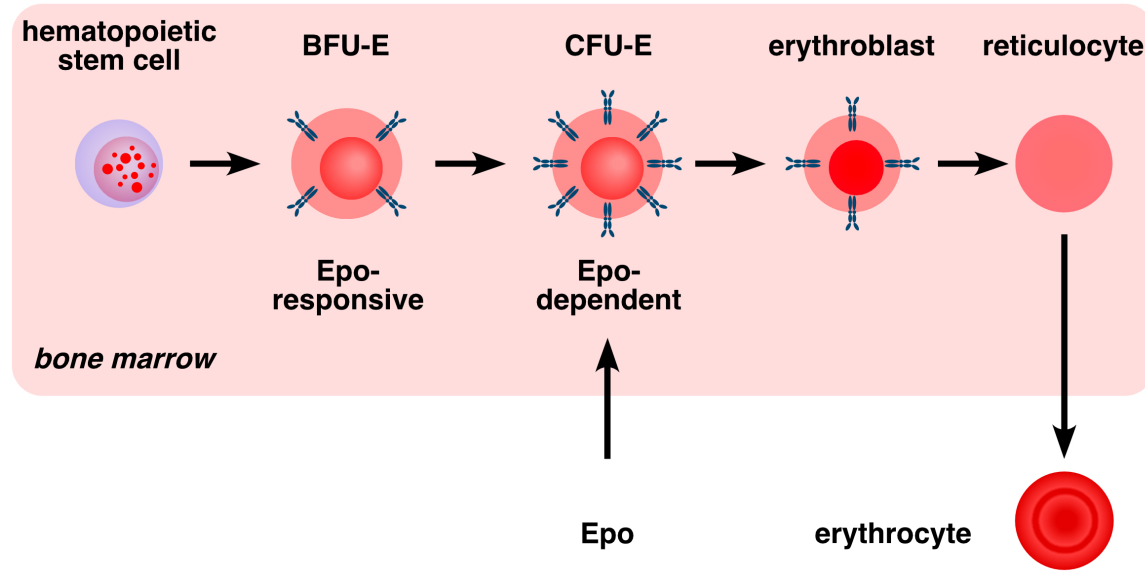


# A Study for Inference in the Presence of Non-Identifiability:

Bayesian MCMC sampling  
vs.  
profile likelihood approach

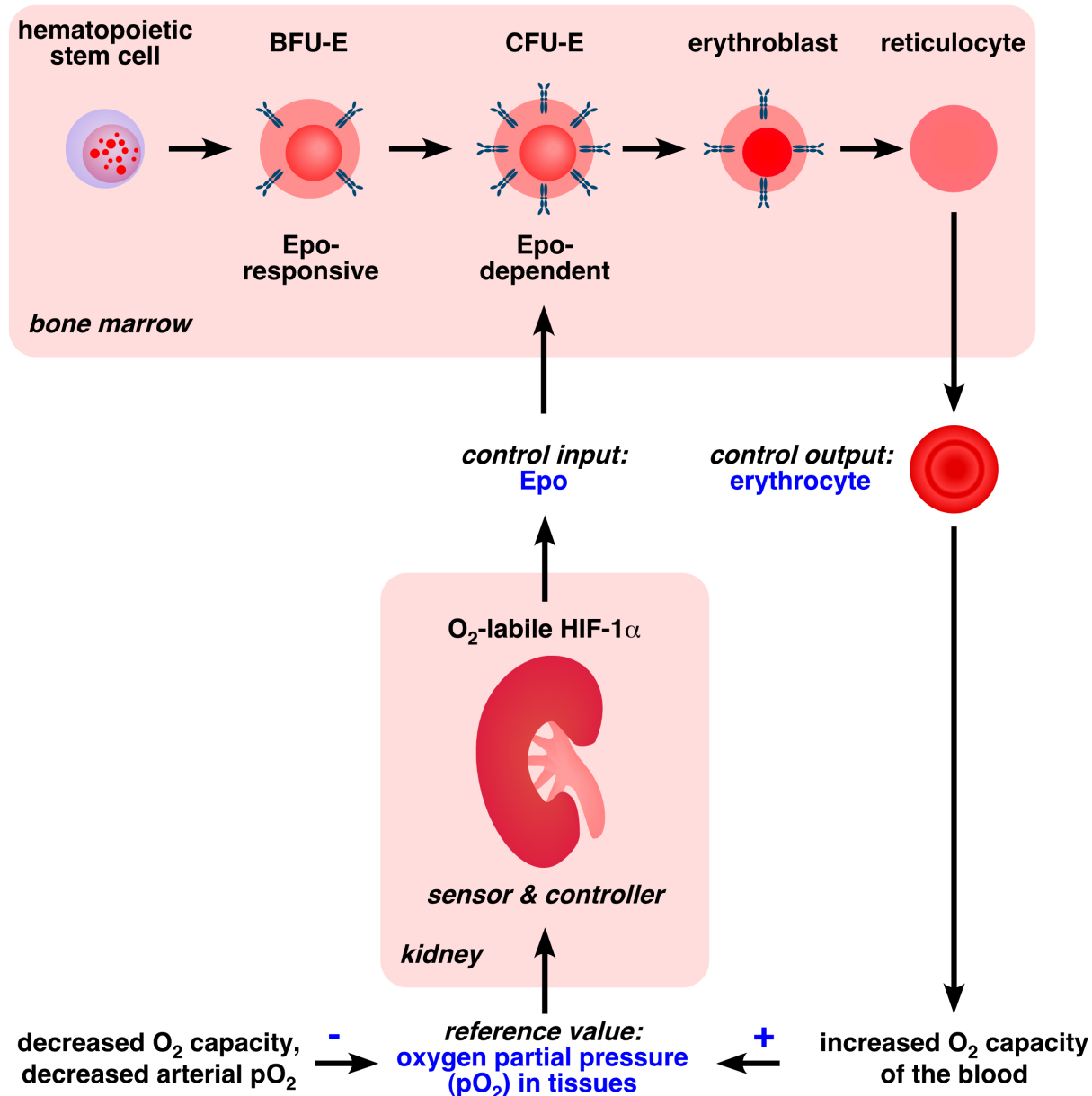


# Erythropoiesis - A Closed-Loop Control System



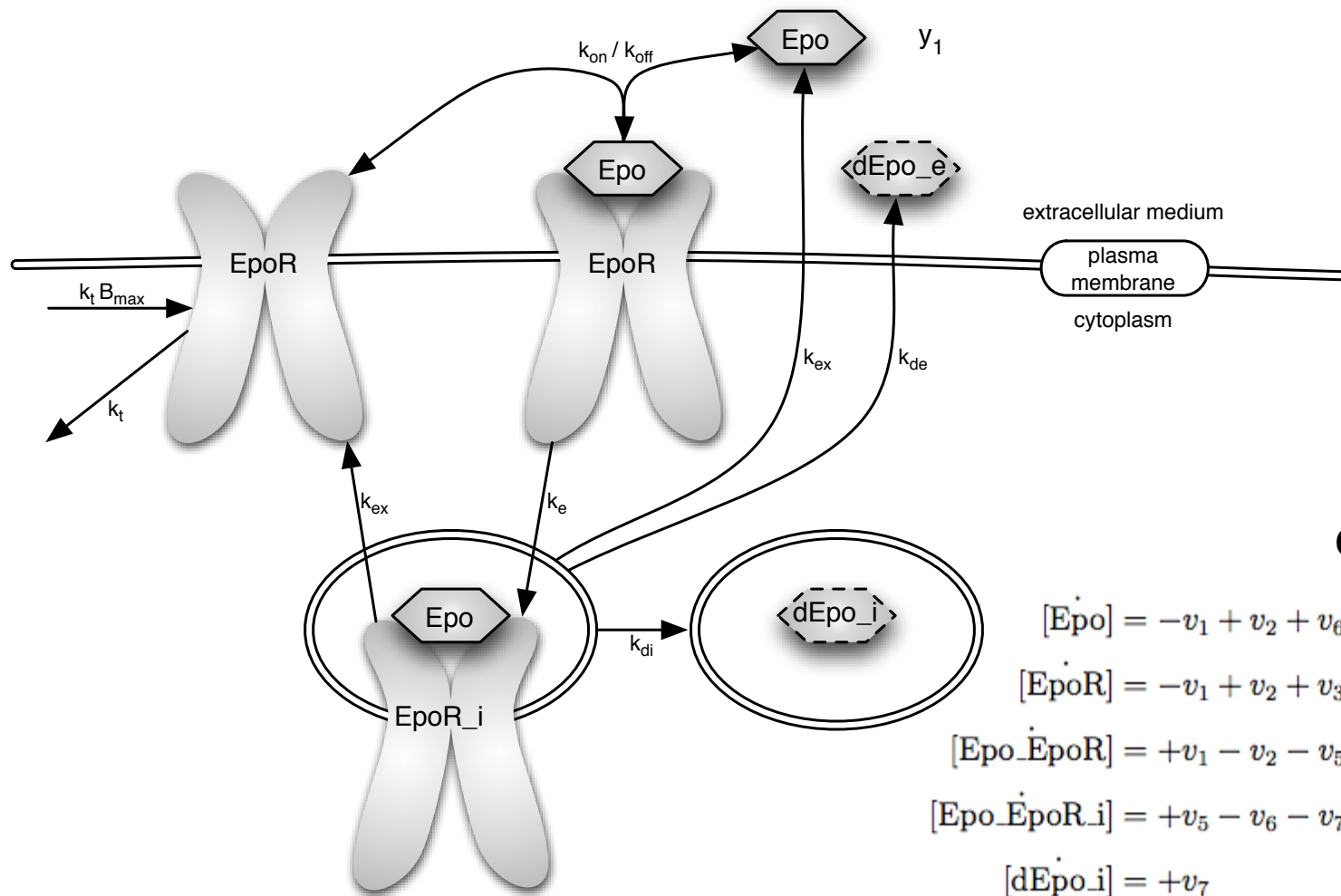
- **Epo**: key regulator of erythropoiesis

# 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

$$[Epo] = -v_1 + v_2 + v_6 \quad v_1 = k_{on} \cdot [Epo] \cdot [EpoR]$$

$$[EpoR] = -v_1 + v_2 + v_3 - v_4 + v_6 \quad v_2 = k_{on} \cdot k_D \cdot [Epo \cdot EpoR]$$

$$[Epo \cdot EpoR] = +v_1 - v_2 - v_5 \quad v_3 = k_t \cdot B_{max}$$

$$[Epo \cdot EpoR_i] = +v_5 - v_6 - v_7 - v_8 \quad v_4 = k_t \cdot [EpoR]$$

$$[dEpo_i] = +v_7 \quad v_5 = k_e \cdot [Epo \cdot EpoR]$$

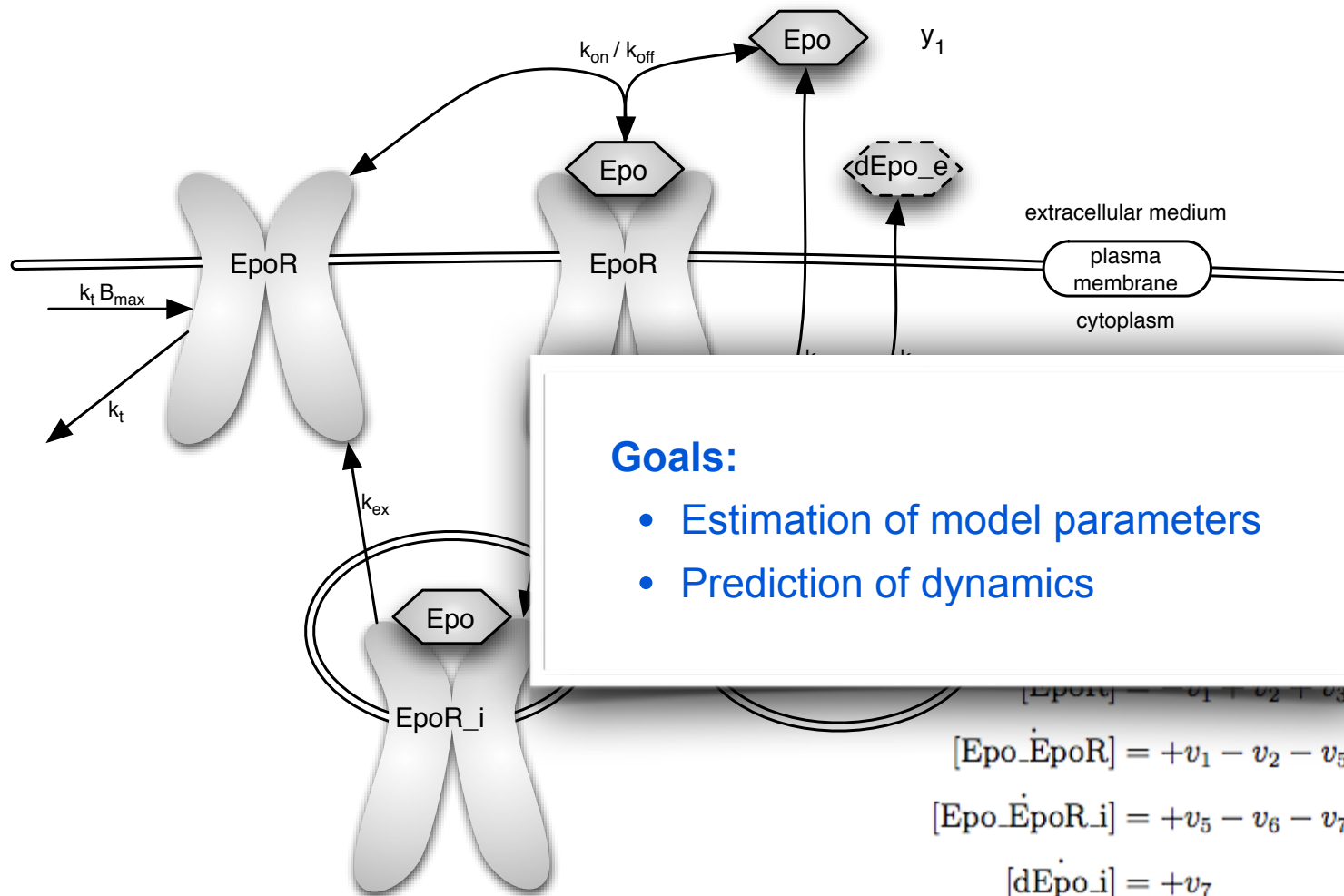
$$[dEpo_e] = +v_8 \quad v_6 = k_{ex} \cdot [Epo \cdot EpoR_i]$$

$$v_7 = k_{di} \cdot [Epo \cdot EpoR_i]$$

$$v_8 = k_{de} \cdot [Epo \cdot EpoR_i]$$



# Epo and Epo receptor interaction and trafficking



## Goals:

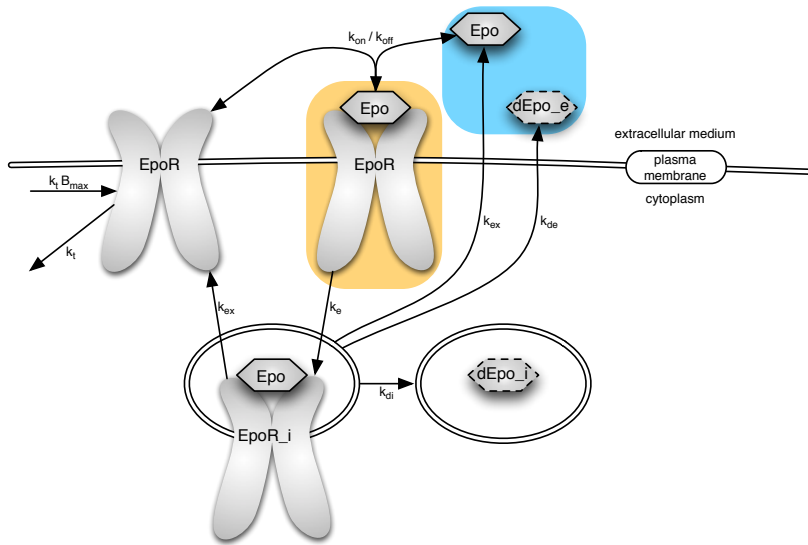
- Estimation of model parameters
- Prediction of dynamics

## DE model

$$\begin{aligned}
 v_1 &= k_{on} \cdot [Epo] \cdot [EpoR] \\
 v_2 &= k_{on} \cdot k_D \cdot [Epo\_EpoR] \\
 v_3 &= k_t \cdot B_{max} \\
 v_4 &= k_t \cdot [EpoR] \\
 v_5 &= k_e \cdot [Epo\_EpoR] \\
 v_6 &= k_{ex} \cdot [Epo\_EpoR\_i] \\
 v_7 &= k_{di} \cdot [Epo\_EpoR\_i] \\
 v_8 &= k_{de} \cdot [Epo\_EpoR\_i]
 \end{aligned}$$

$$\begin{aligned}
 [EpoR] &= +v_1 - v_2 - v_3 - v_4 + v_6 \\
 [Epo\_EpoR] &= +v_1 - v_2 - v_5 \\
 [Epo\_EpoR\_i] &= +v_5 - v_6 - v_7 - v_8 \\
 [dEpo\_i] &= +v_7 \\
 [dEpo\_e] &= +v_8
 \end{aligned}$$

