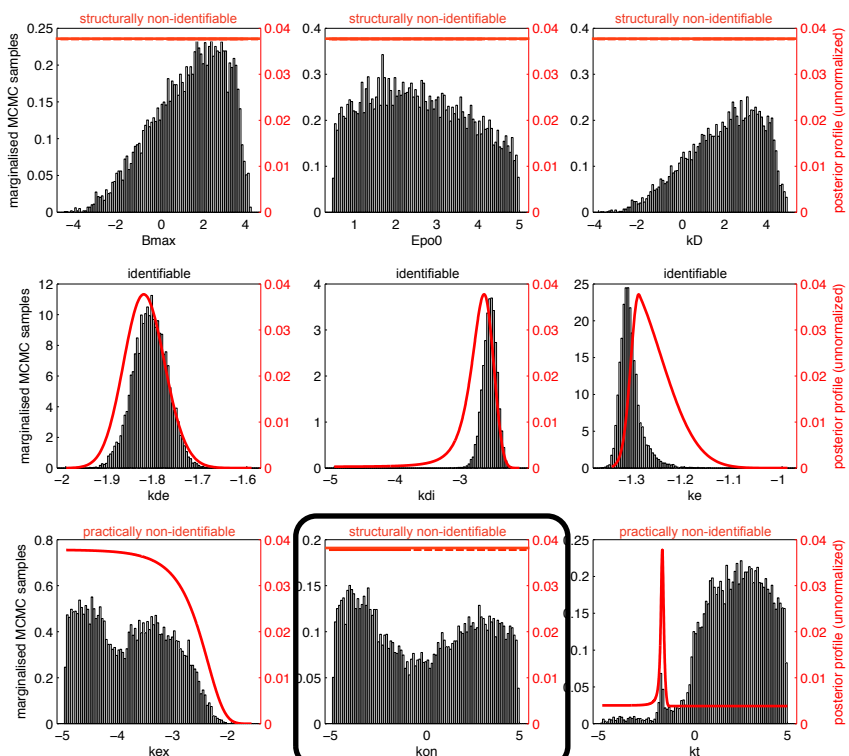


Results for Initial Setup



Experimental Design





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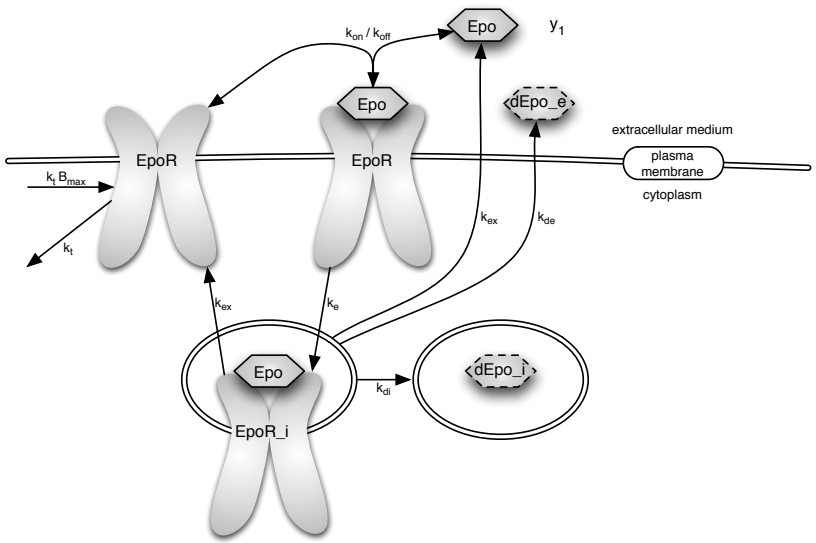
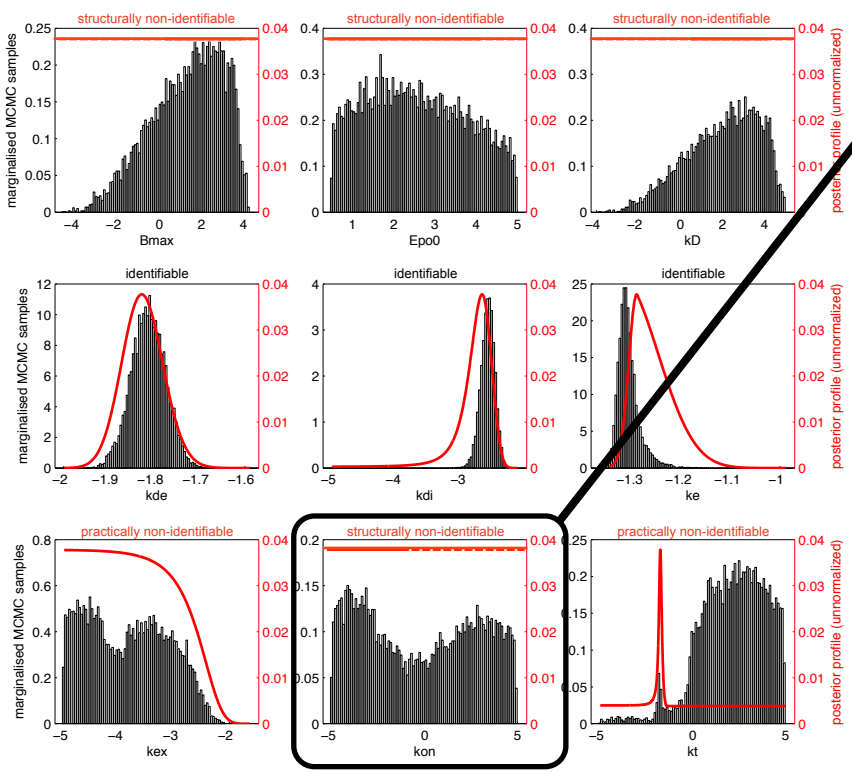
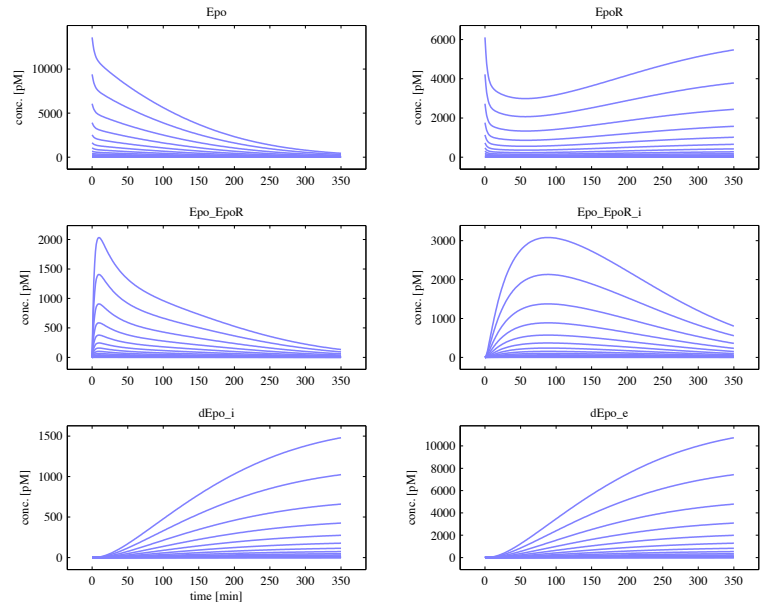




Non-observability of model dynamics:



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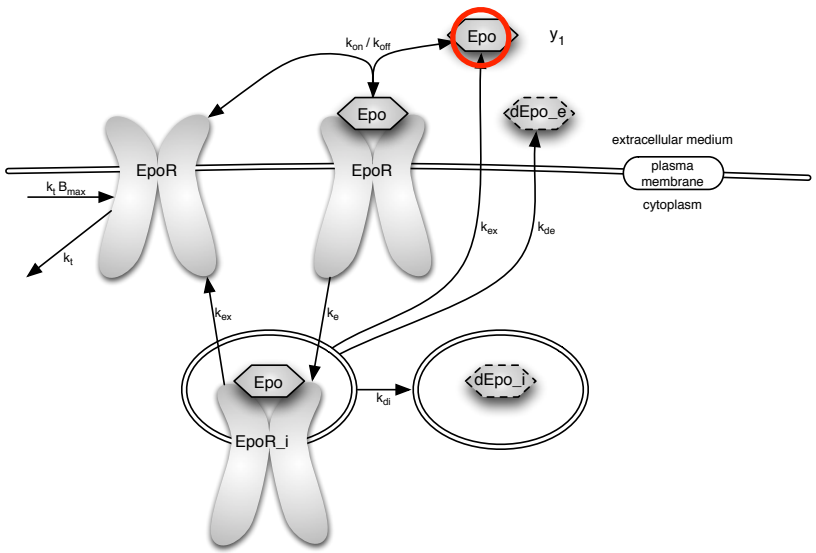