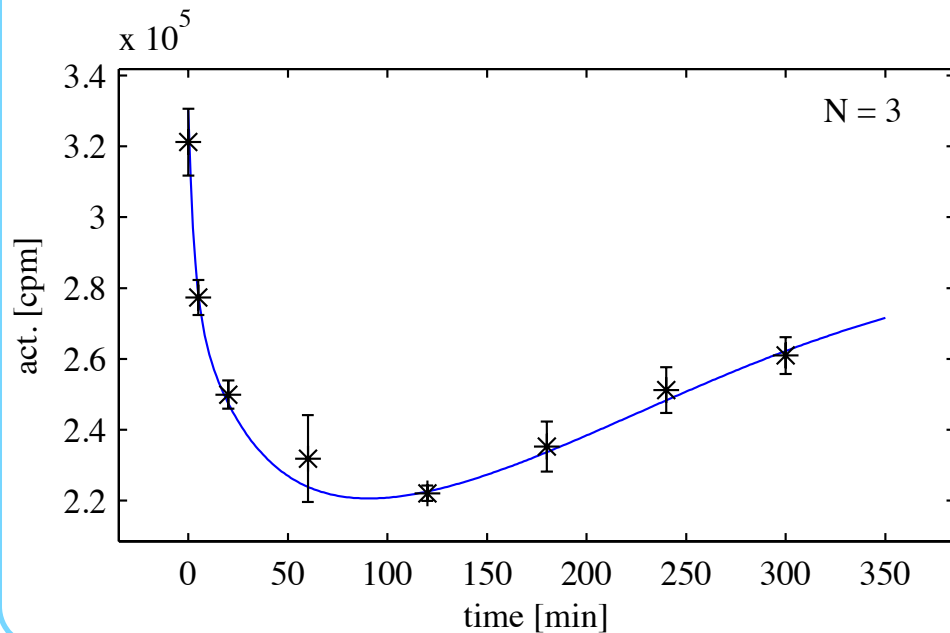
# Initial Experimental Setup



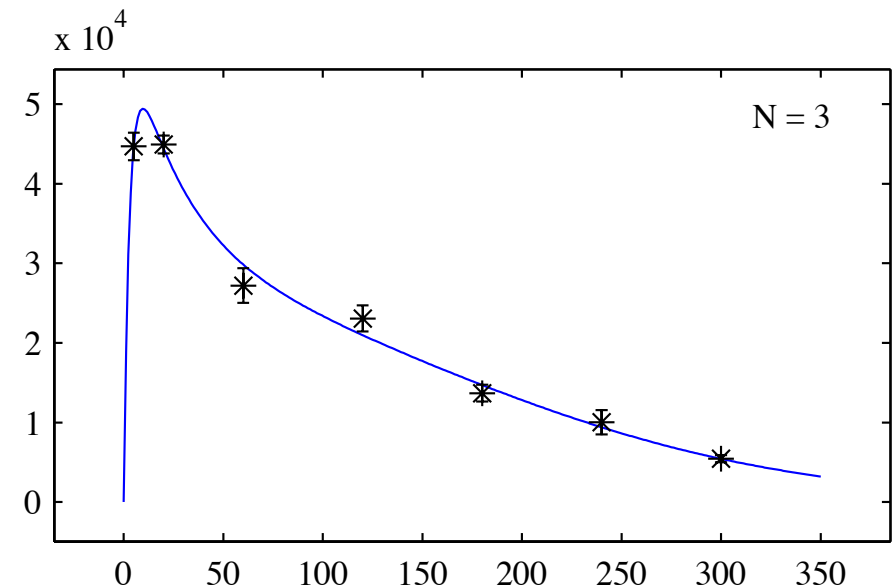
## Maximum Likelihood Estimation

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

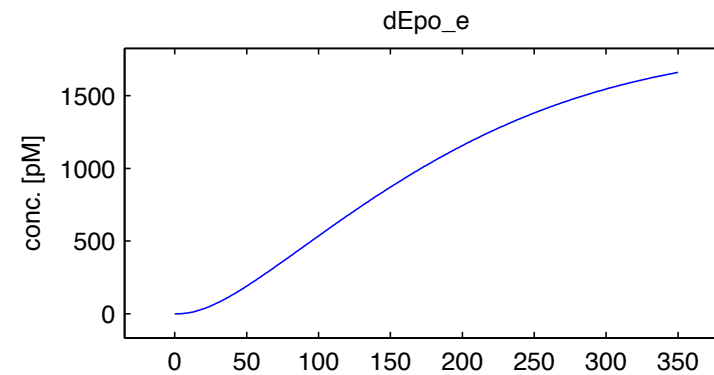
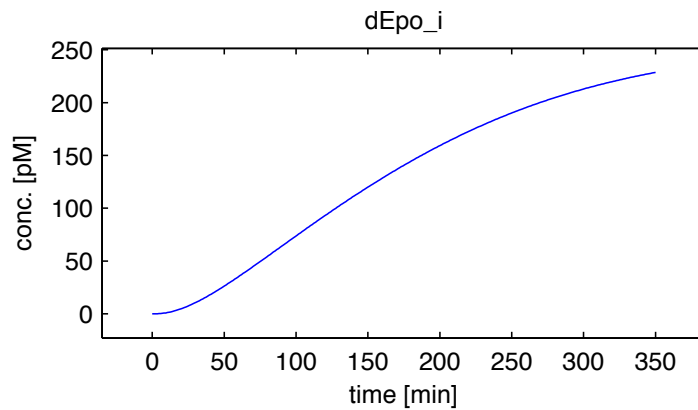
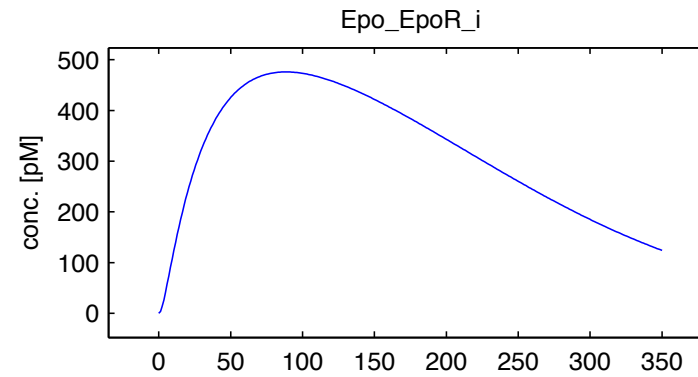
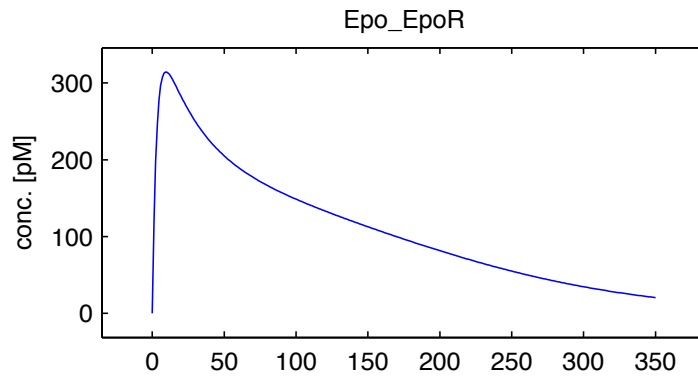
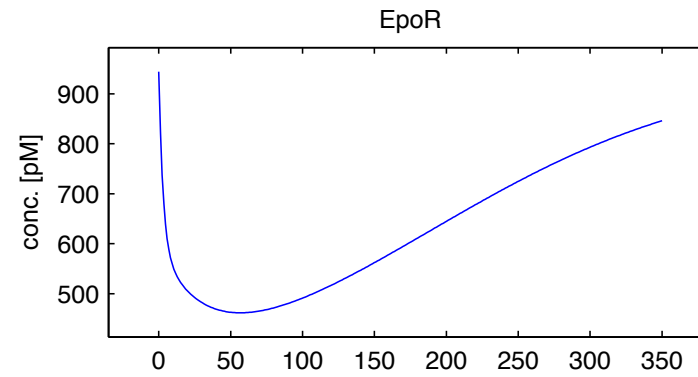
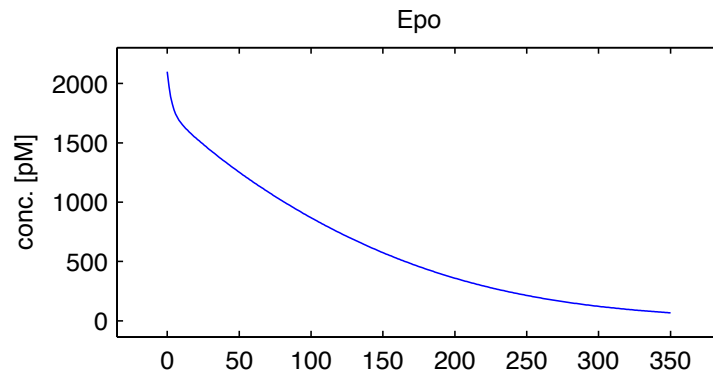
Epo in extracellular medium



Epo bound to receptor on membrane



# Predicted Model Dynamics



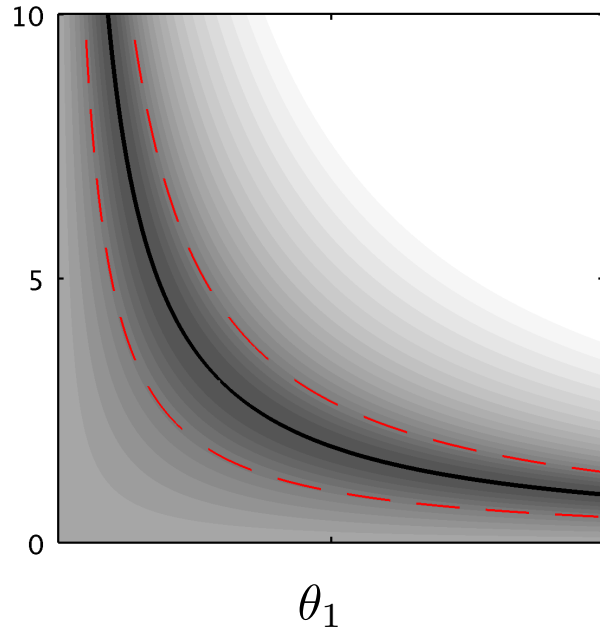
Are the predictions reliable ?

Are the estimated model parameters well constrained / identified ?

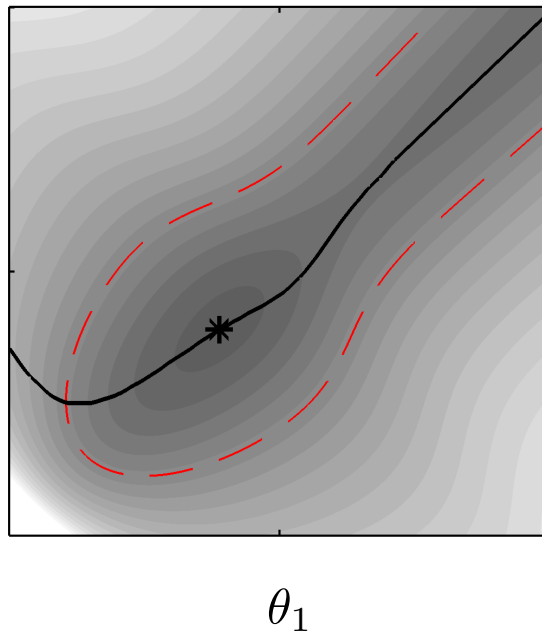
# Parameter Identifiability

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

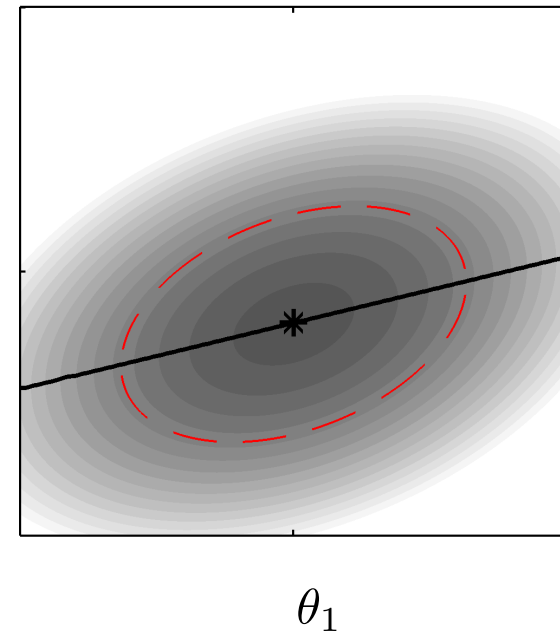
(a): structural non-identifiability



(c): practical non-identifiability



(e): parameters identifiable



ODE

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

Observables

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

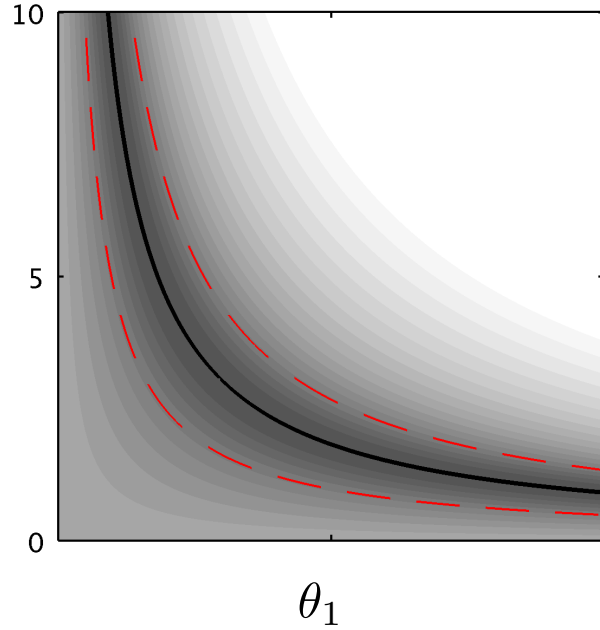
Likelihood

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

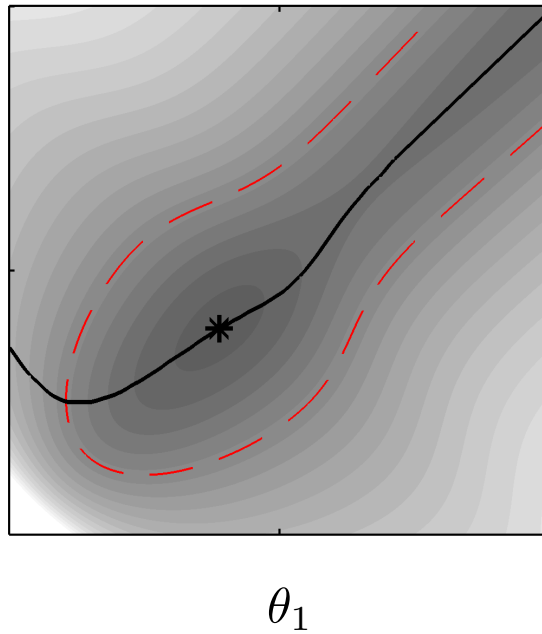
# Parameter Identifiability

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

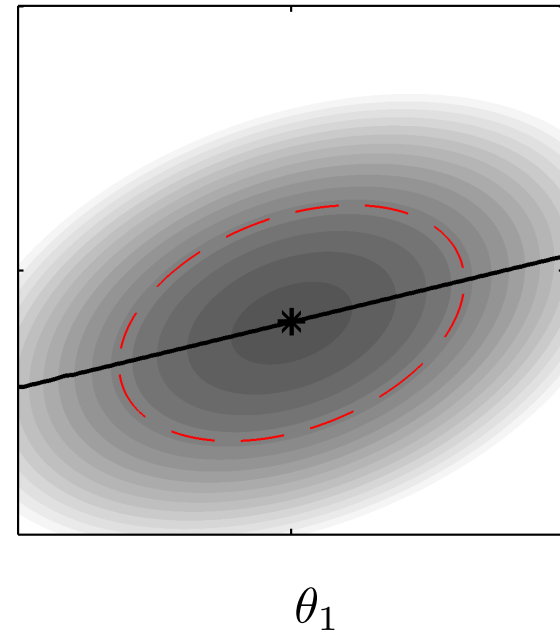
(a): structural non-identifiability



(c): practical non-identifiability



(e): parameters identifiable



## → Profile Likelihood Approach

Raue *et al.* Bioinformatics 2009

Likelihood

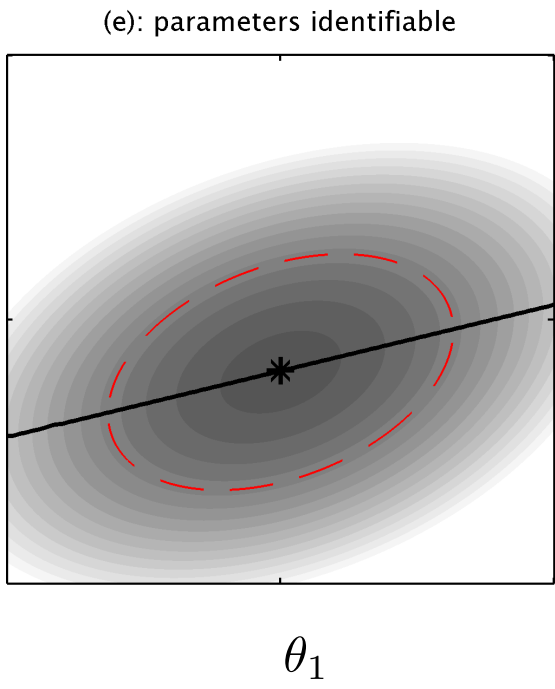
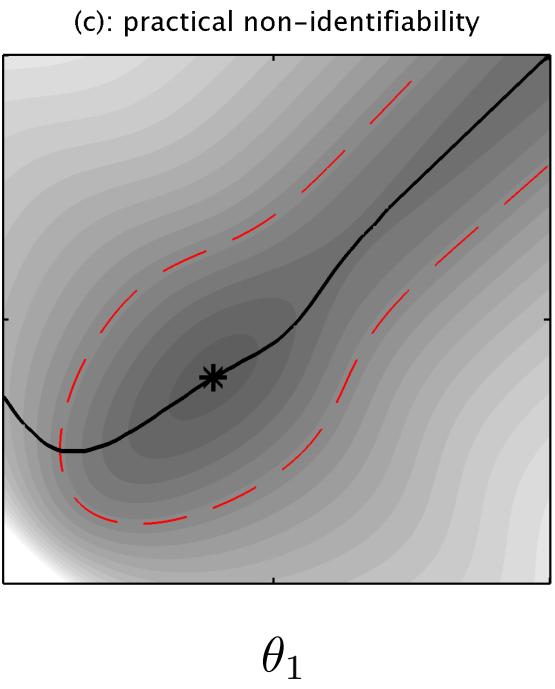
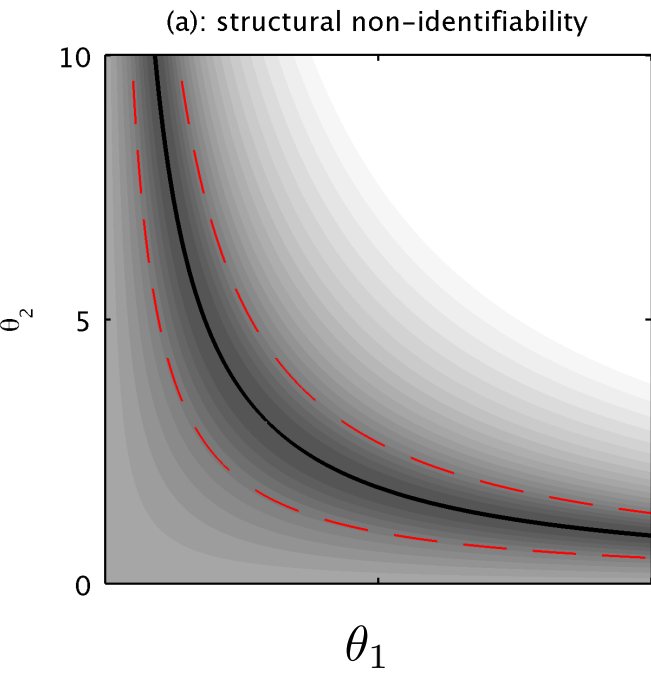
$$L(y|\theta) = \prod_{k=1}^m \prod_{l=1}^{d_k} \frac{1}{\sqrt{2\pi\sigma_{kl}^2}} \exp \left( -\frac{1}{2} \left( \frac{y_{kl} - y_k(t_l, \theta)}{\sigma_{kl}} \right)^2 \right)$$