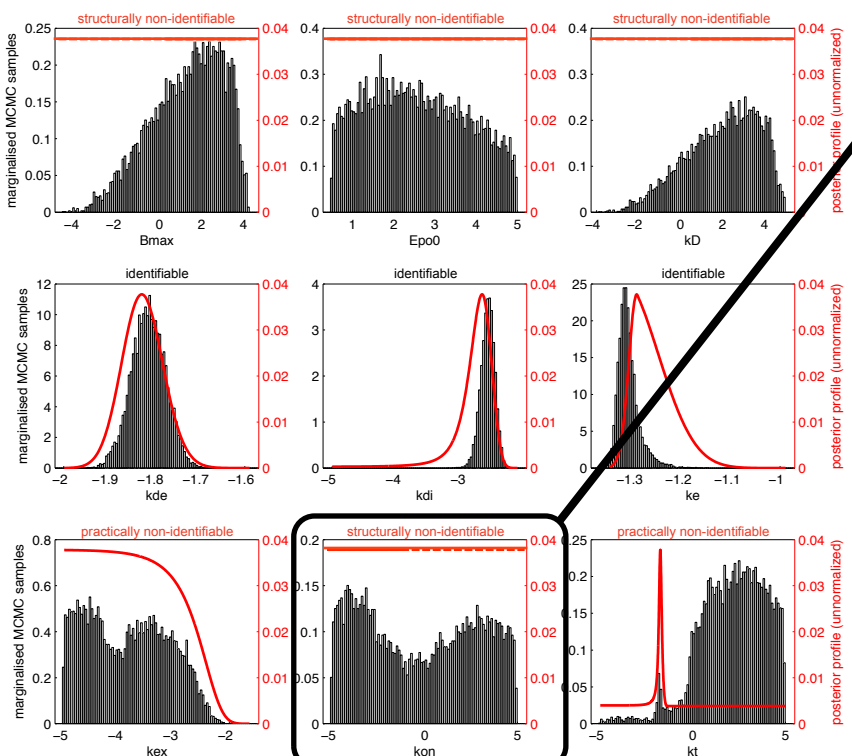

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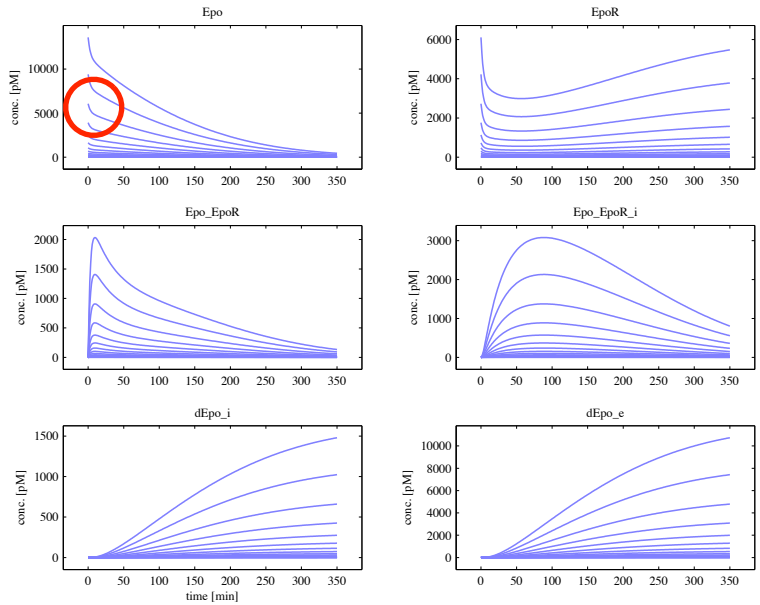

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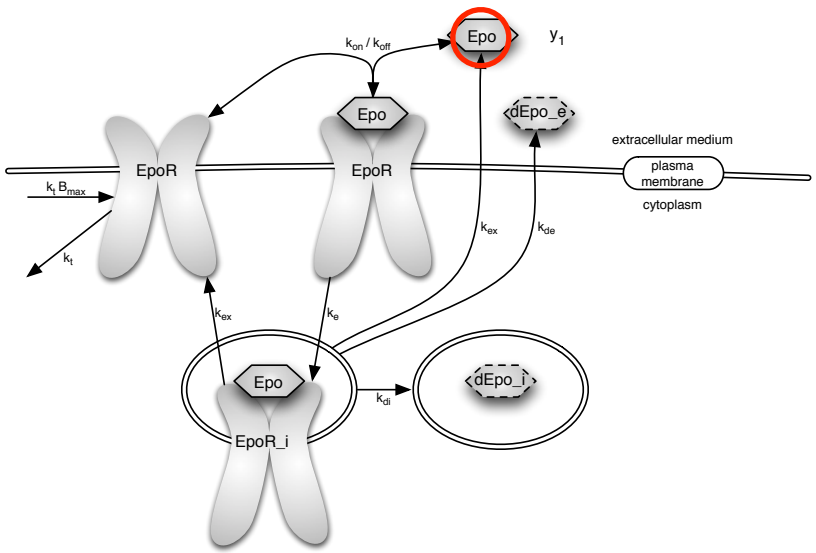

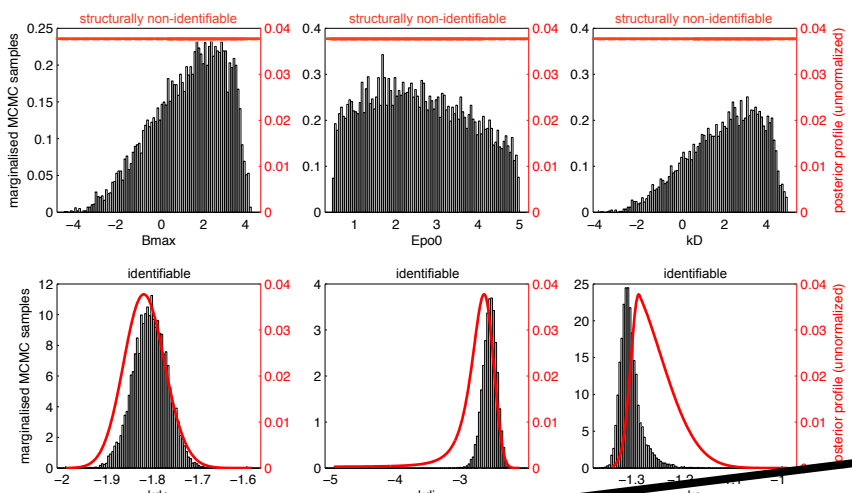

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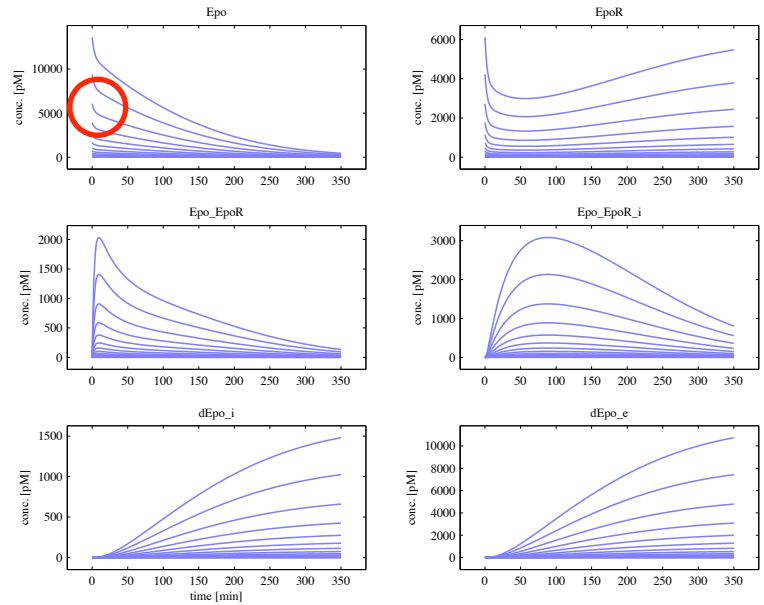
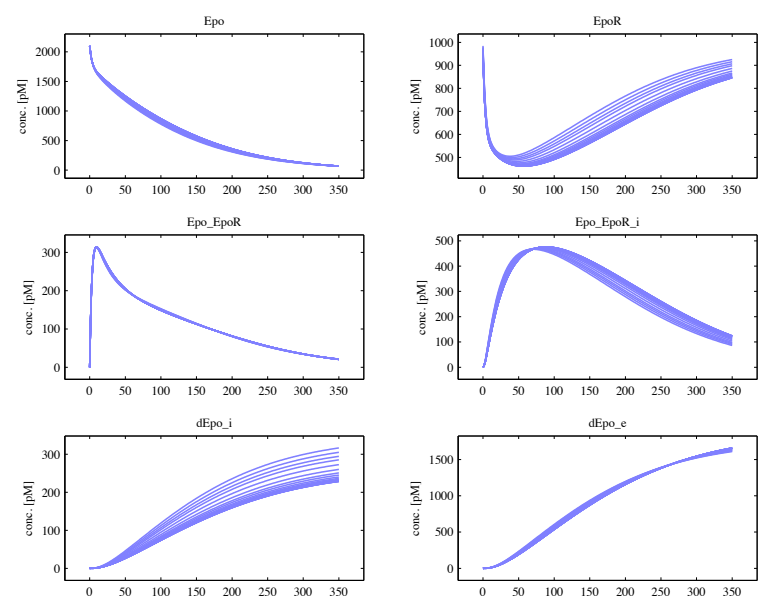
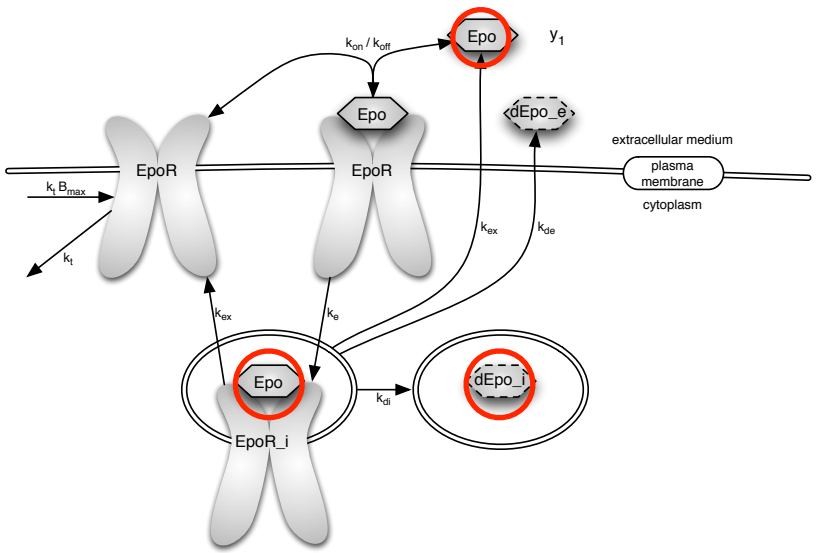
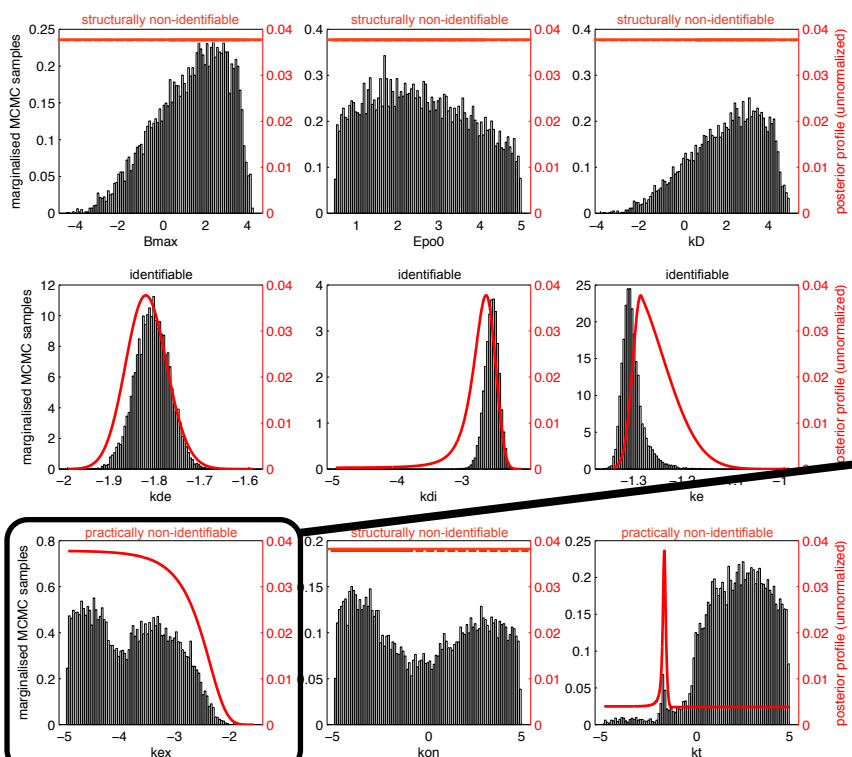