Profile Likelihood

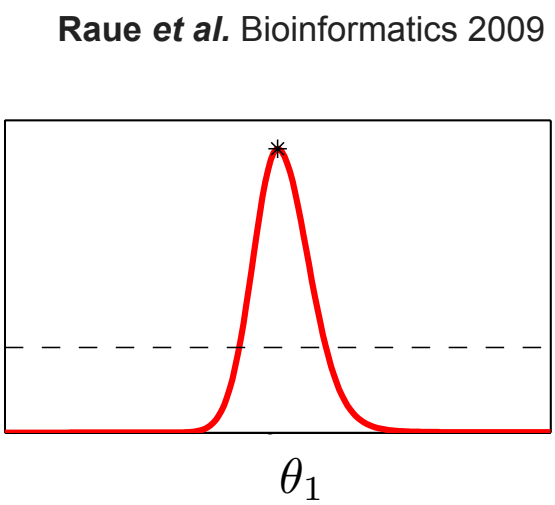
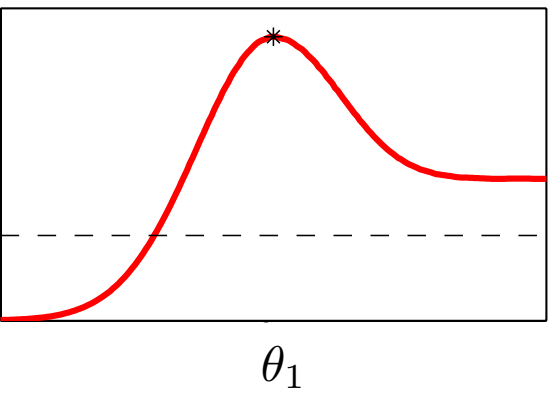
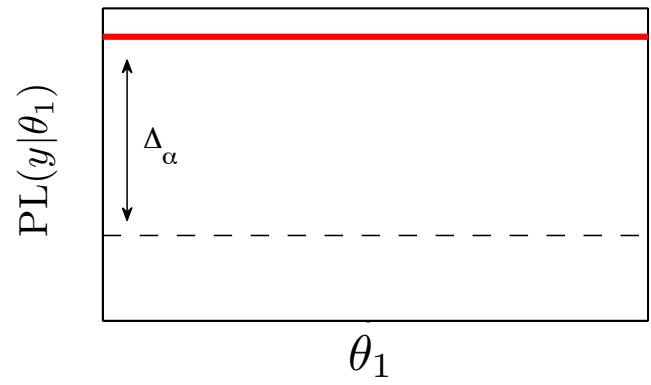
$$PL(y|\theta_i) = \max_{\theta_{j \neq i}} [L(y|\theta)]$$

# Parameter Identifiability

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



→ **Profile Likelihood Approach**



# Markov chain Monte Carlo

Posterior

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

Likelihood      Prior  
                    ↘        ↙  
                    ↗        ↘  
normalisation factor

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

## Metropolis-Hastings algorithm

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

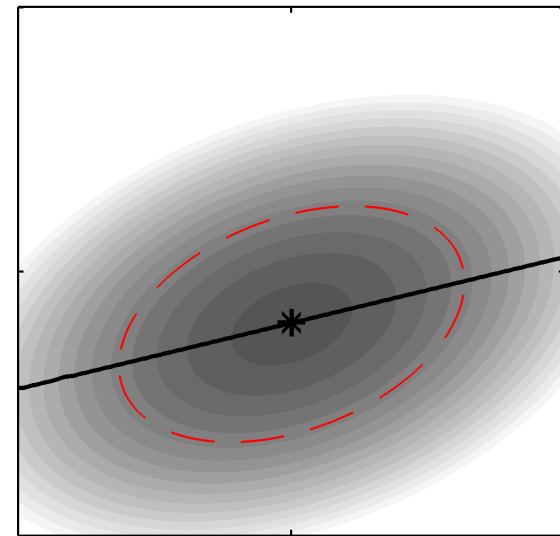
Acceptance probability

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

→ simplified MMALA algorithm

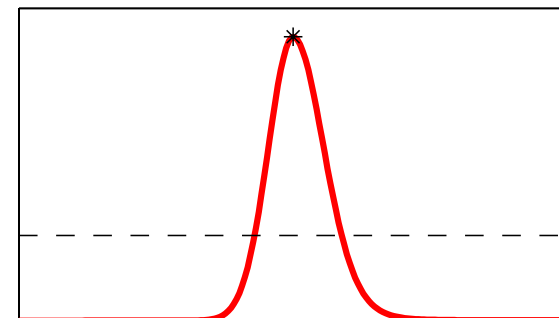
Girolami *et al.* J. R. Statist. Soc. B 2011