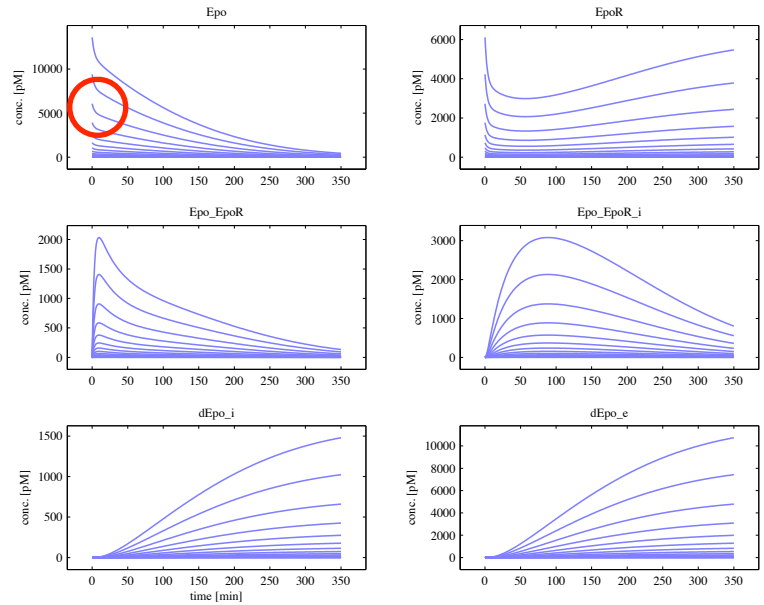


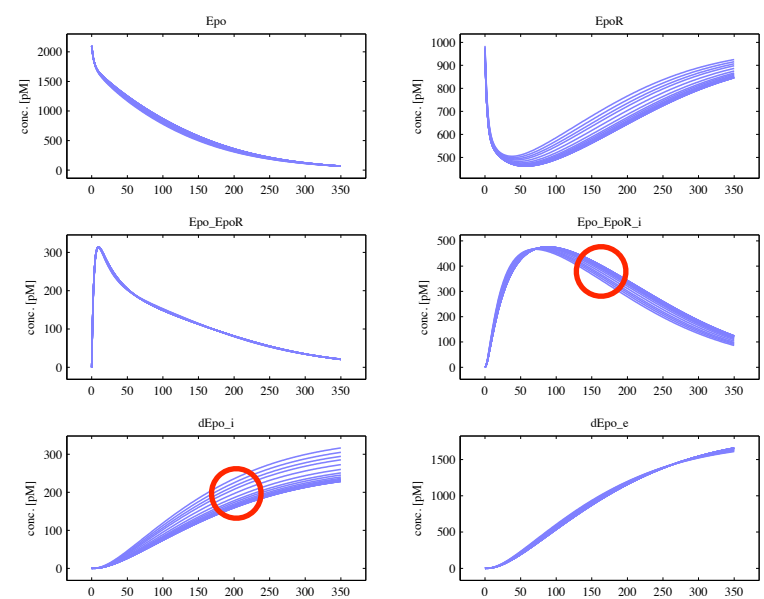
Experimental Design



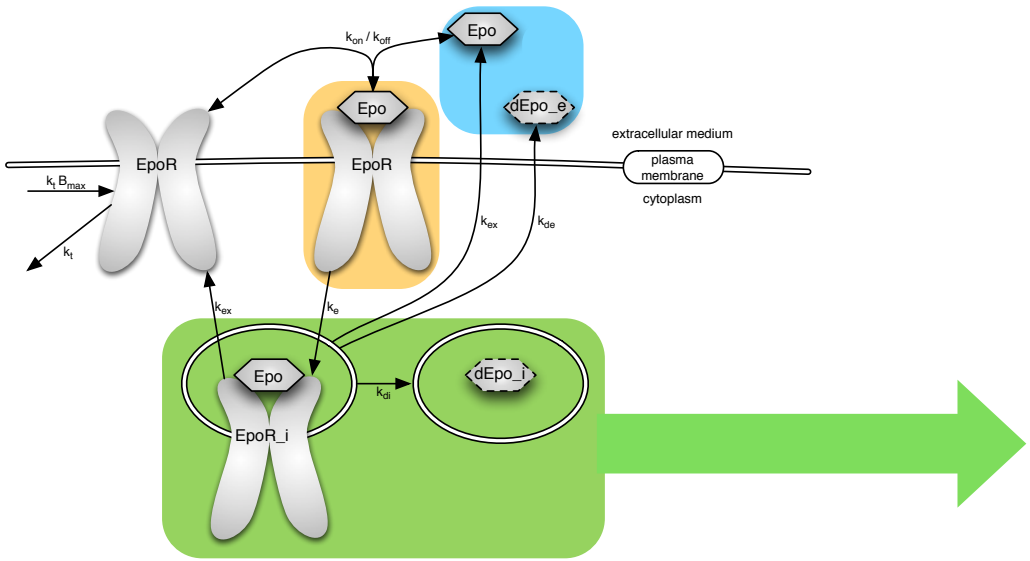


Non-observability of model dynamics:

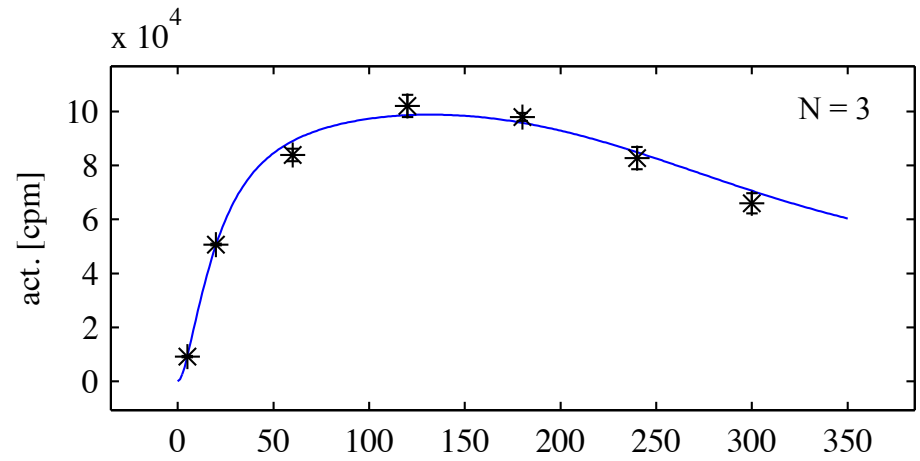




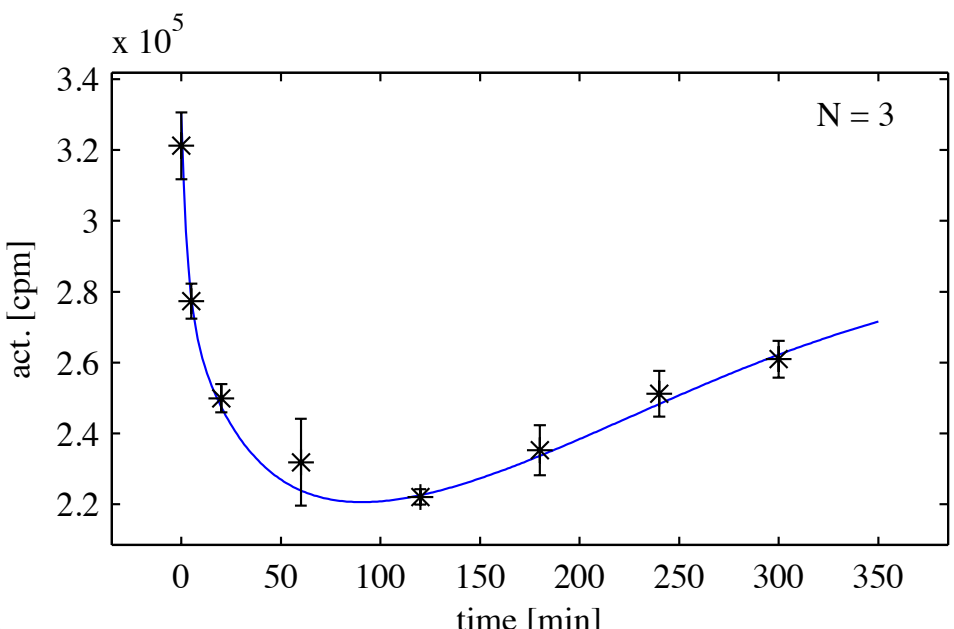
Extended Experimental Setup



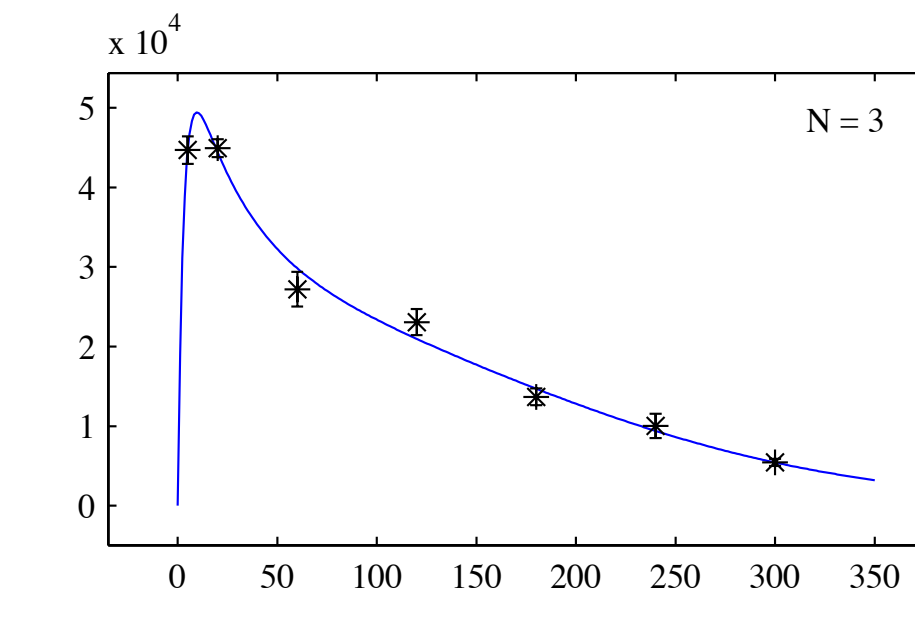
Epo inside the cell



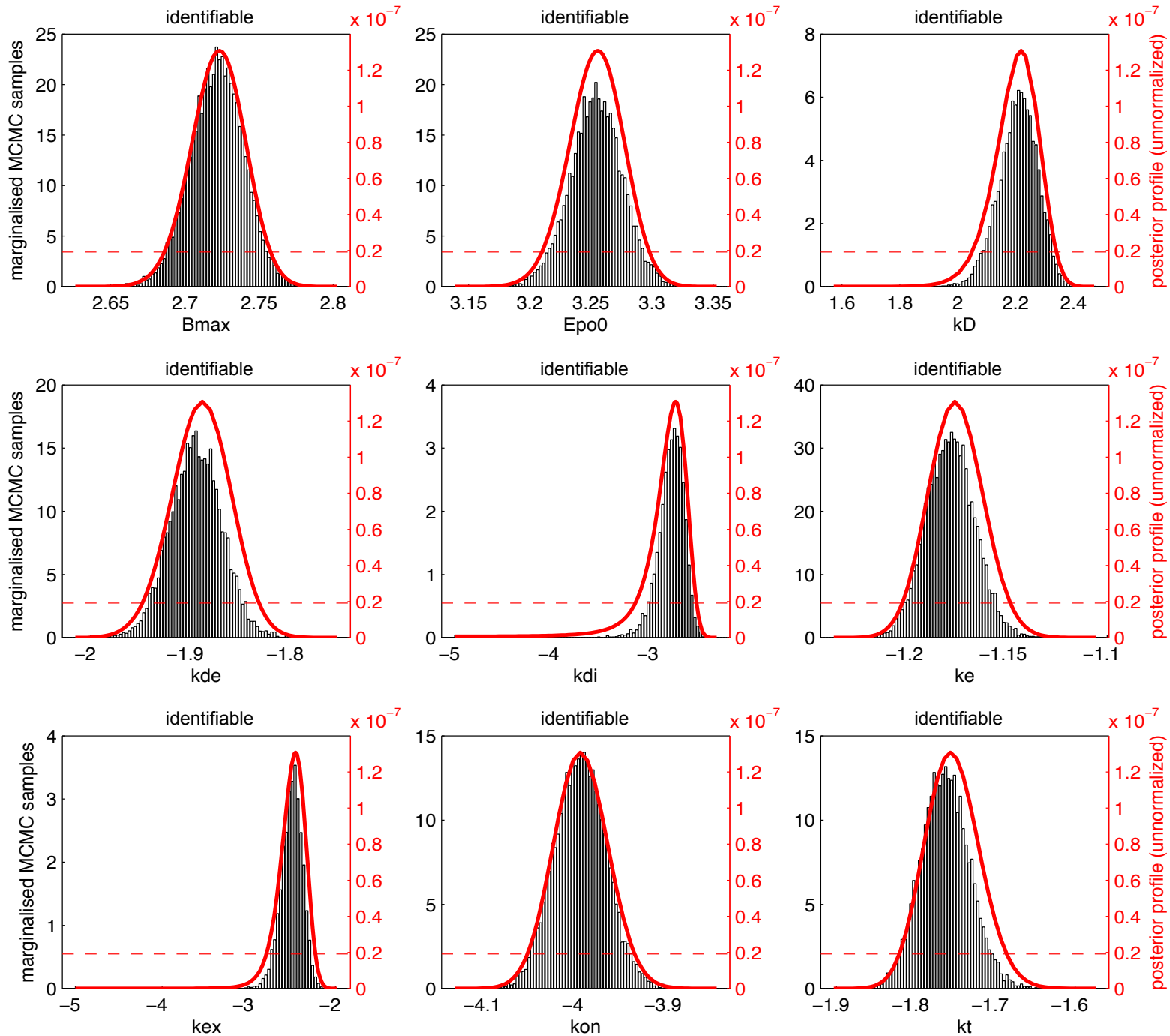
Epo in extracellular medium



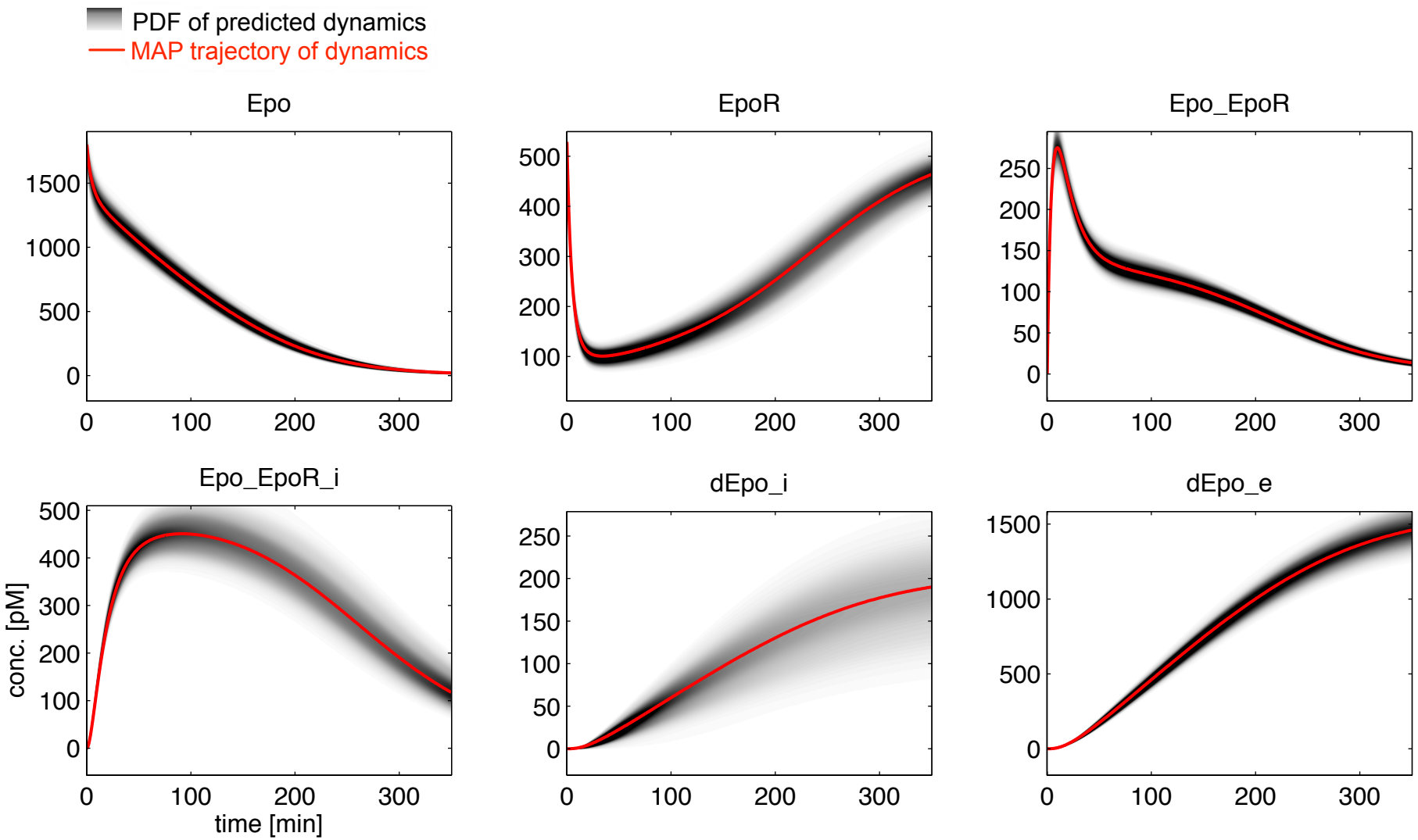
Epo bound to receptor on membrane



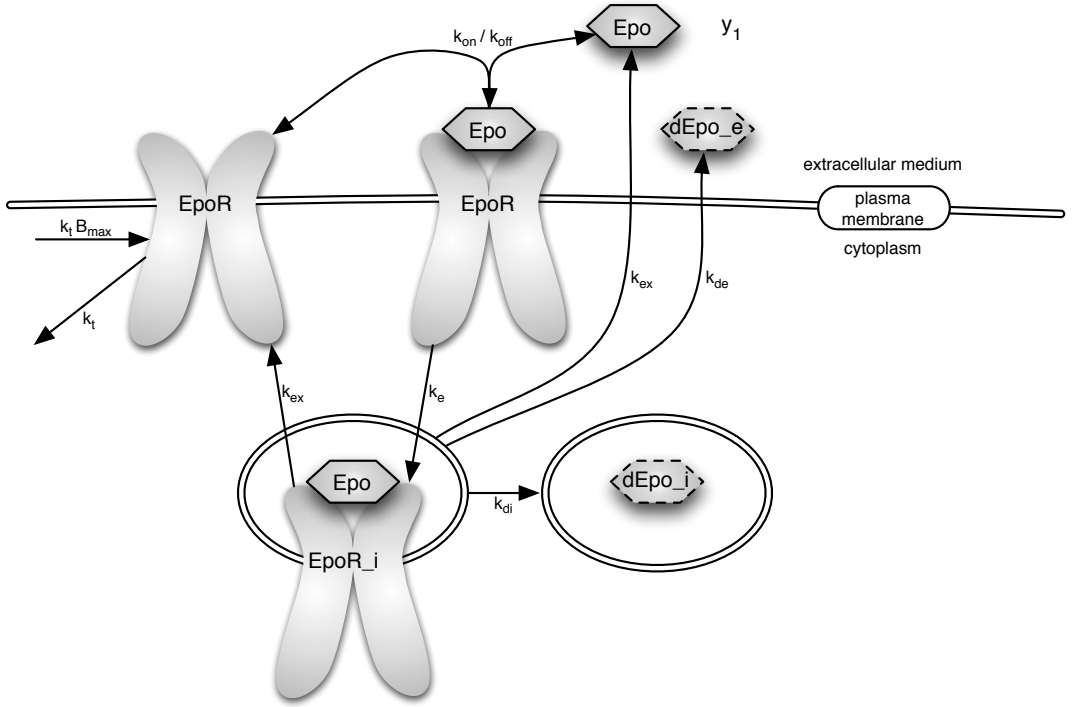
Results for Extended Setup

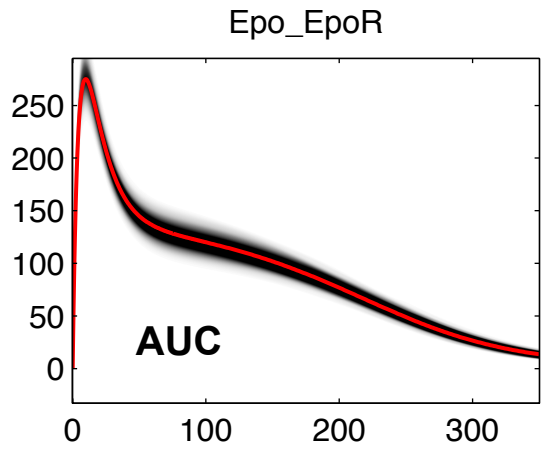


Predicted Model Dynamics



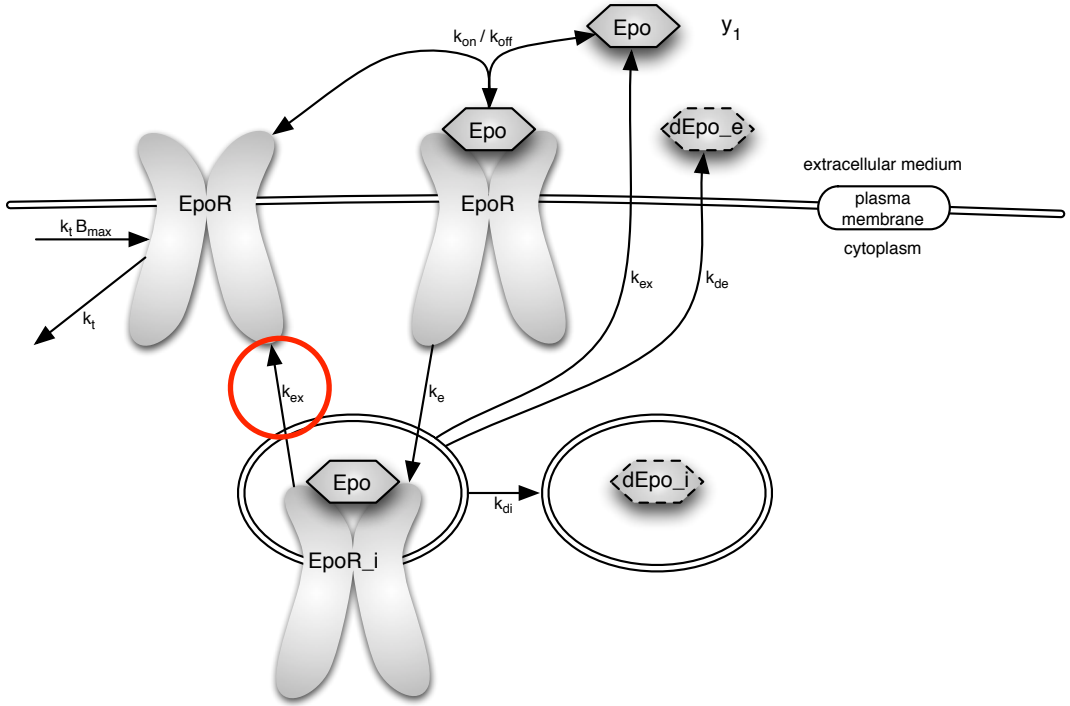
Predicted Model Dynamics - Biological Interpretation