(e): parameters identifiable



$\theta_1$

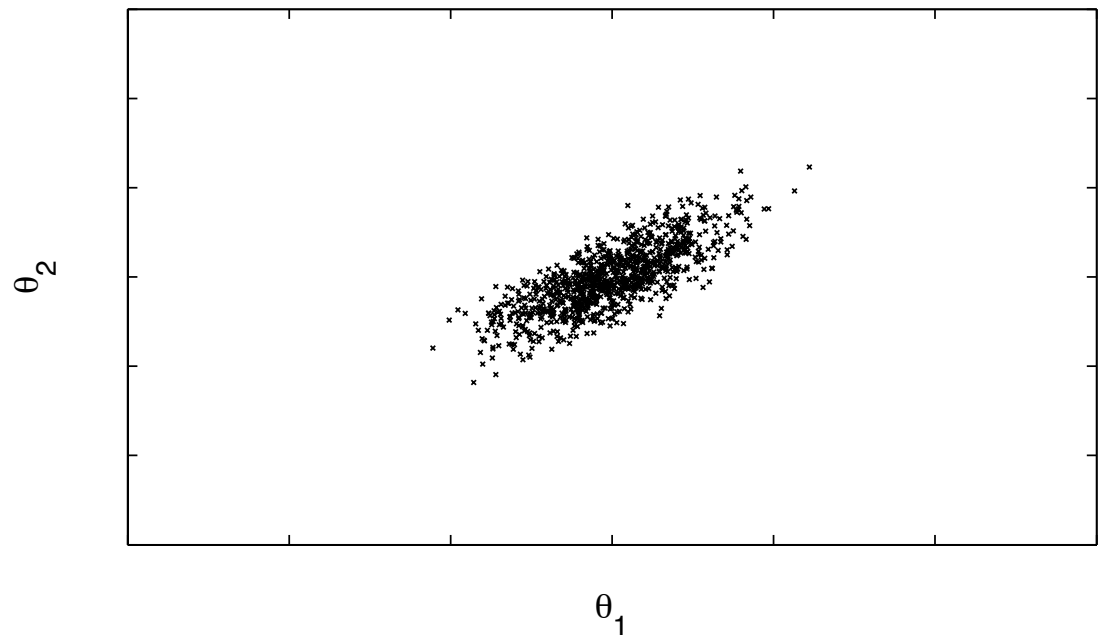
Profile Likelihood



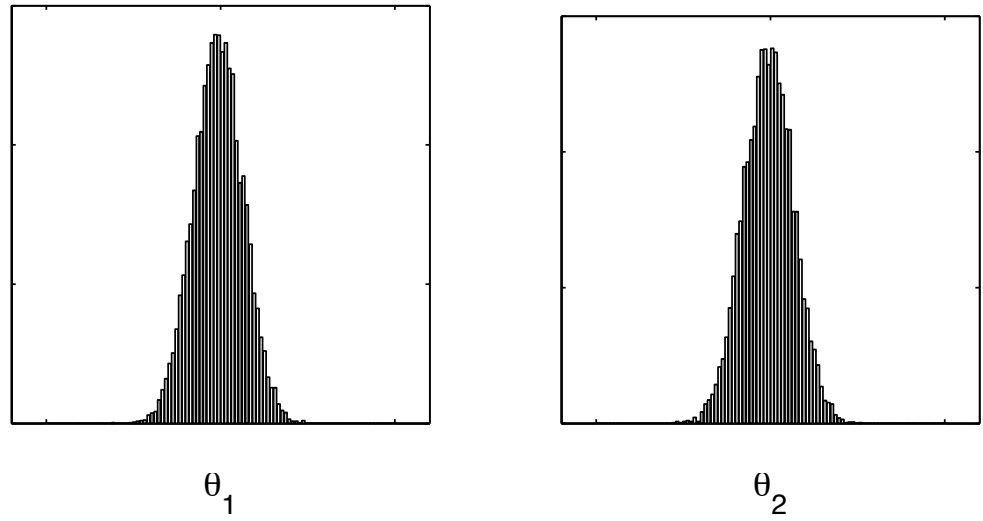
$\theta_1$

# Markov chain Monte Carlo

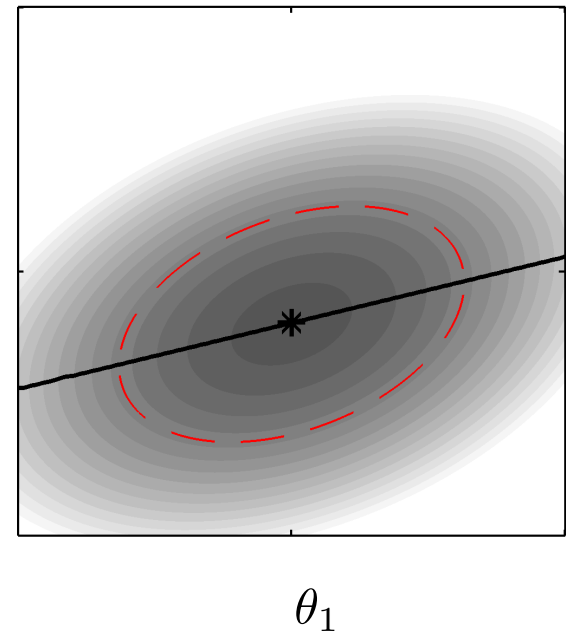
MCMC samples



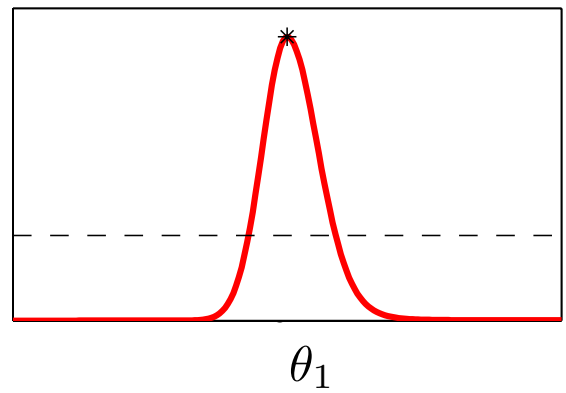
marginalized MCMC samples



(e): parameters identifiable

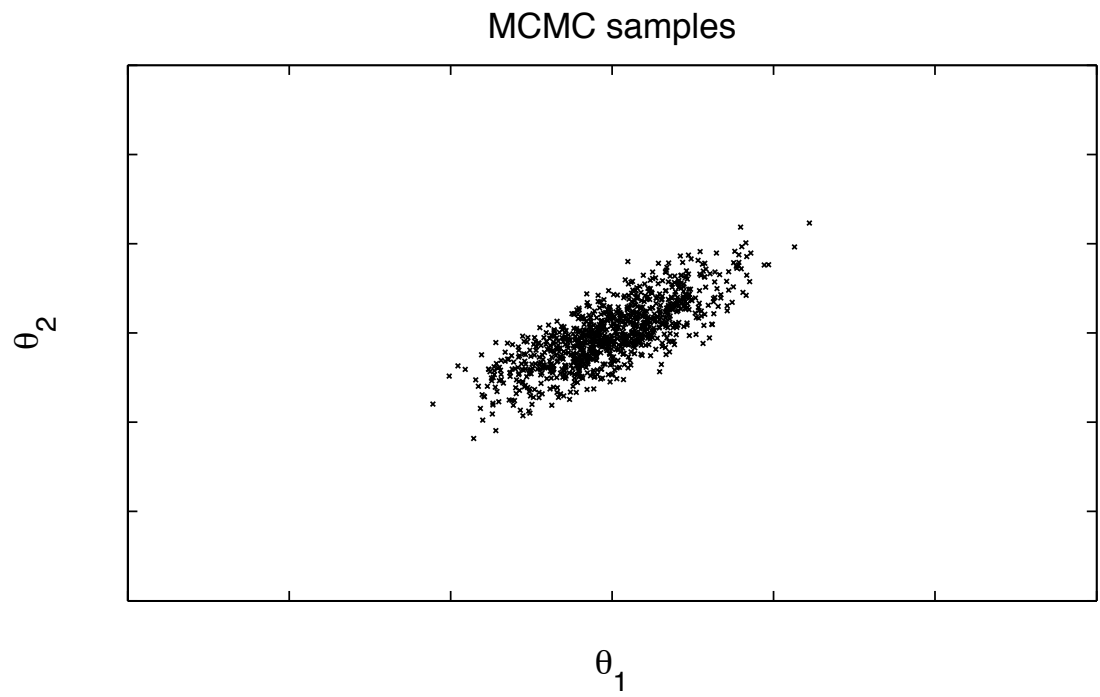


Profile Likelihood

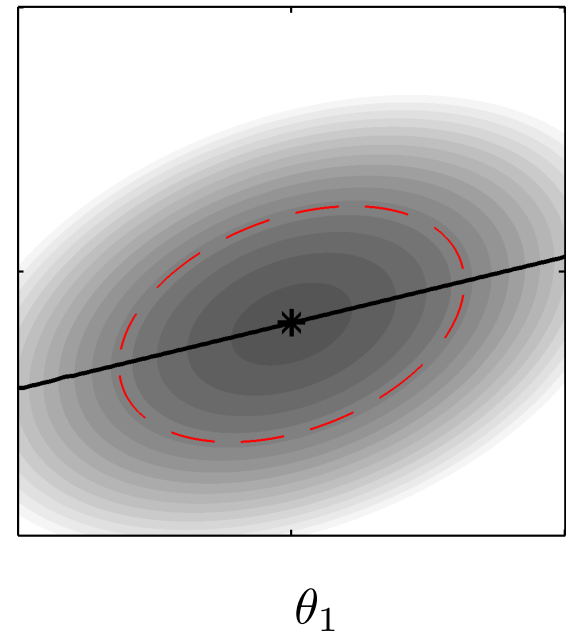




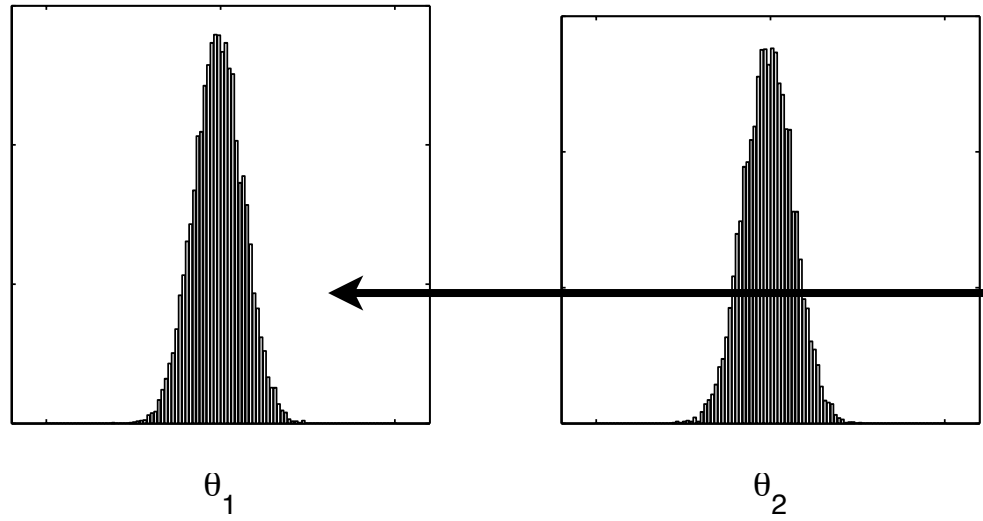
# Markov chain Monte Carlo



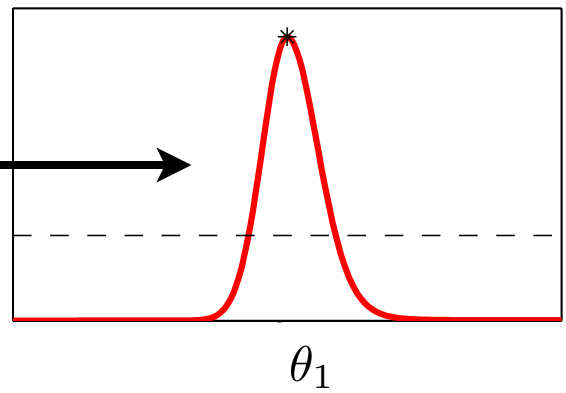
(e): parameters identifiable



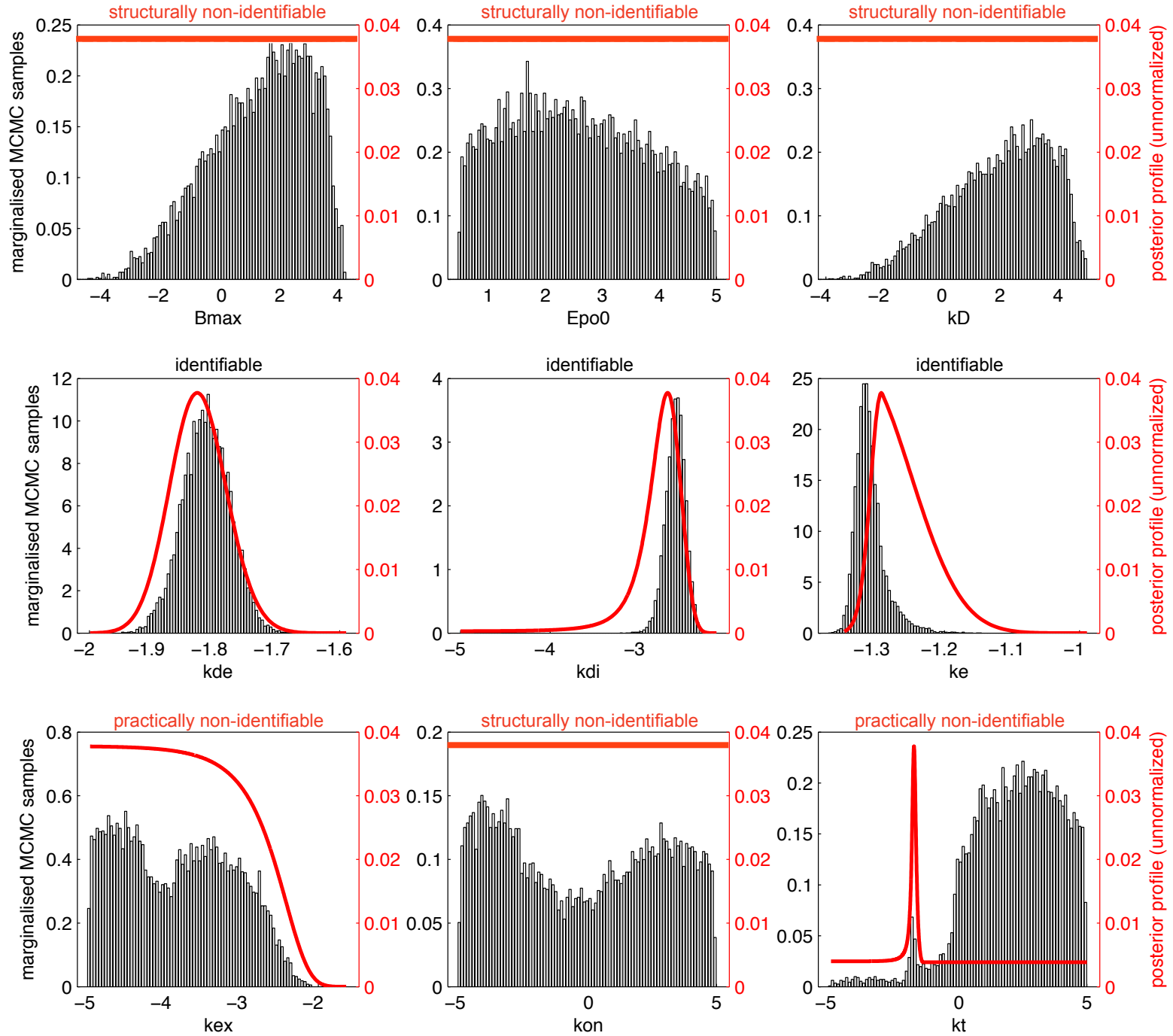
marginalized MCMC samples



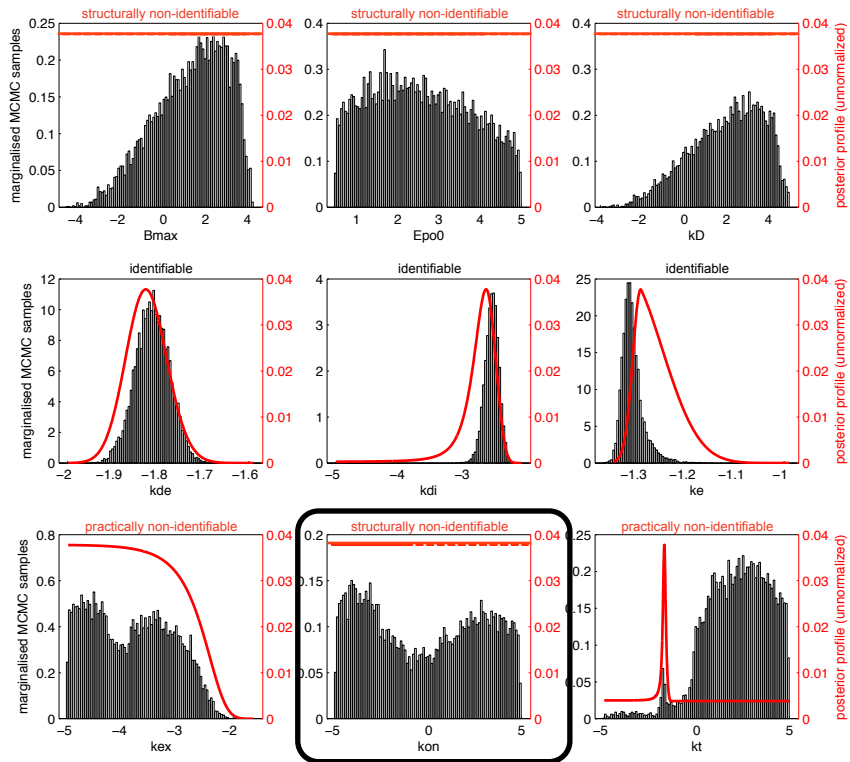
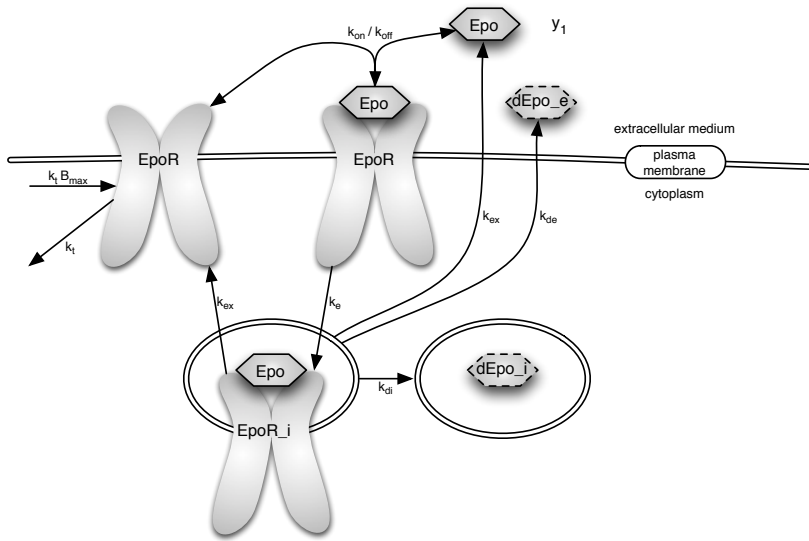
Profile Likelihood



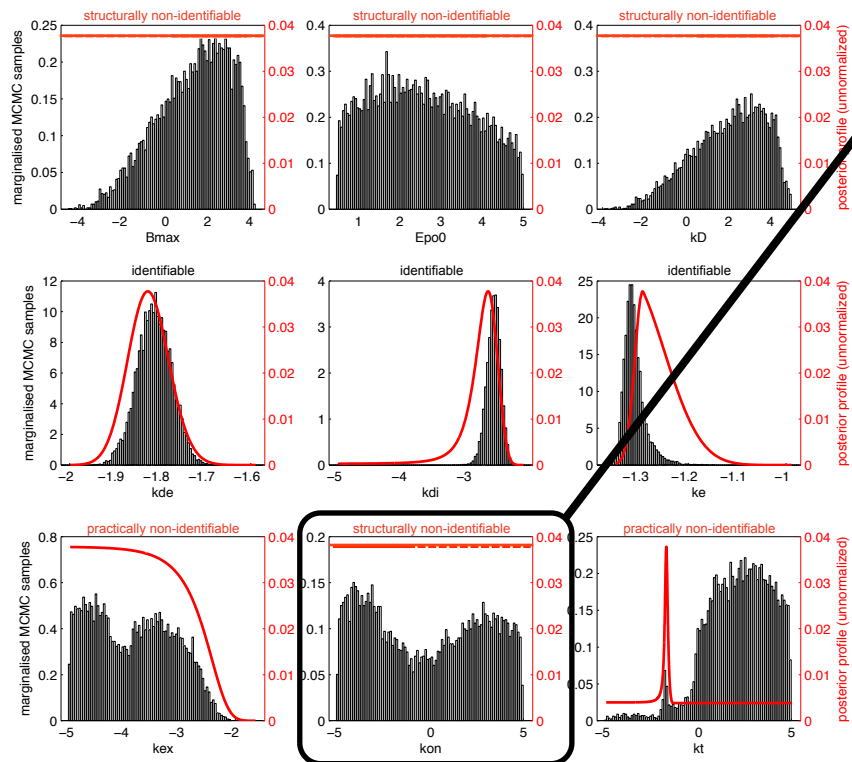
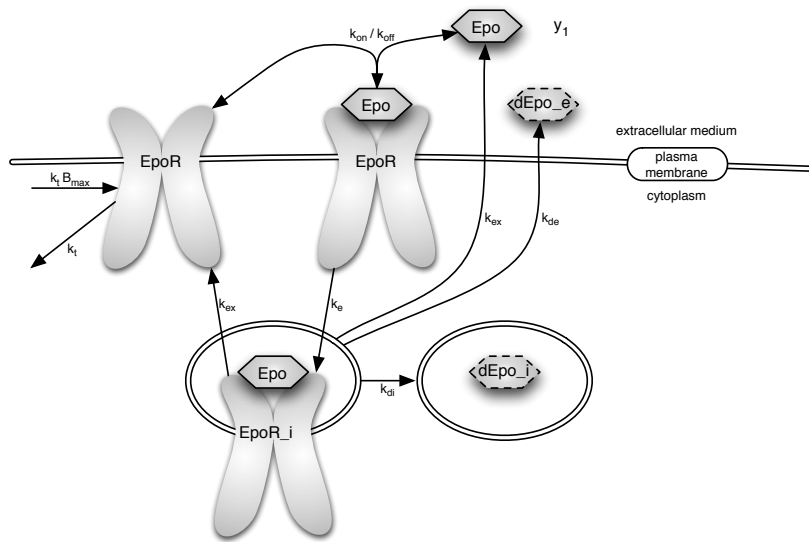
# Results for Initial Setup



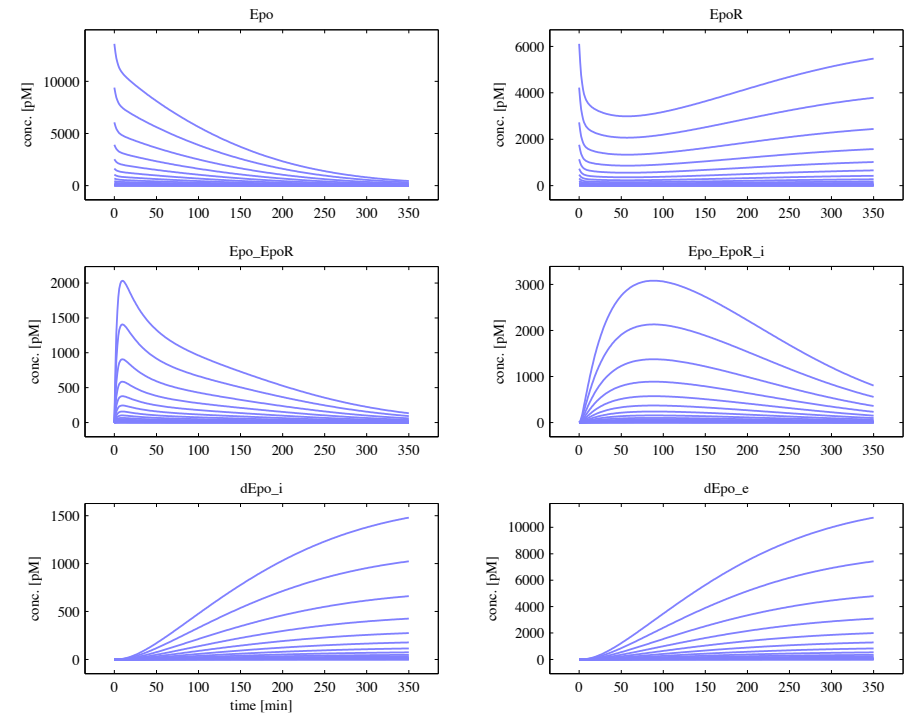
# Experimental Design



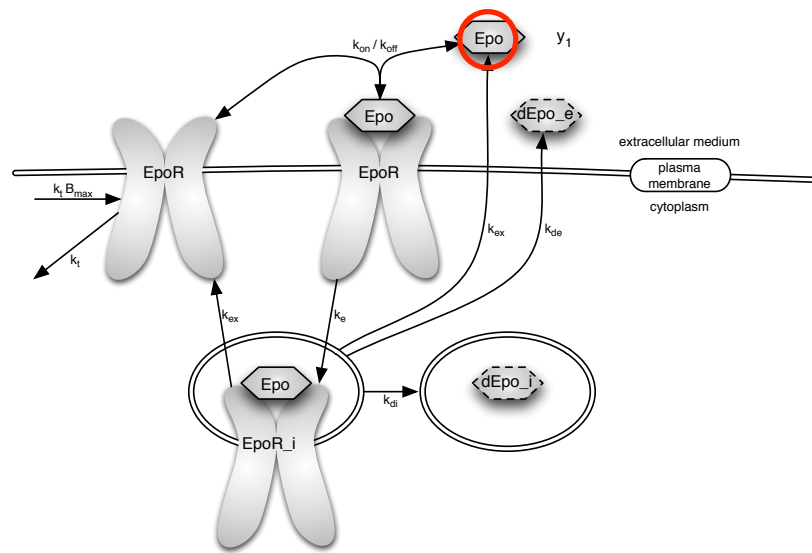
# Experimental Design



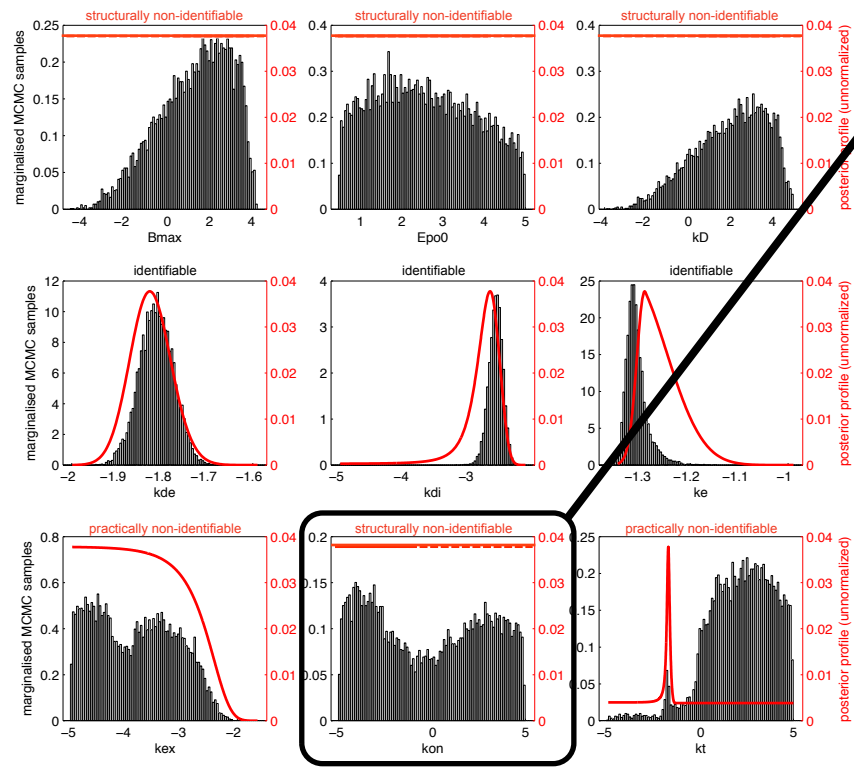
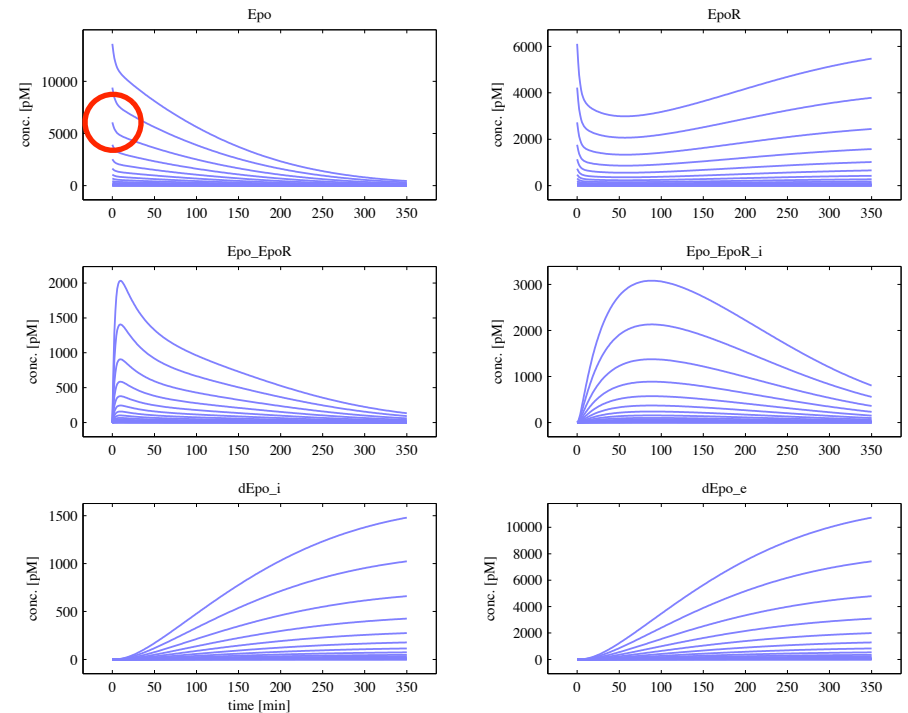
### Non-observability of model dynamics:



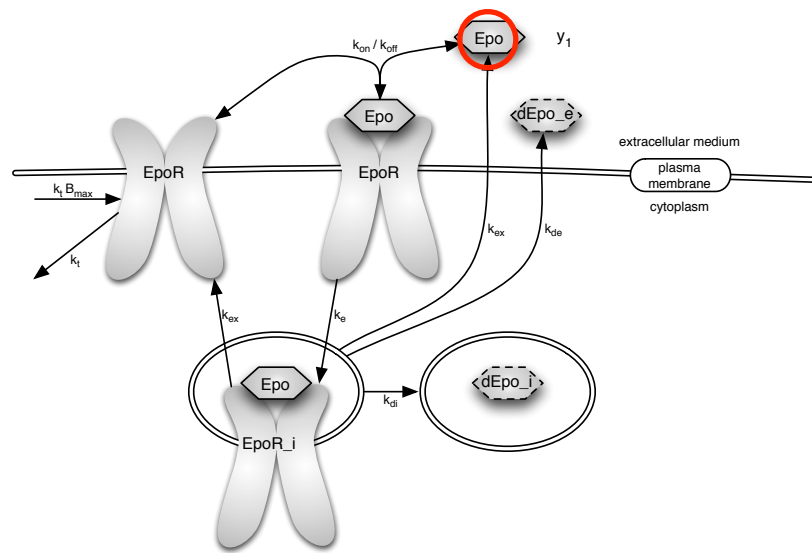
# Experimental Design



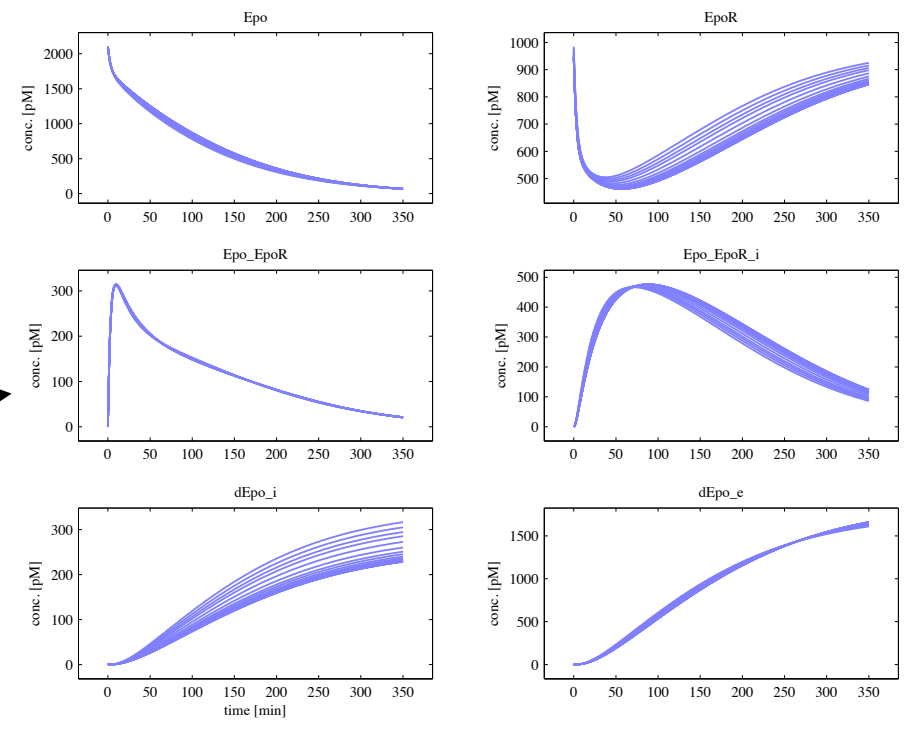
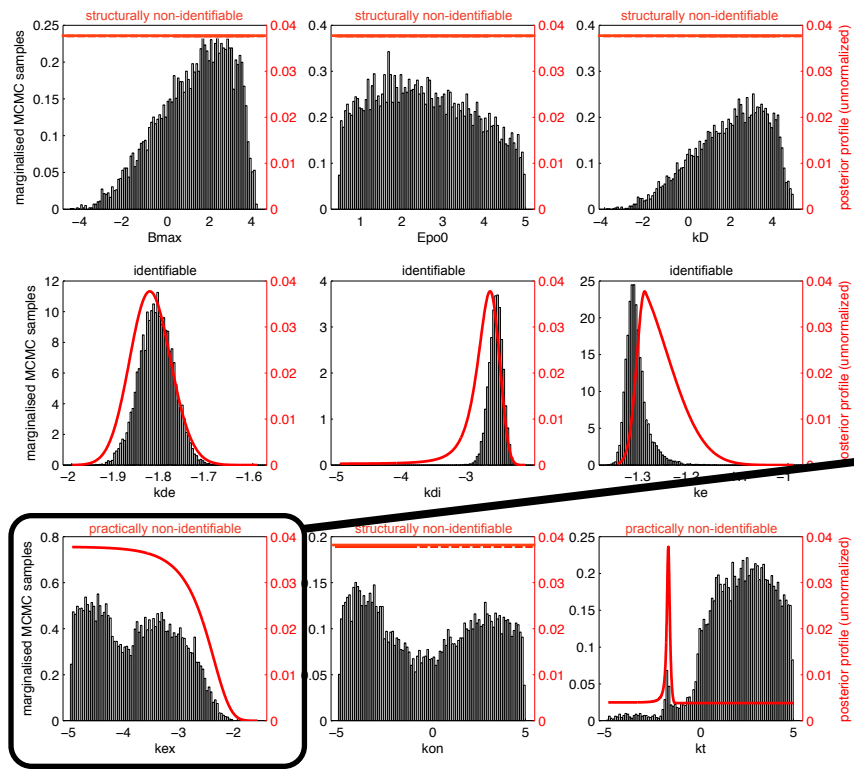
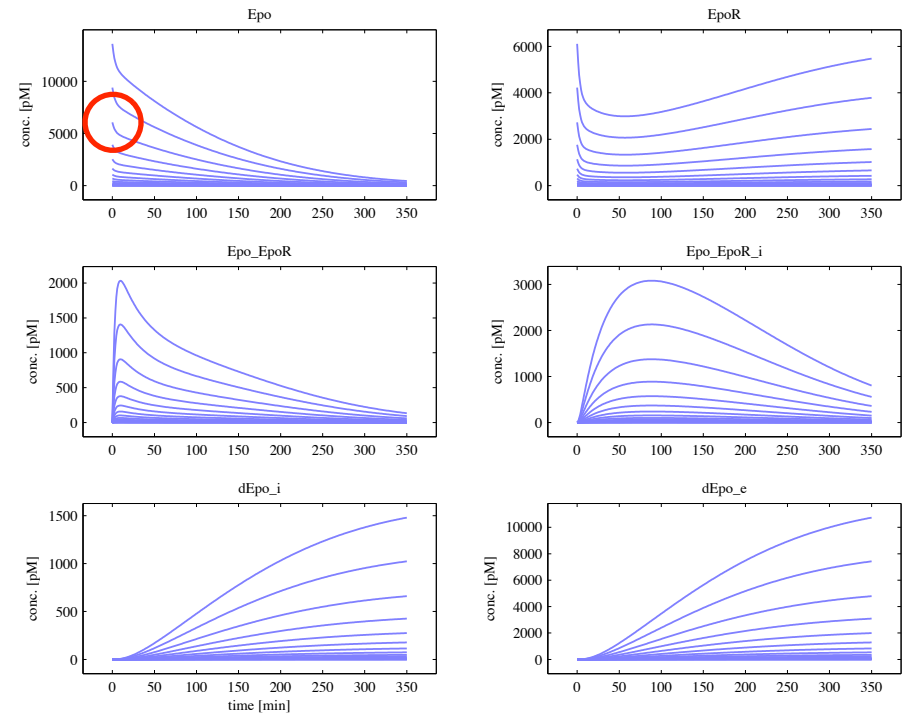
## Non-observability of model dynamics:



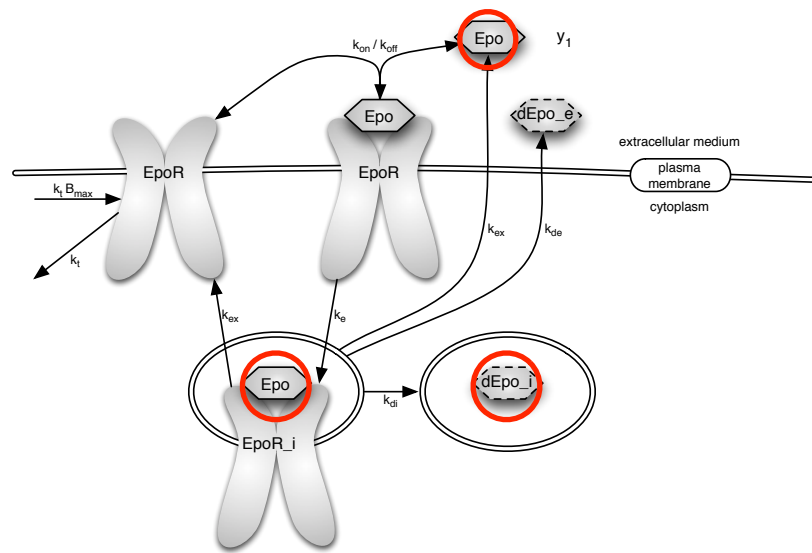
# Experimental Design



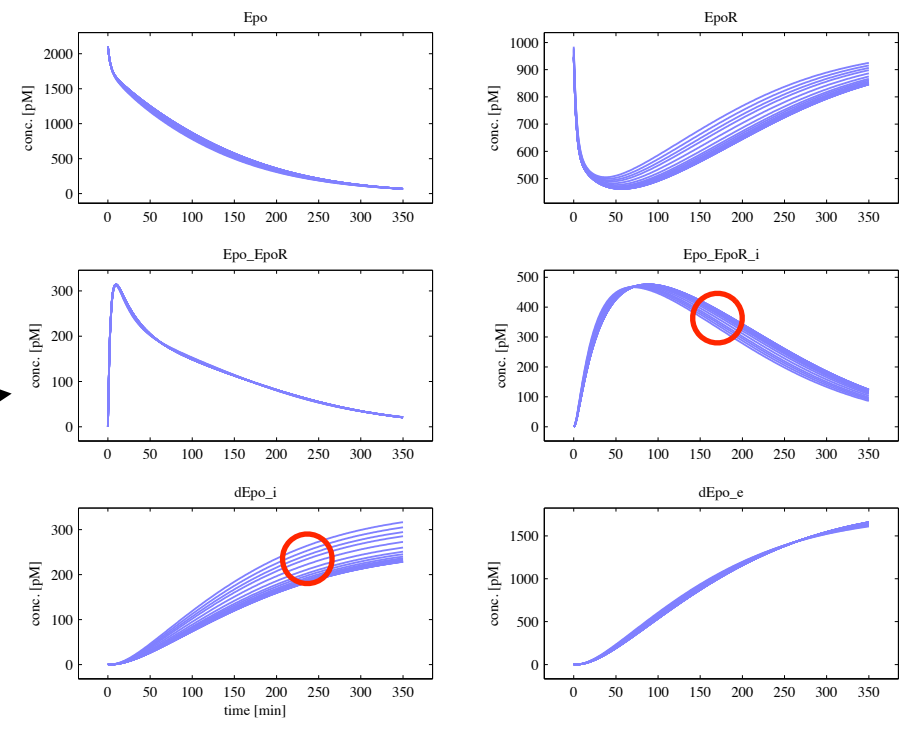
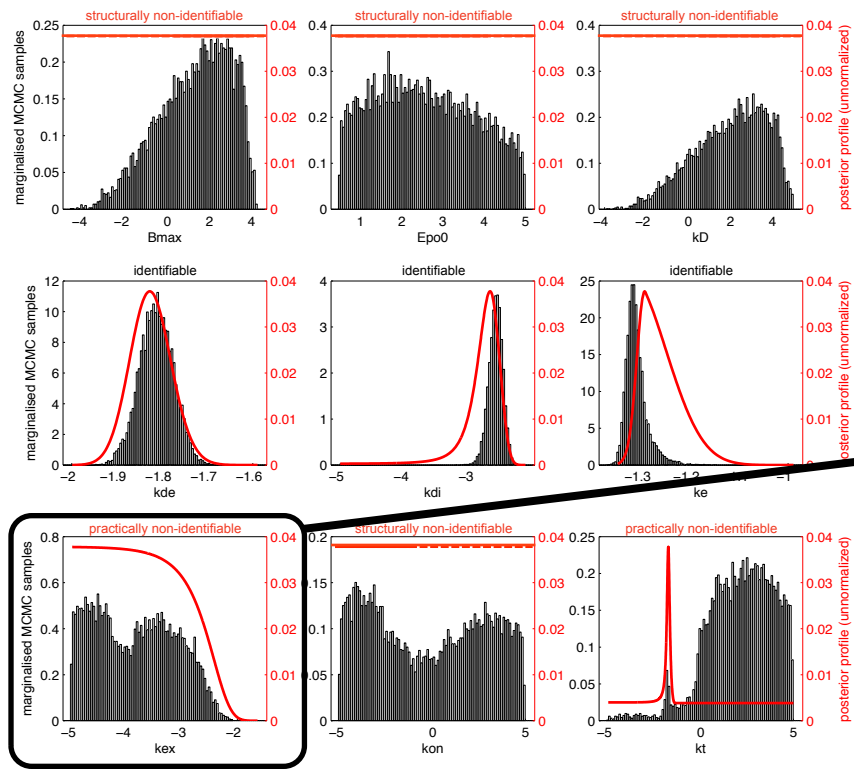
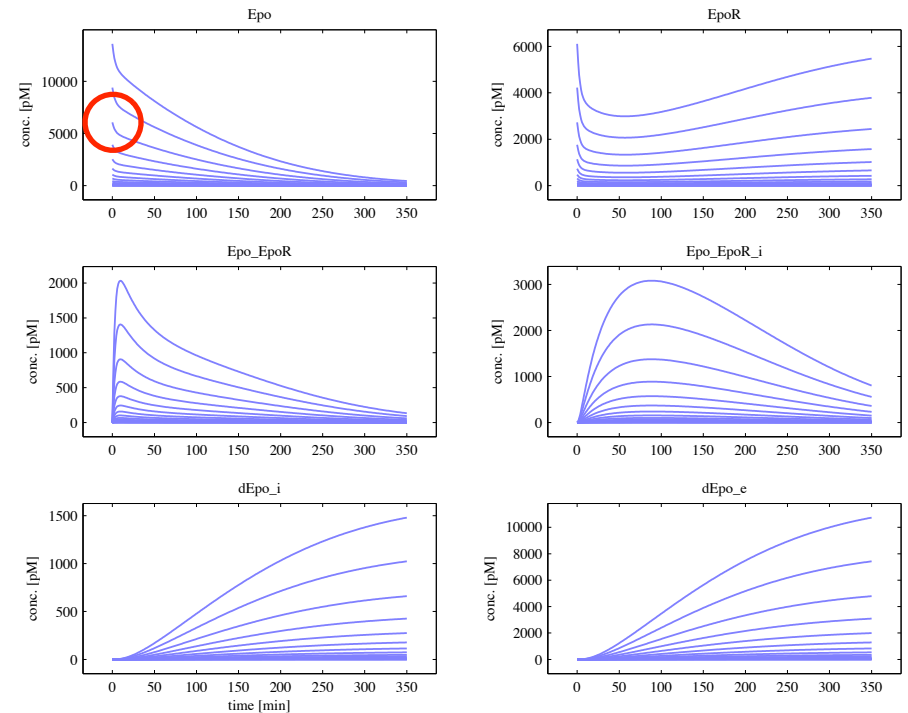
## Non-observability of model dynamics:



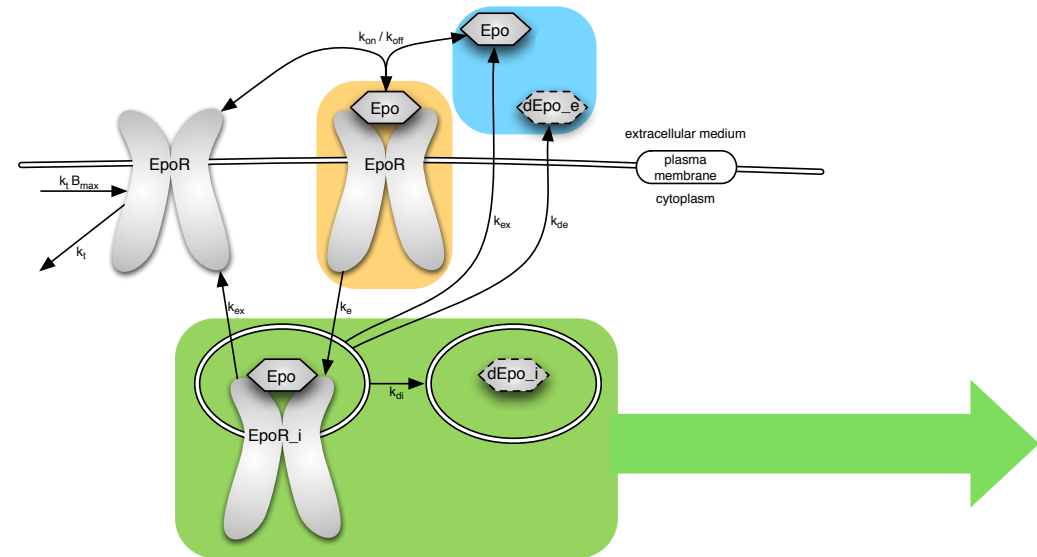
# Experimental Design



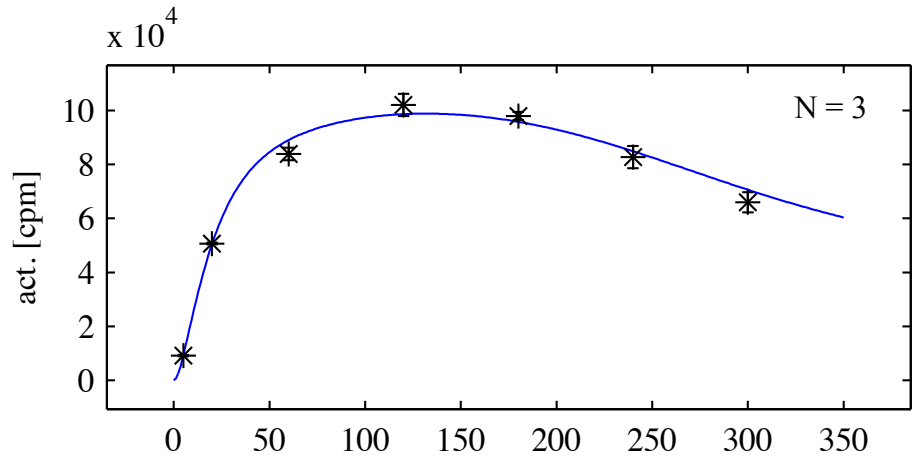
## Non-observability of model dynamics:



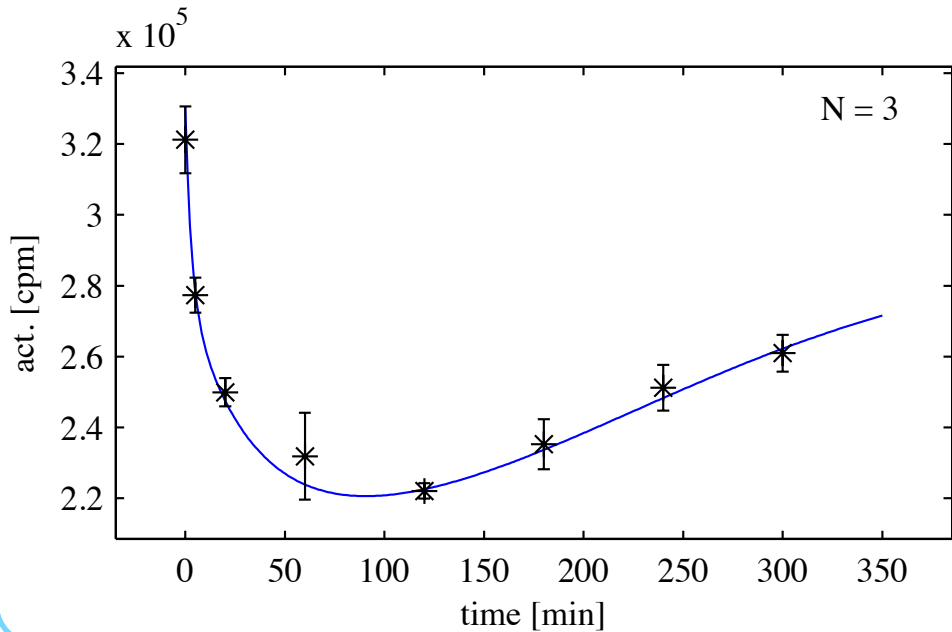
# Extended Experimental Setup



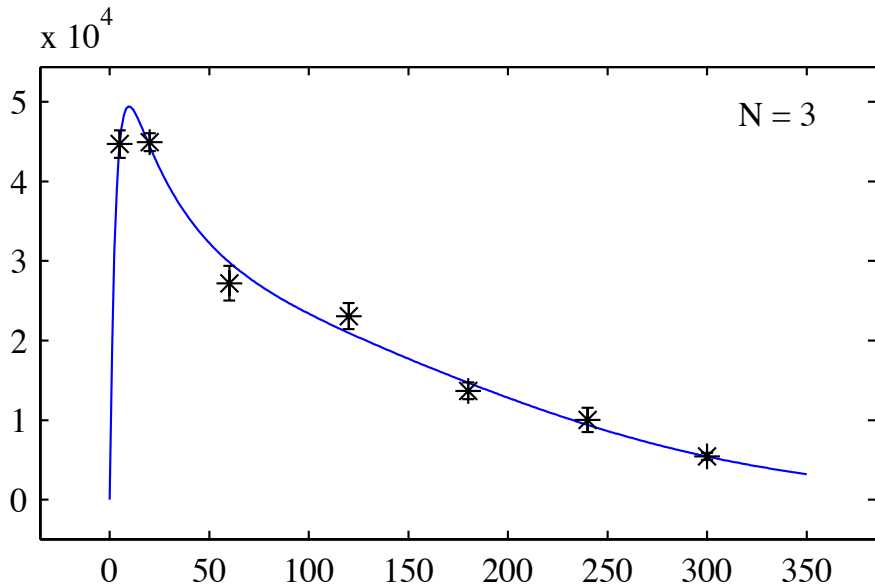
Epo inside the cell



Epo in extracellular medium

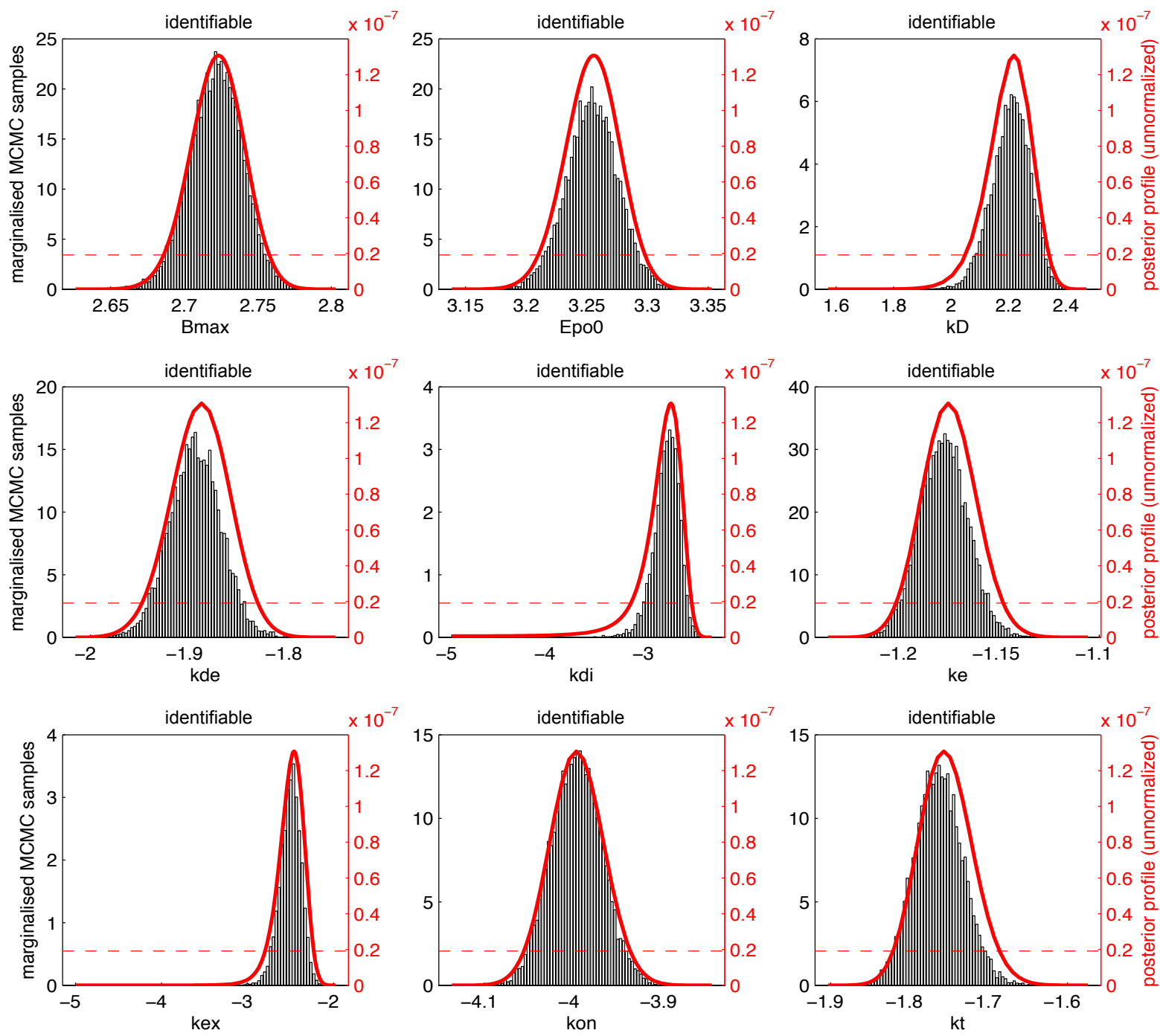


Epo bound to receptor on membrane



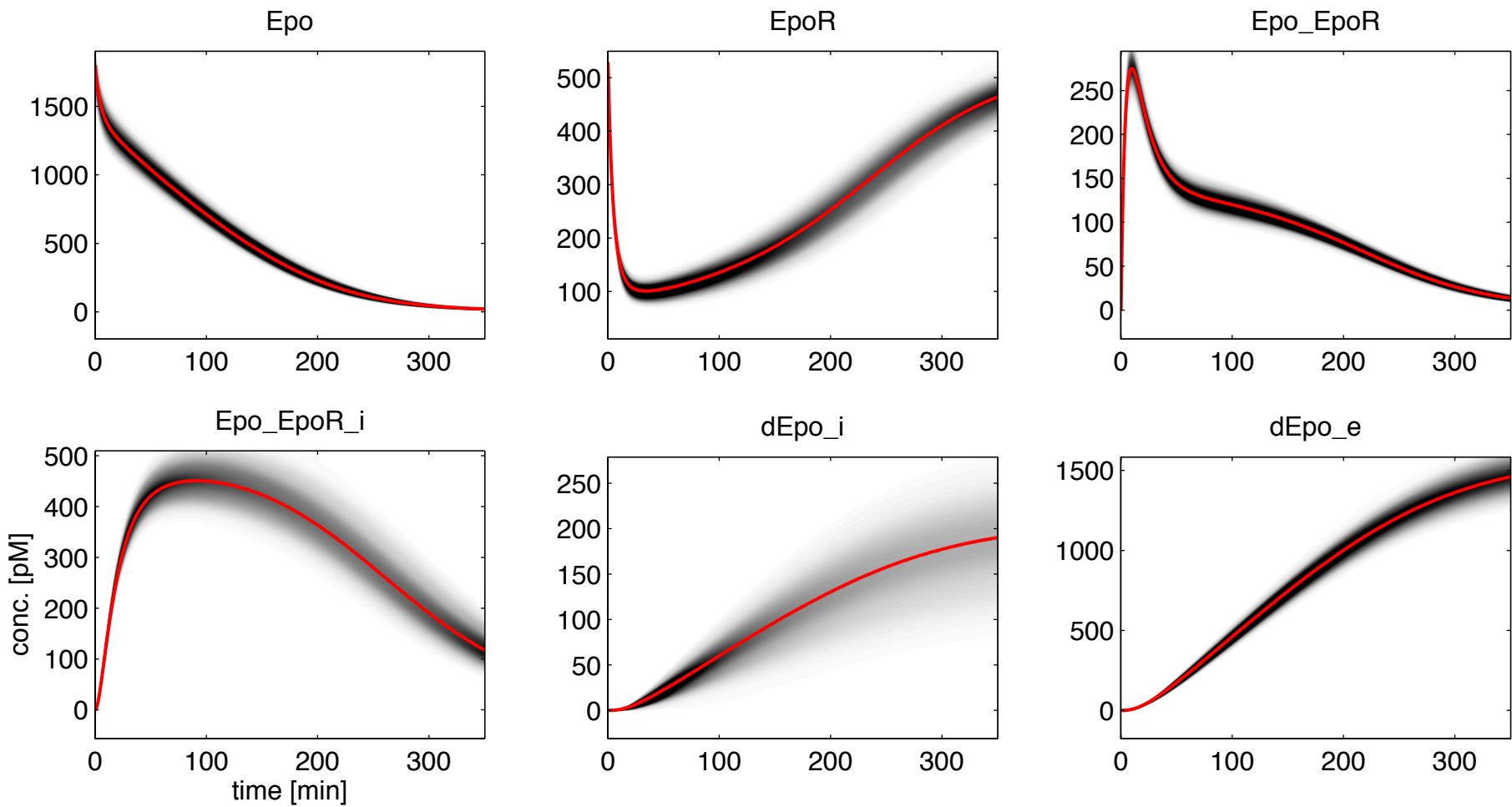


# Results for Extended Setup

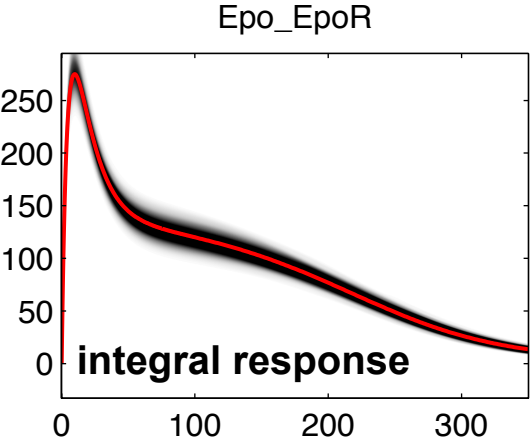
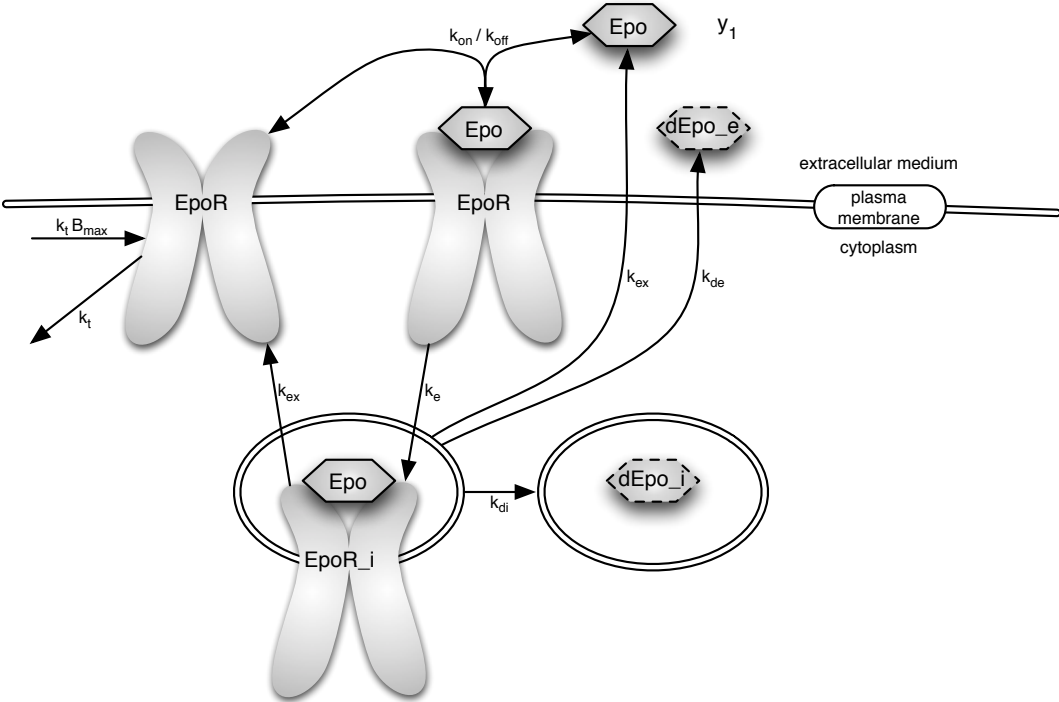