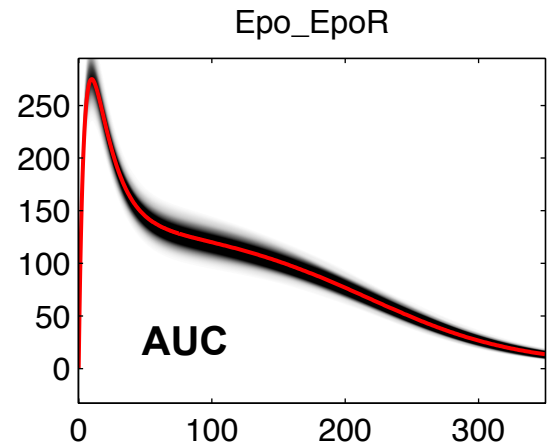




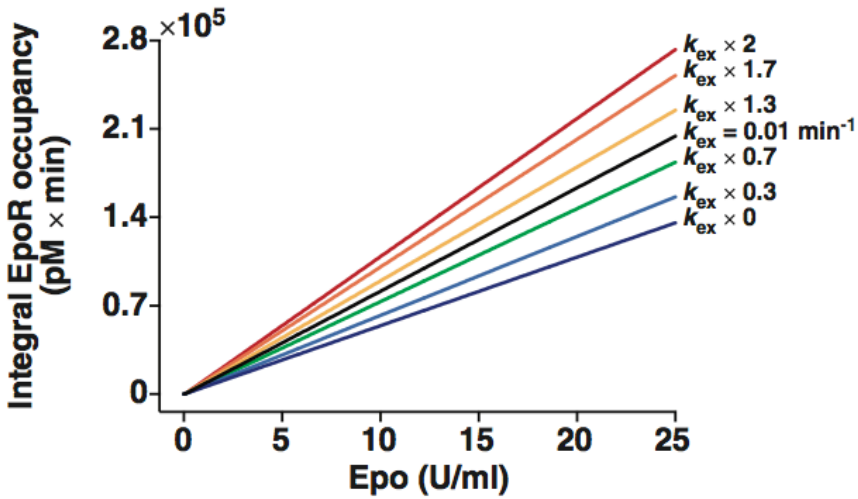
Becker *et al.* Science 2010

Predicted Model Dynamics - Biological Interpretation

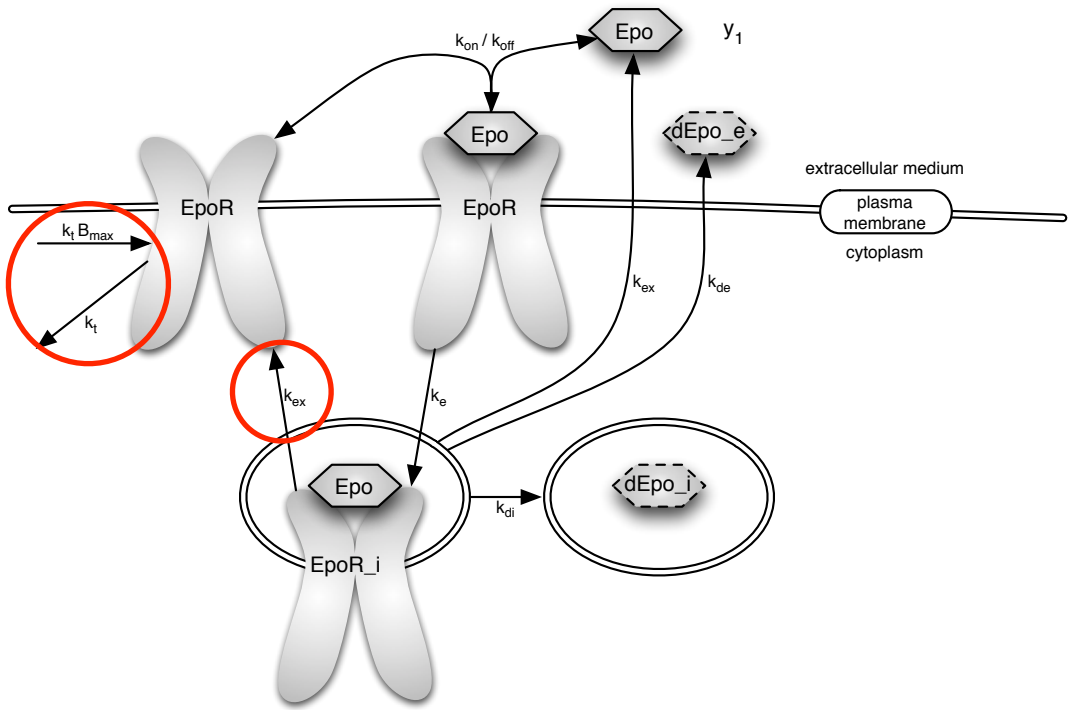


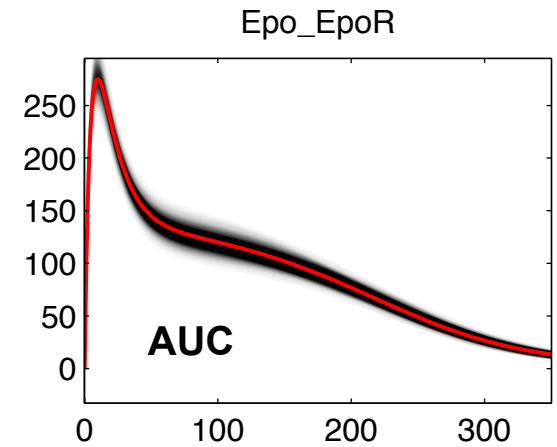


Becker *et al.* Science 2010

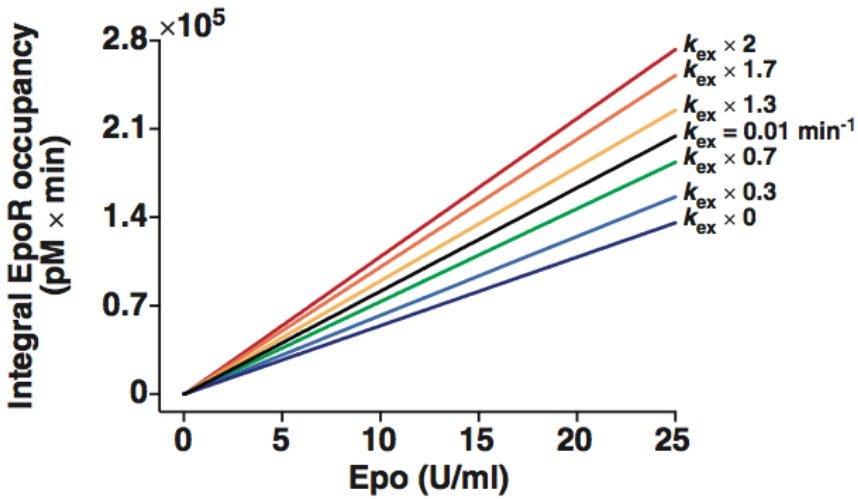


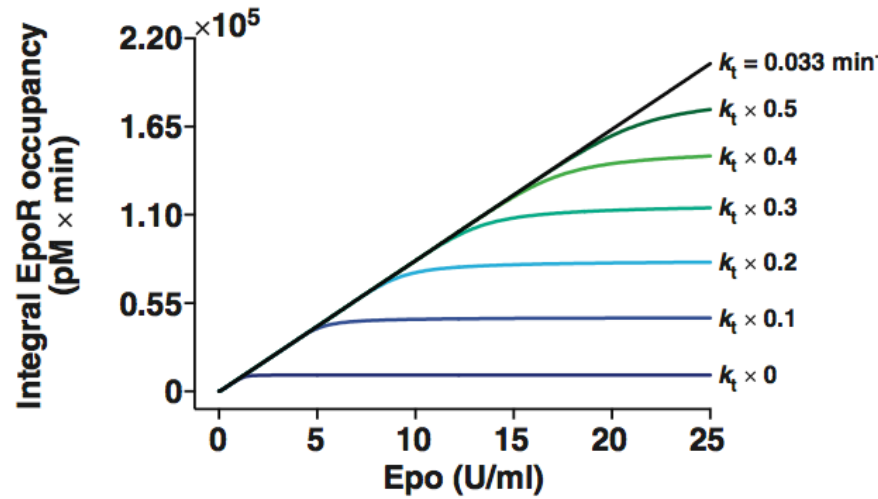
Predicted Model Dynamics - Biological Interpretation





Becker *et al.* Science 2010



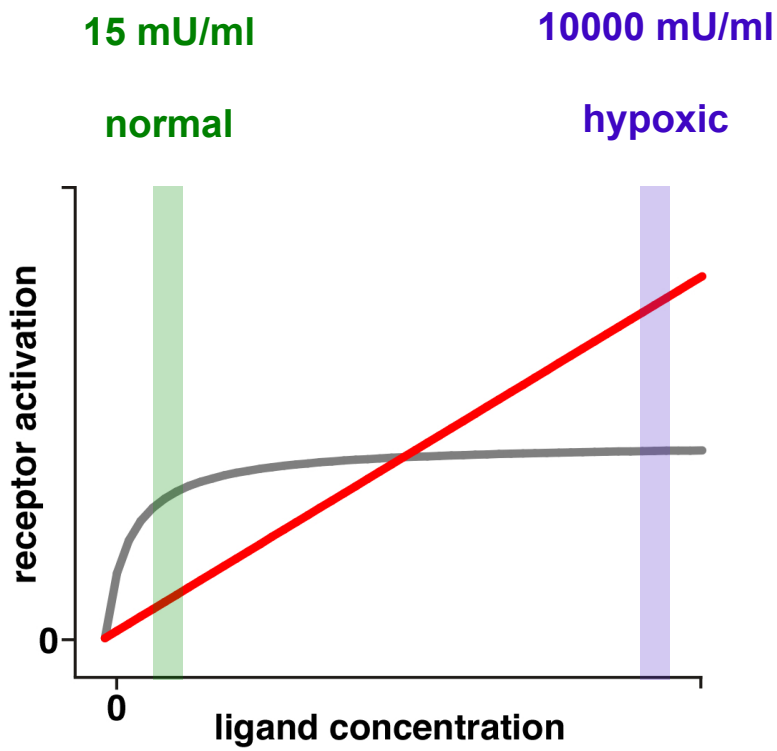


Summary

Cellular information processing through EpoR

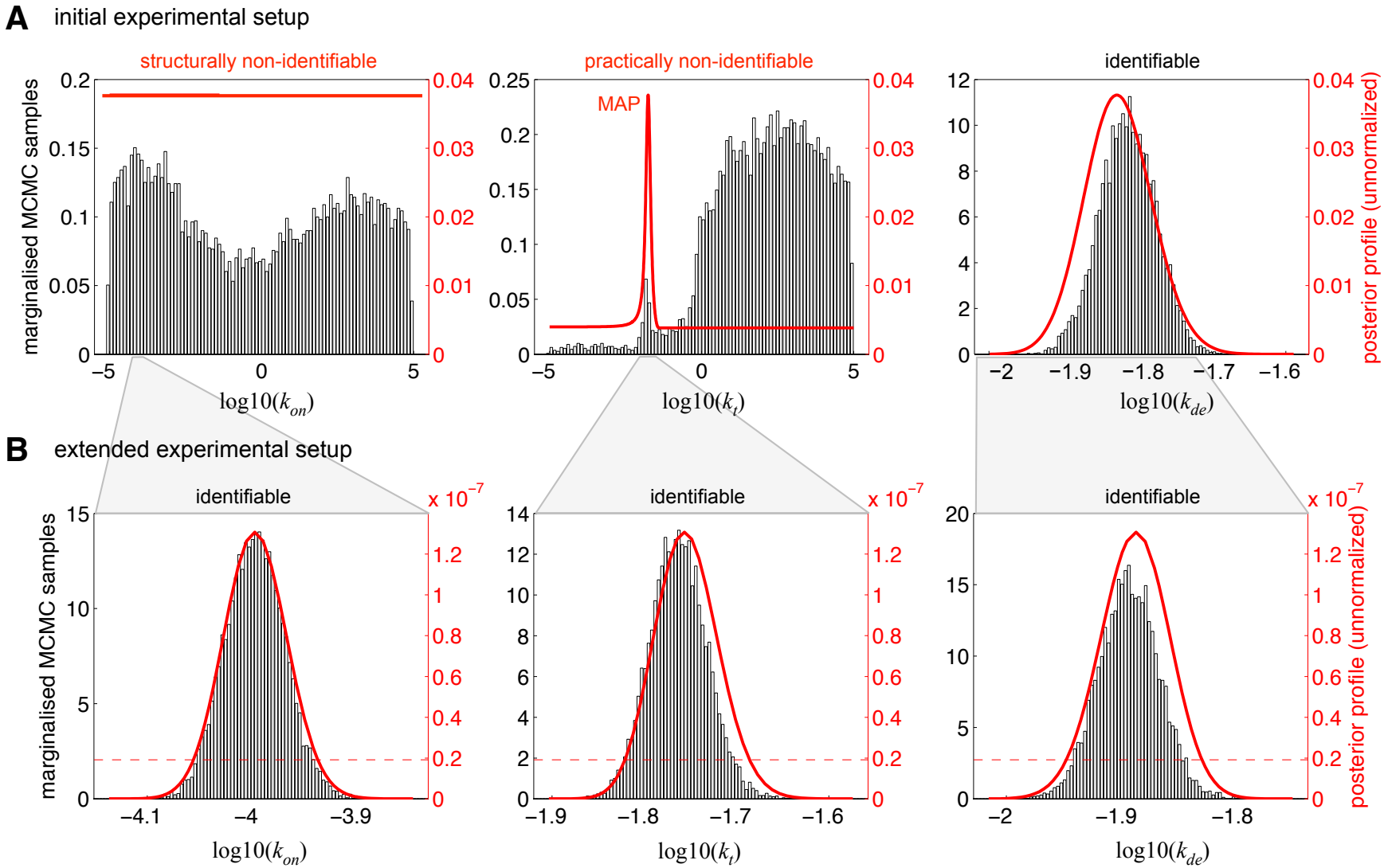
➜ **linear relation of Epo levels and integral EpoR activation over a broad range of ligand concentrations**

➜ **accurate translation of ligand input into erythrocyte production**



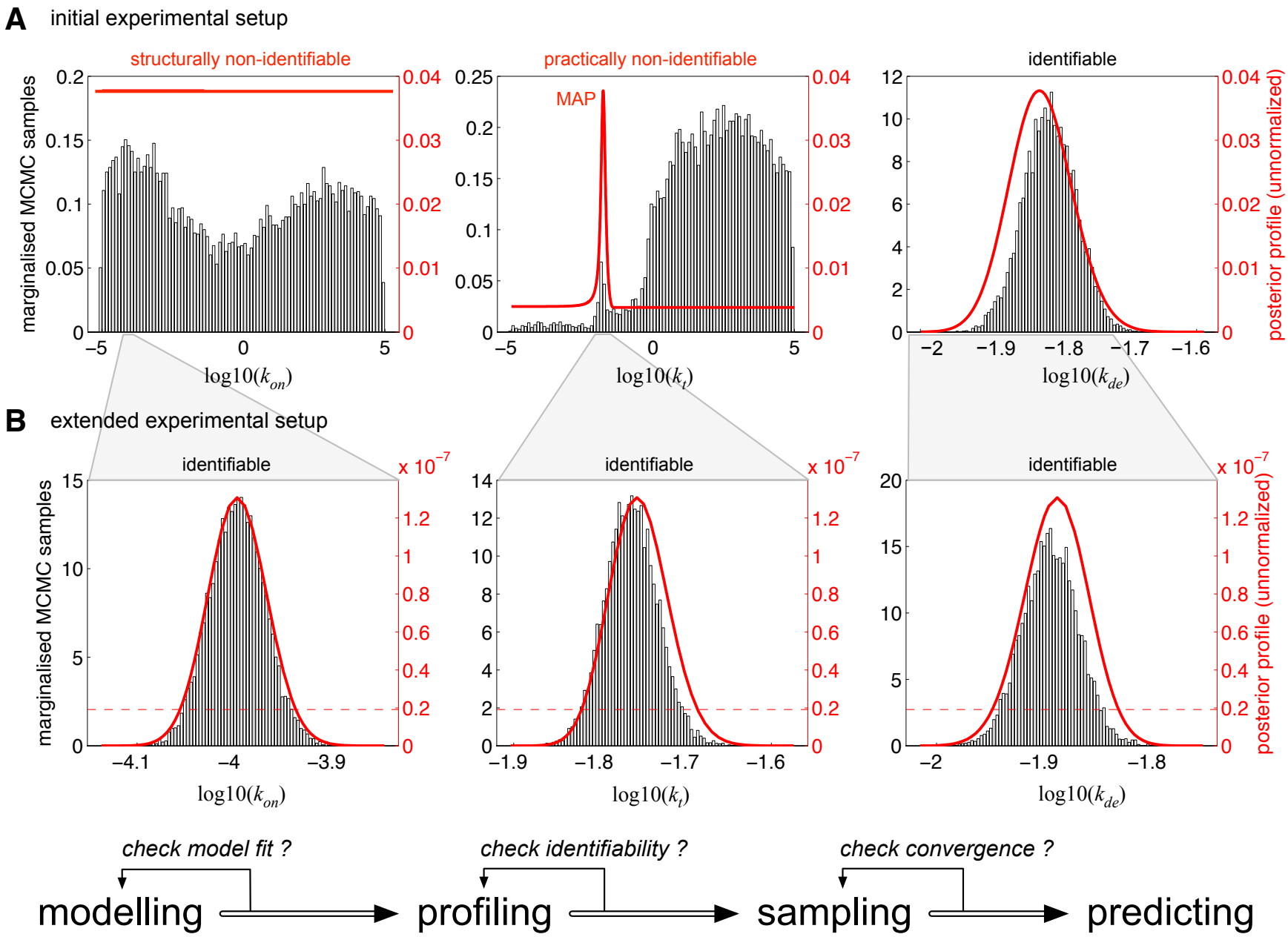
Summary

Comparison of profile likelihood and MCMC sampling

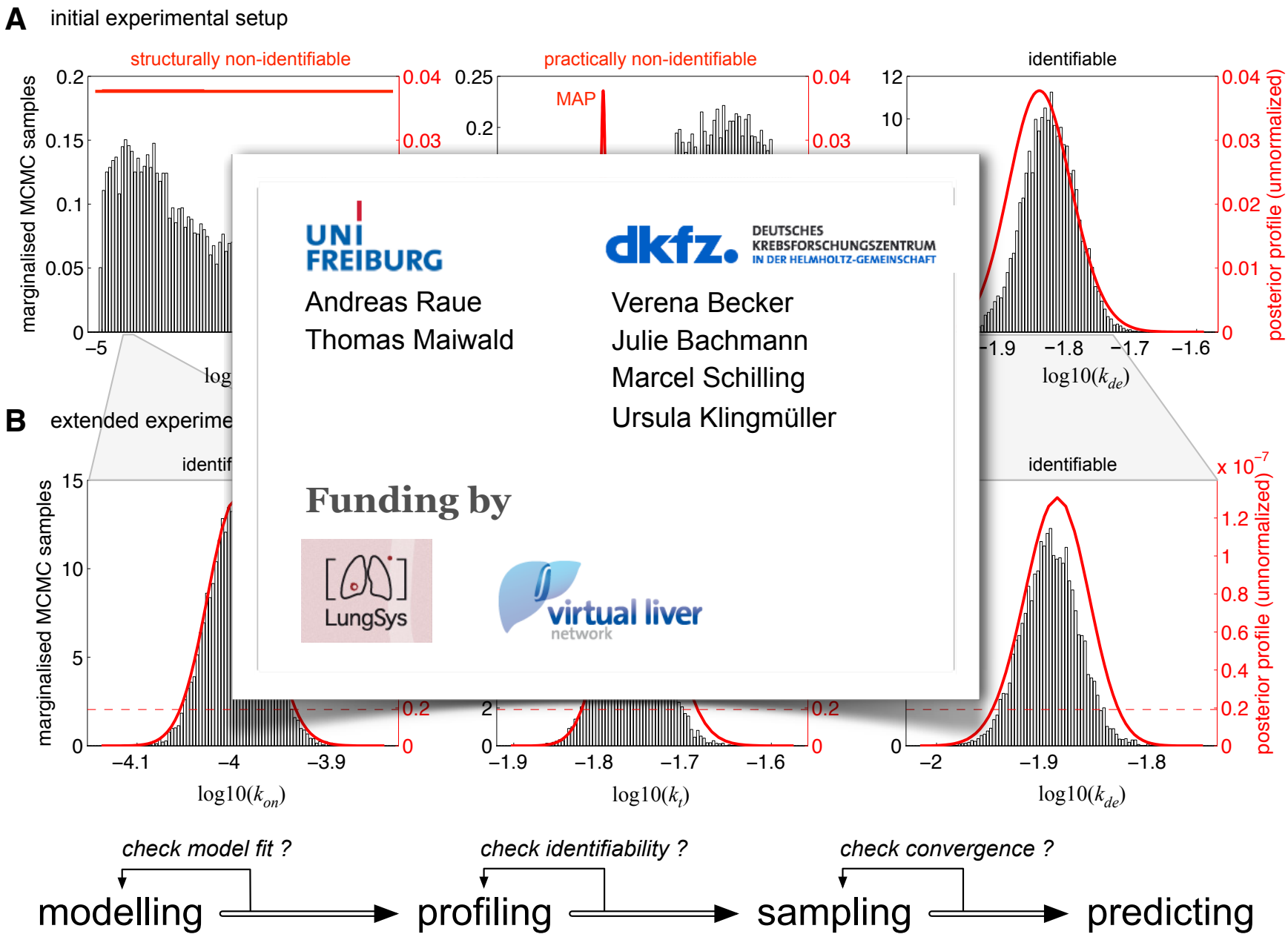


Summary

Comparison of profile likelihood and MCMC sampling



Acknowledgements



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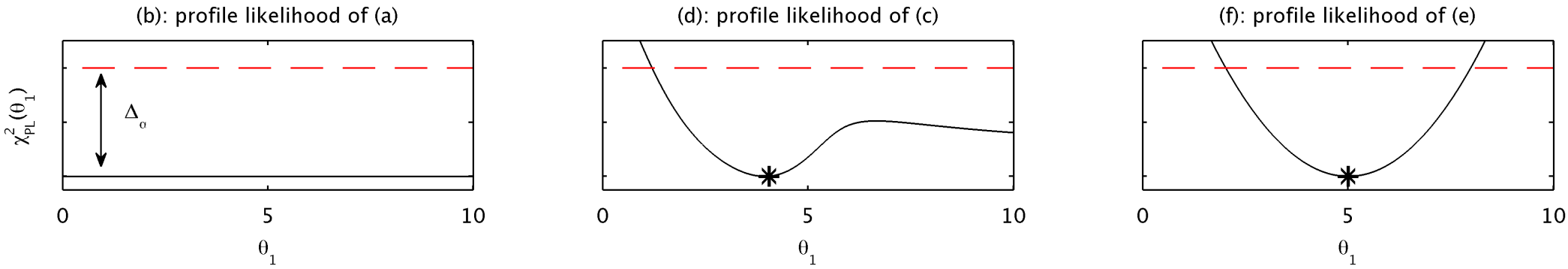
LungSys