# Predicted Model Dynamics

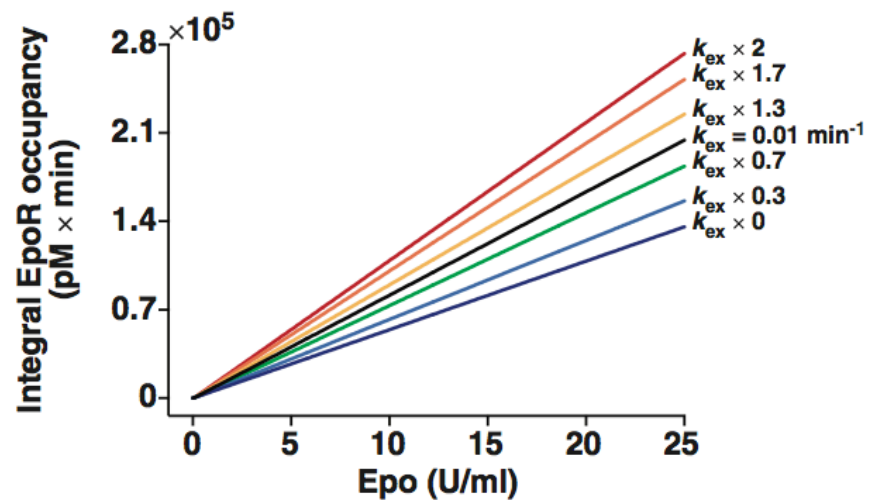
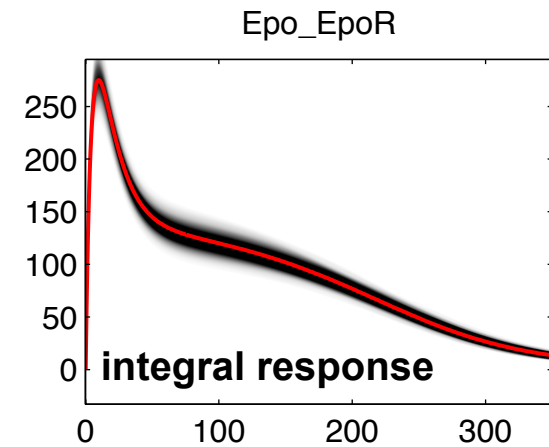
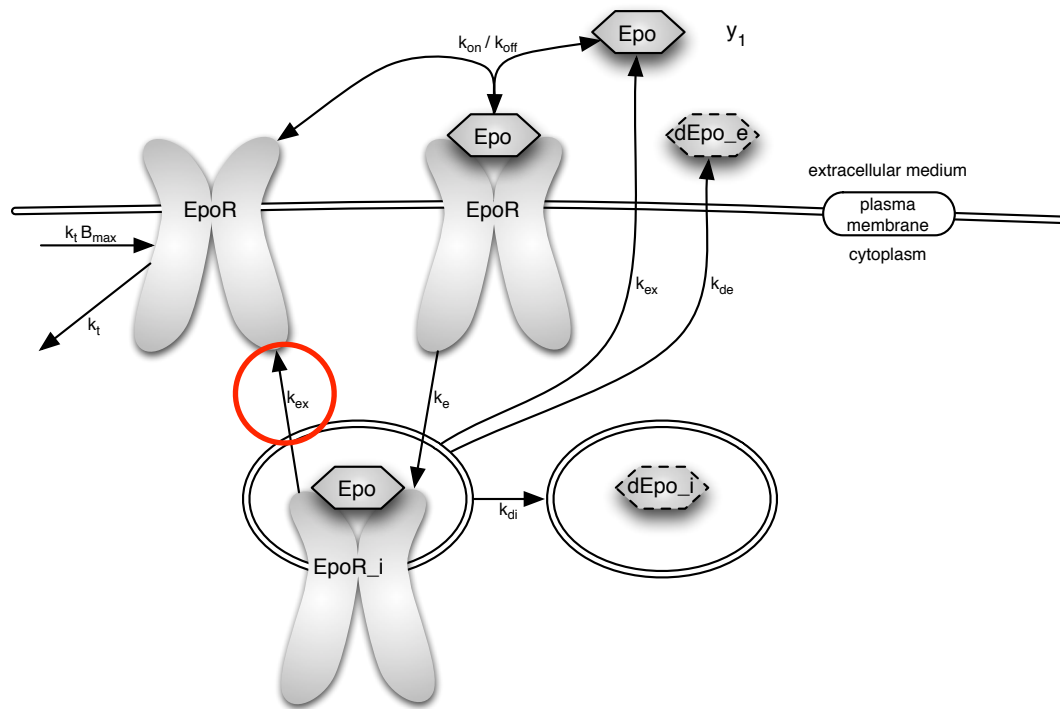
PDF of predicted dynamics  
MAP trajectory of dynamics



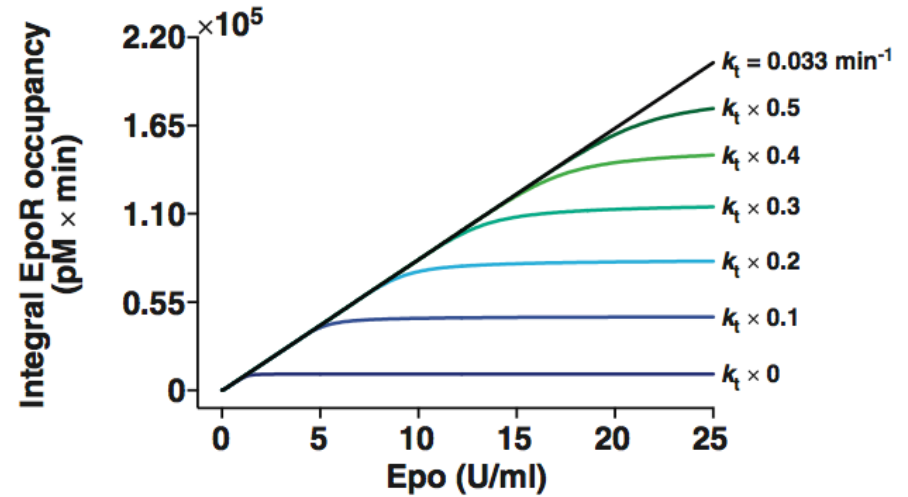
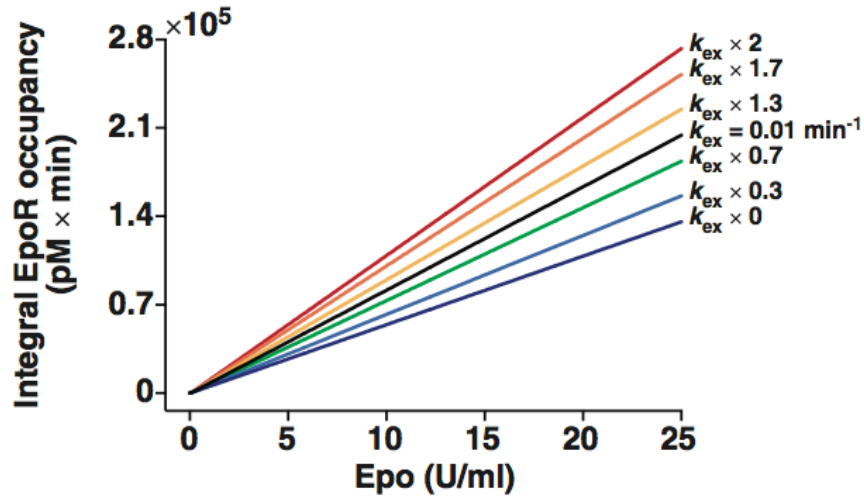
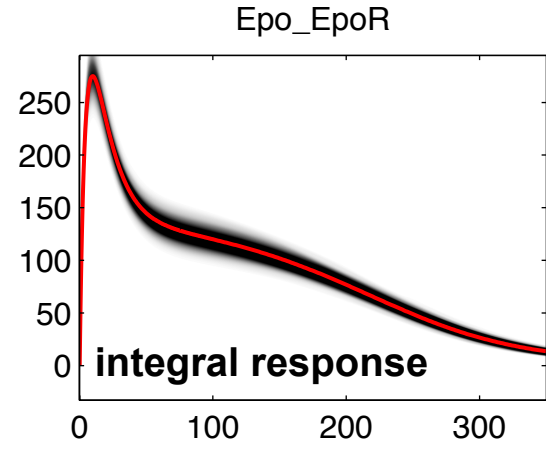
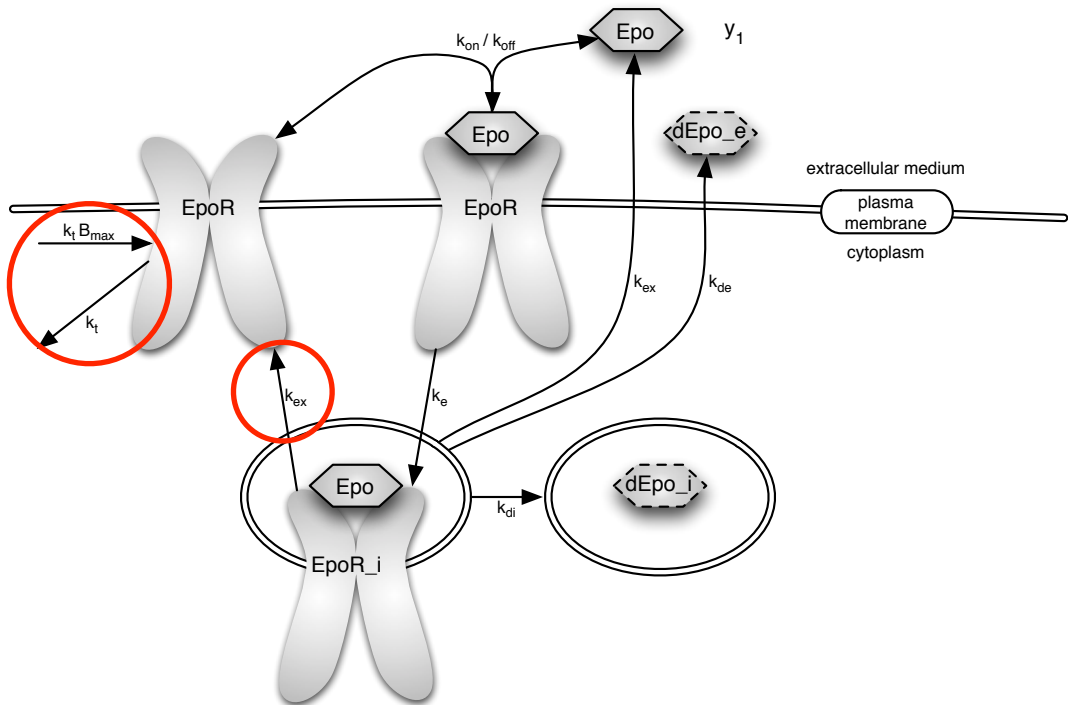
# Predicted Model Dynamics - Biological Interpretation



## Predicted Model Dynamics - Biological Interpretation



# Predicted Model Dynamics - Biological Interpretation

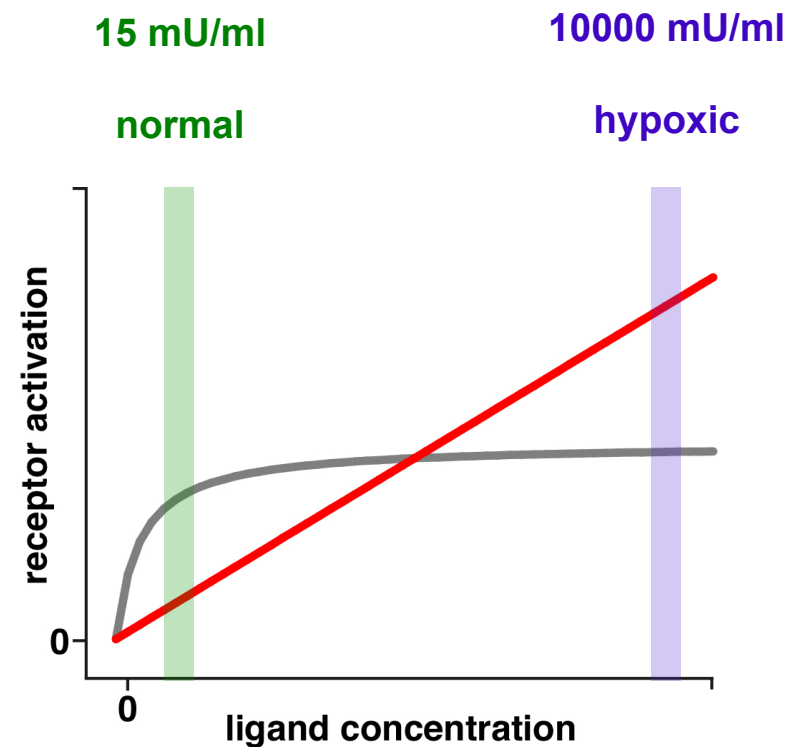


# Summary 1

## 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

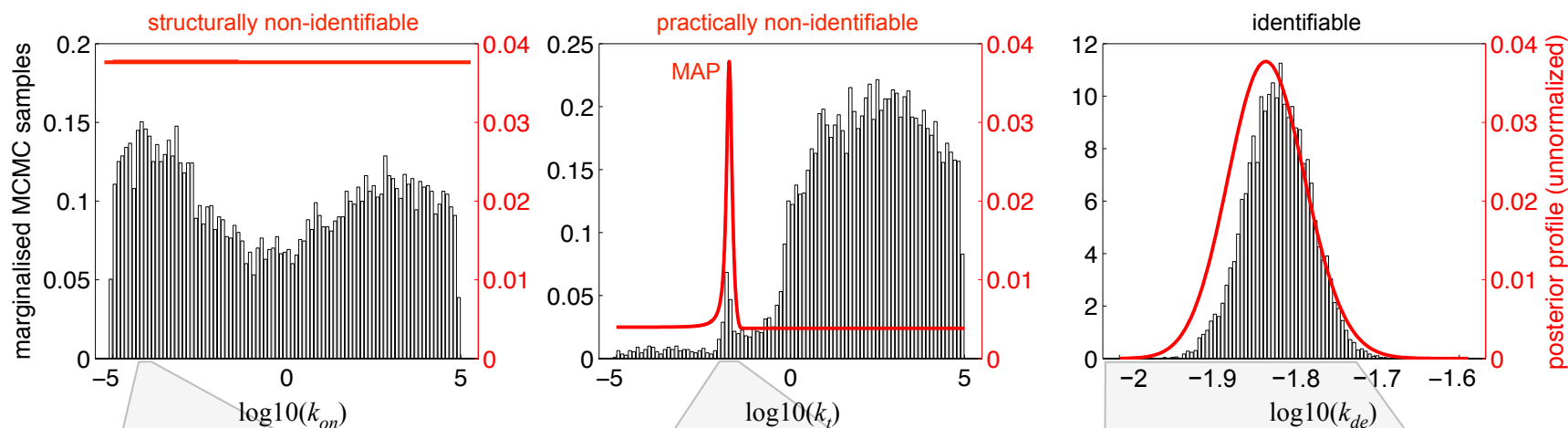
Becker *et al.* Science 2010



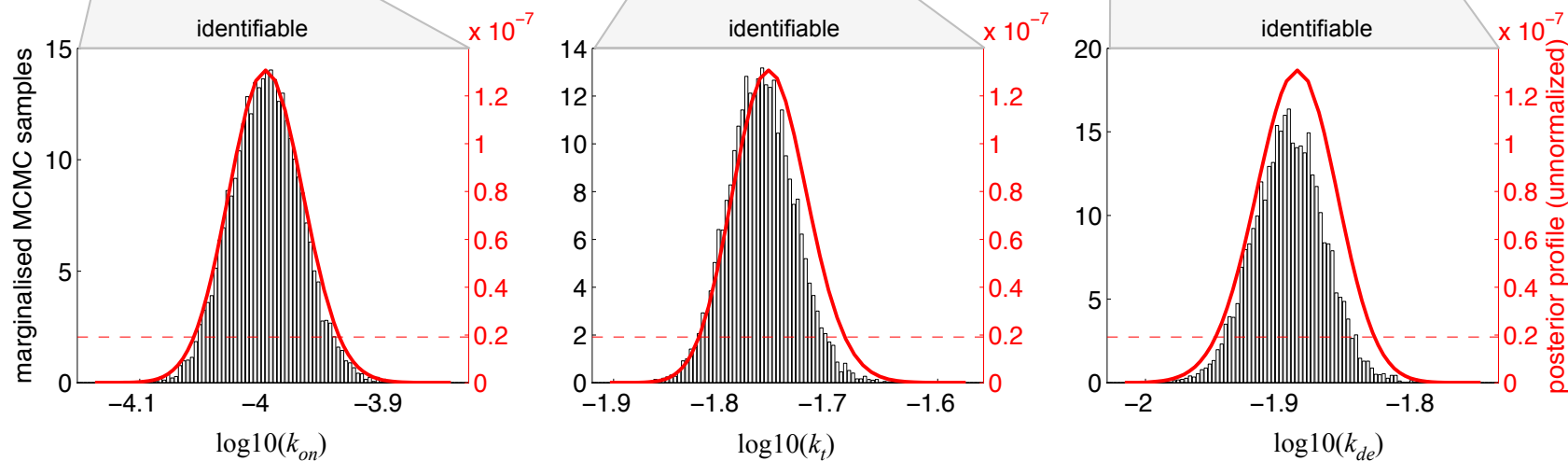
# Summary 2

## Comparison of profile likelihood and MCMC sampling

### A initial experimental setup



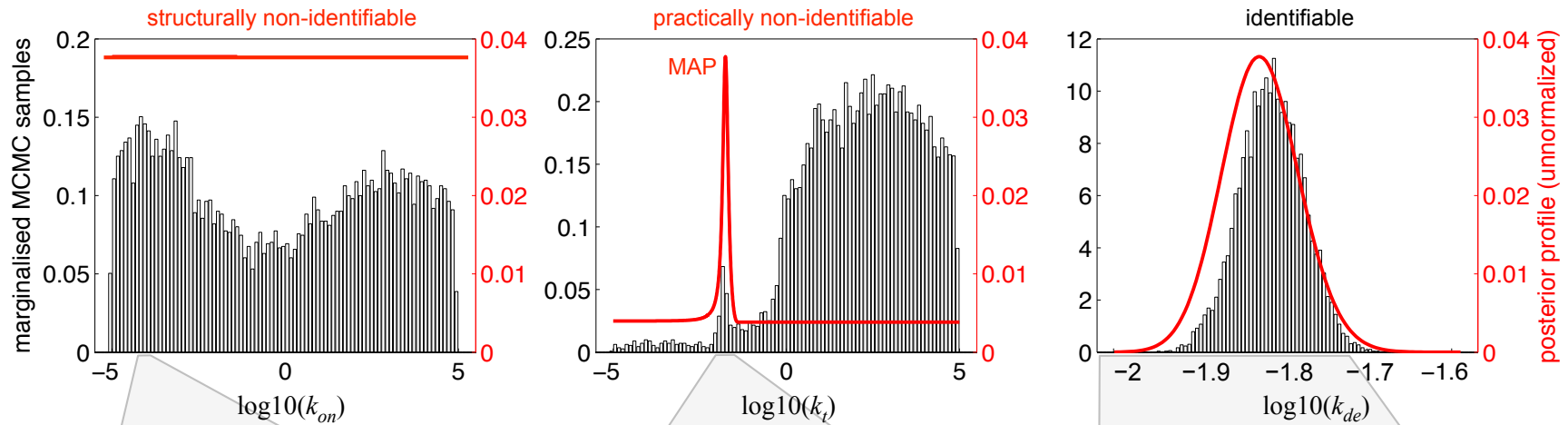
### B extended experimental setup



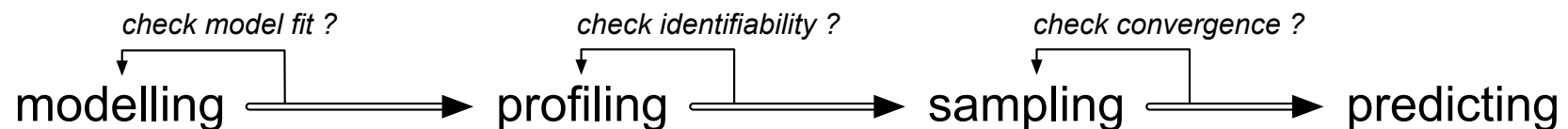
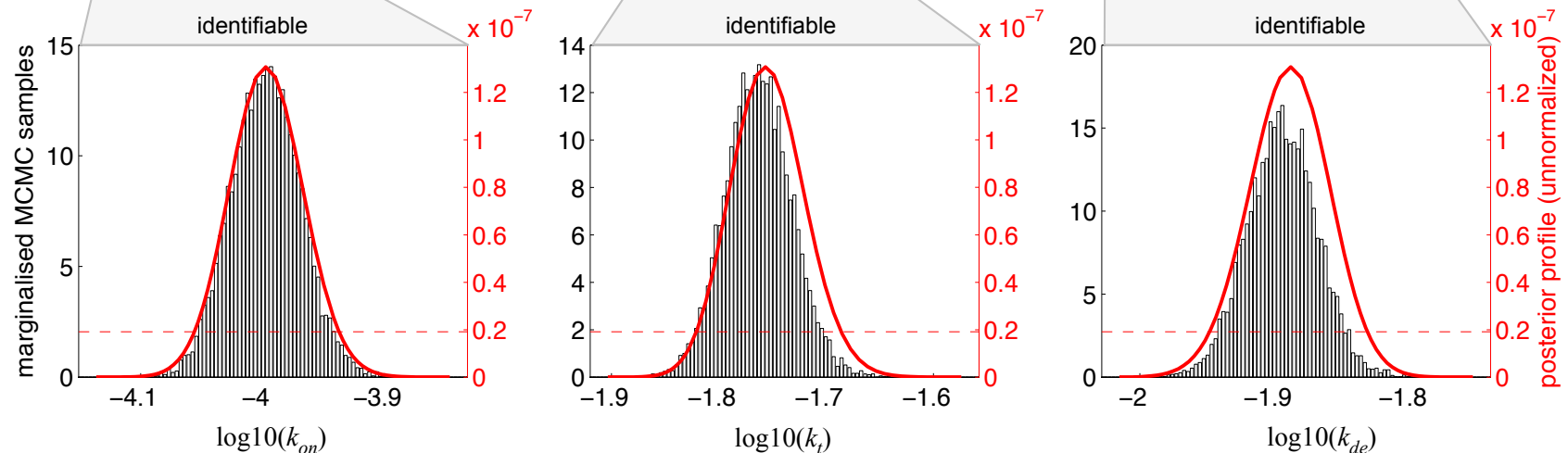
# Summary 2