virtual liver network

Requirements for Profile Likelihood Approach



Raue *et al.* Bioinformatics 2009

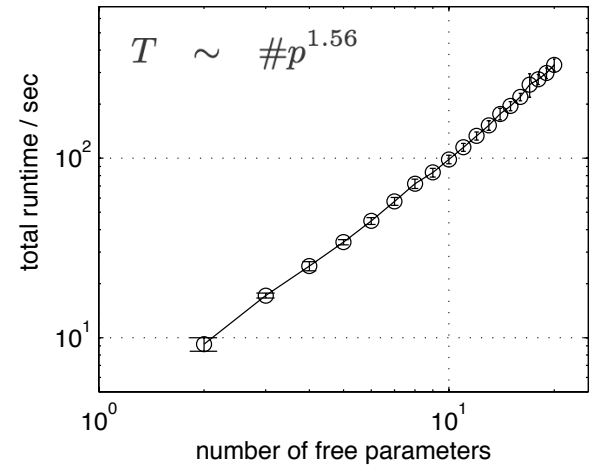
- Profile Likelihood Approach is not limited to ODE models
- Only requirement: a working Maximum Likelihood Estimation
- Freely available software implementation:

PottersWheel Toolbox (MATLAB)

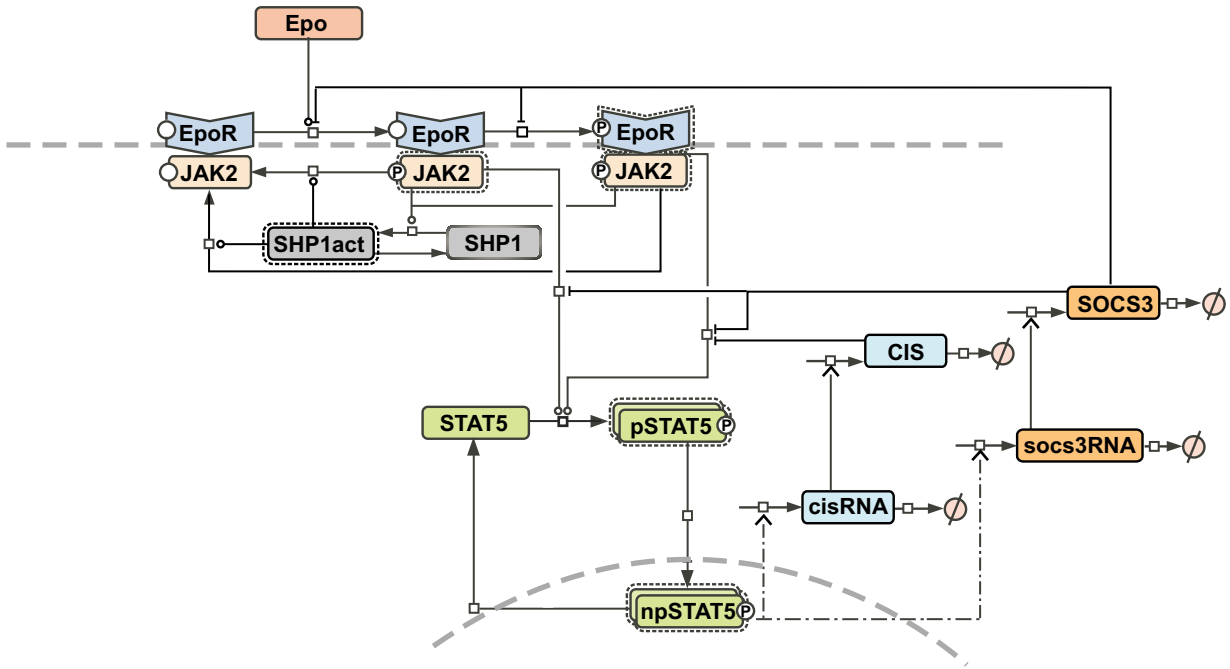
Scaling of Profile Likelihood Approach

Runtime analysis for increasing number of parameters:

Calculation can also be parallelized perfectly!



Model of downstream signaling events:



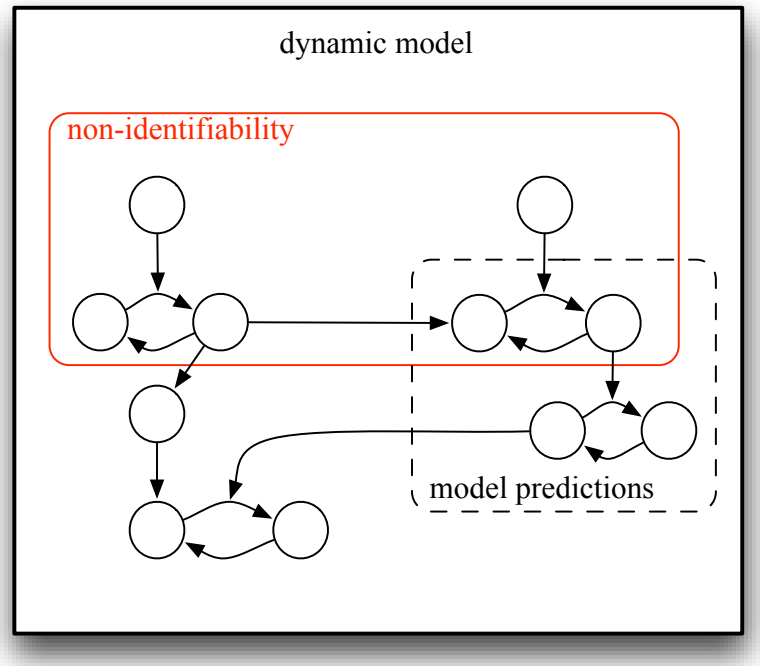
25 ODEs
24 experimental conditions
541 data points
115 free parameters

~10 minutes per profile

Bachmann *et al.* Molecular Systems Biology 2011

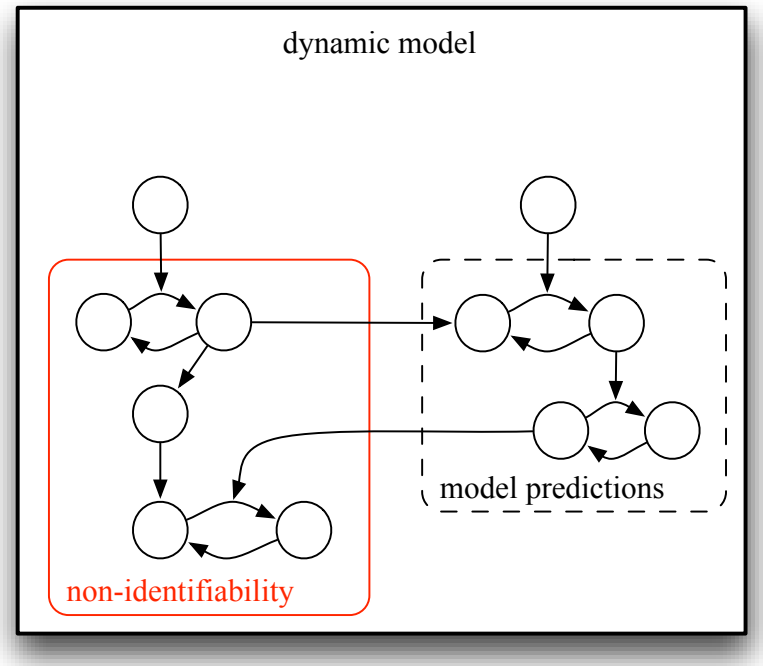
Model-Based Experimentation

(a) scenario 1



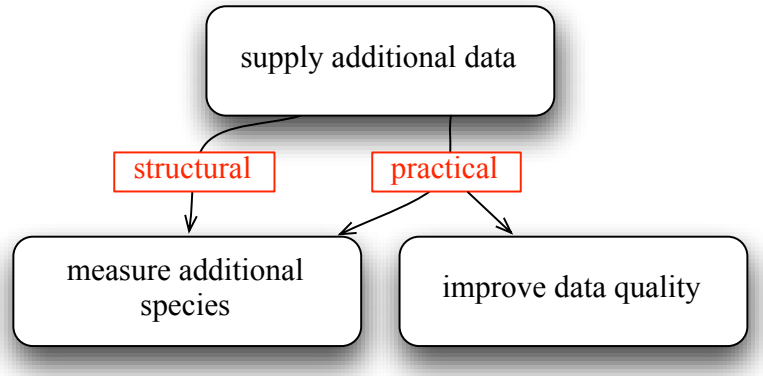
model predictions affected by non-identifiability
→ model predictions not reliable

(b) scenario 2



model predictions not or only negligibly affected by non-identifiability

experimental design:



model reduction:

simplify ODE system with respect to non-identifiability

Raue *et al.* IET Systems Biology 2011