## Comparison of profile likelihood and MCMC sampling

### A initial experimental setup



### B extended experimental setup





# Summary 3

Approach is applicable for larger models (24 x 25 ODEs, 113 parameters)

# Summary 3

Approach is applicable for larger models (24 x 25 ODEs, 113 parameters)

→ NCSB workshop on  
*Parameter Estimation and Uncertainty Analysis in Systems Biology*  
(tomorrow, 10:40 - 11:40, [here](#))

# Acknowledgements

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Clemens Kreutz  
Jens Timmer

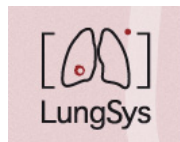


Sabine Hug  
Fabian Theis

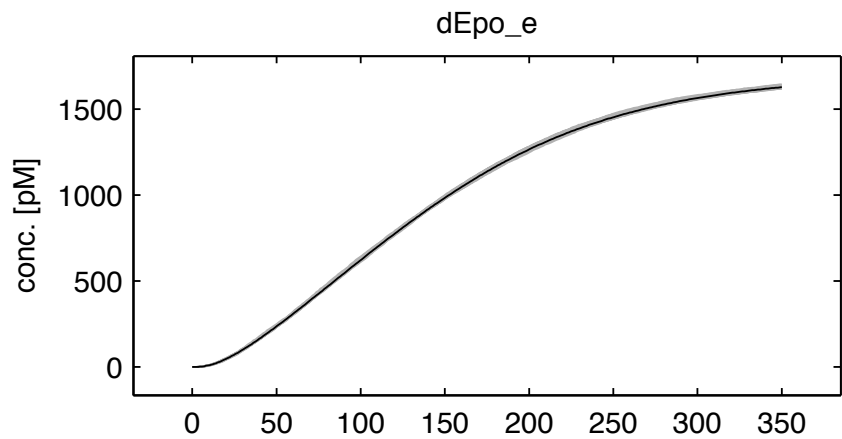
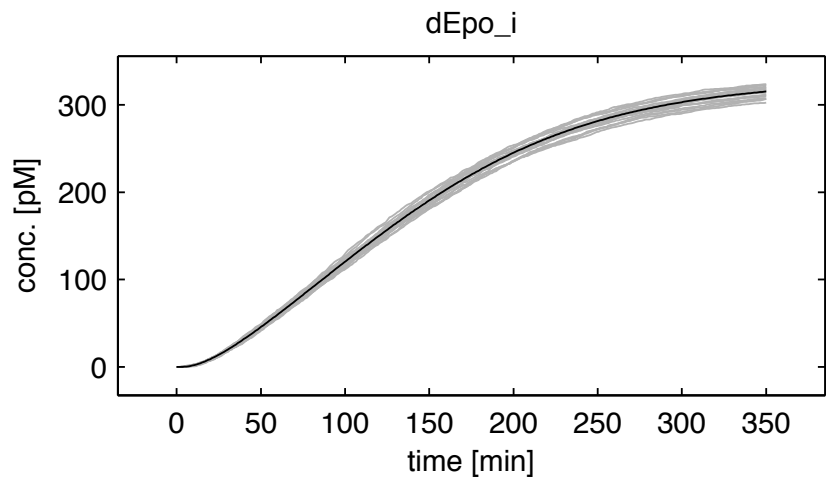
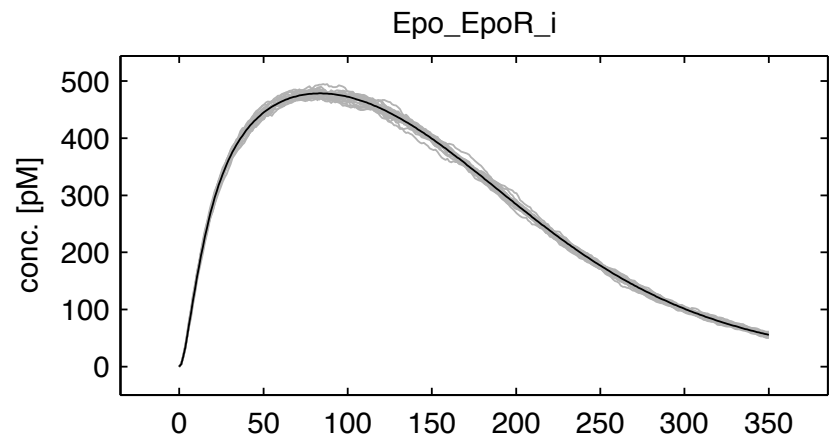
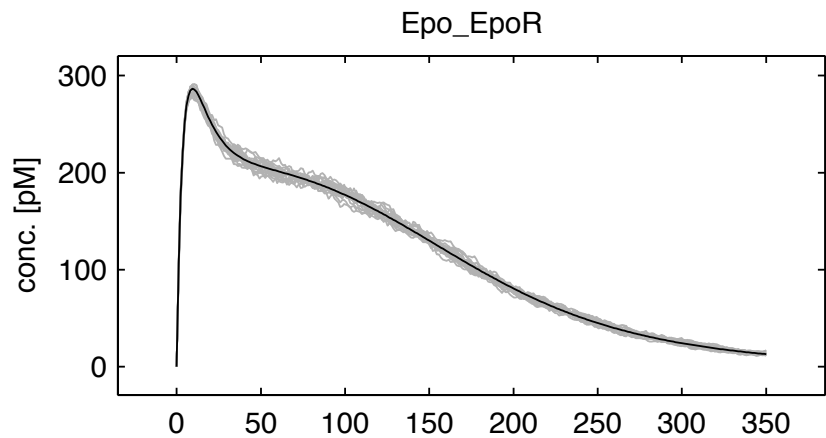
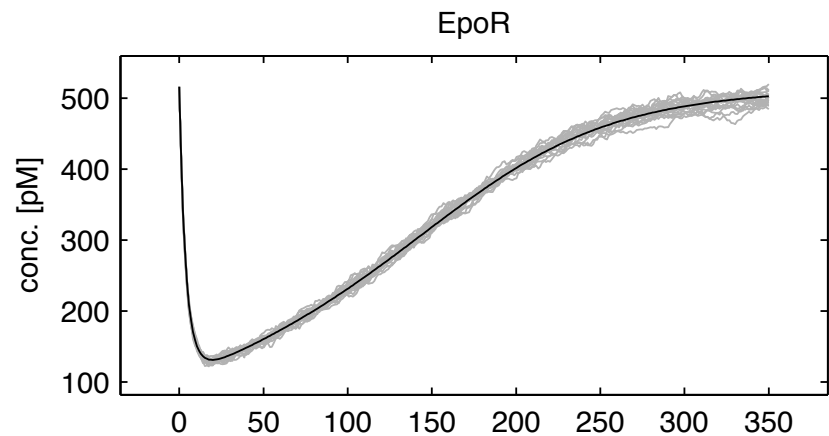
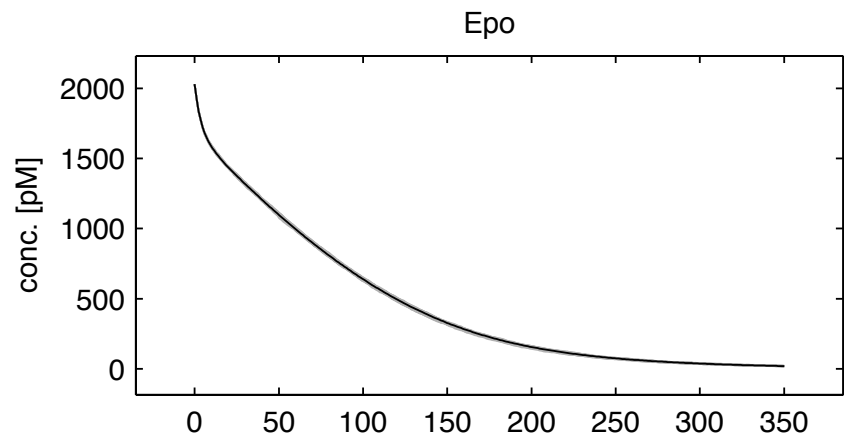


Verena Becker  
Julie Bachmann  
Marcel Schilling  
Ursula Klingmüller

Funding by



# Comparison of ODE and SSA

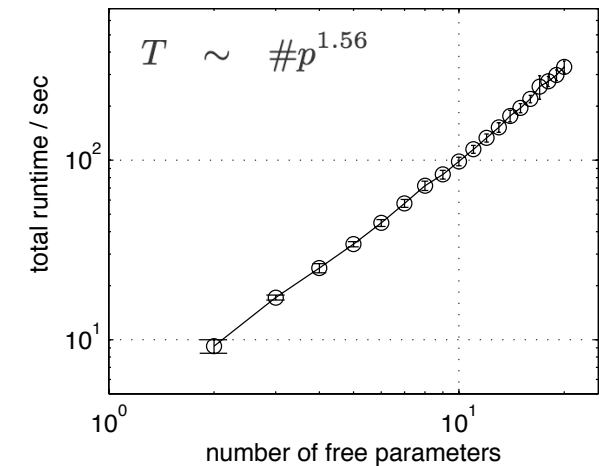
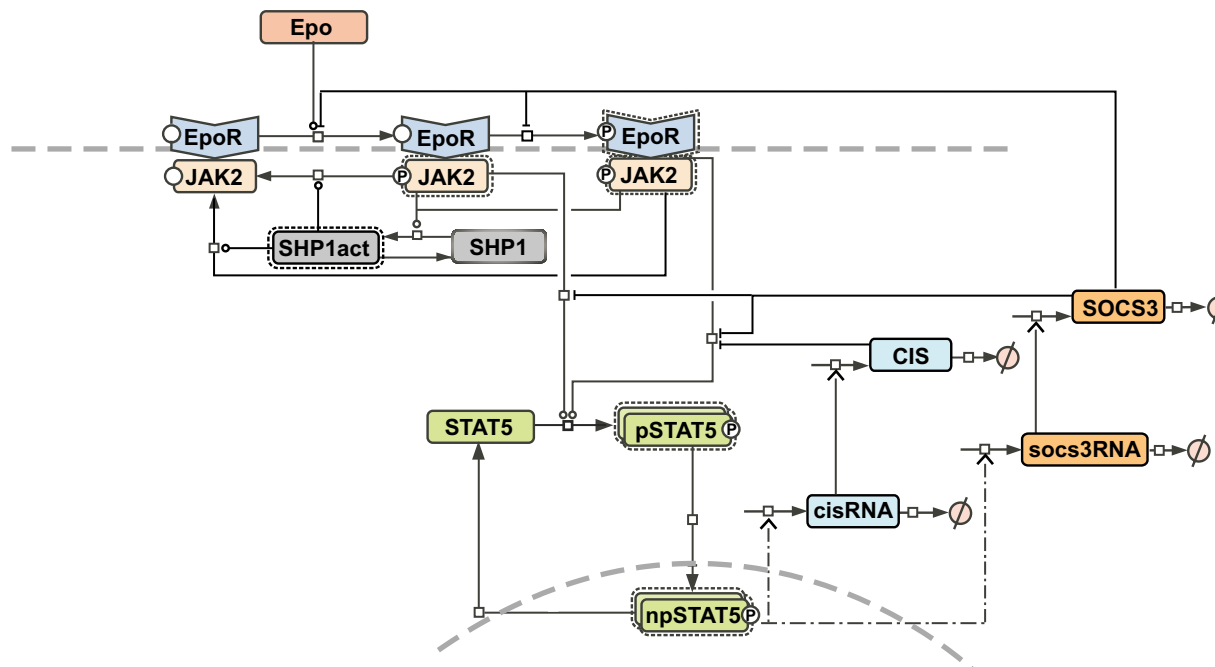


# Scaling of Profile Likelihood Approach

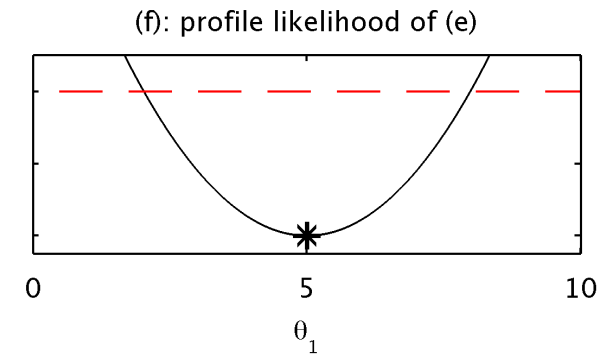
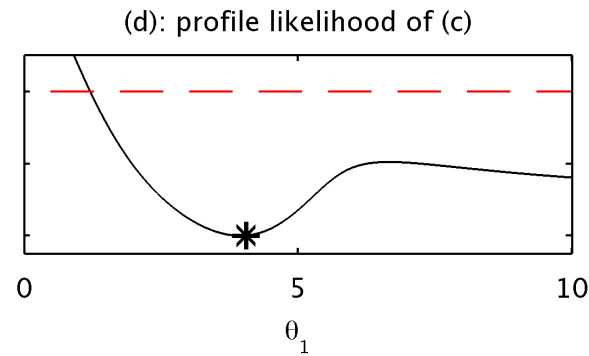
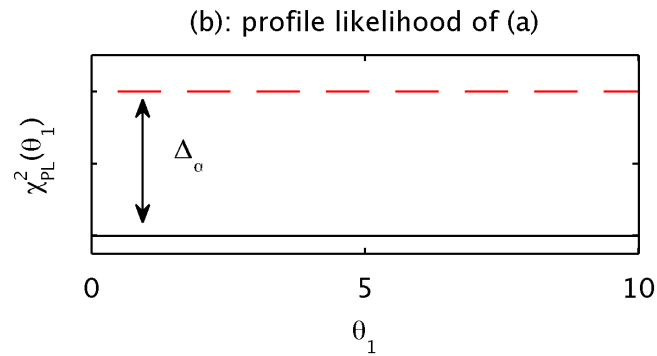
Runtime analysis for increasing number of parameters:

**Calculation can also be parallelized perfectly!**

Model of downstream signaling events:



# Requirements for Profile Likelihood Approach



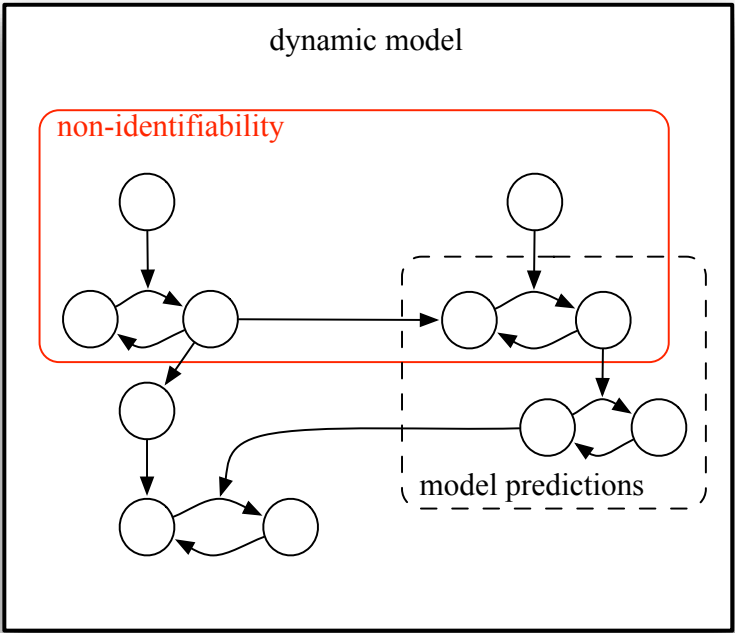
**Raue *et al.* Bioinformatics 2009**

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

**PottersWheel Toolbox (MATLAB)**

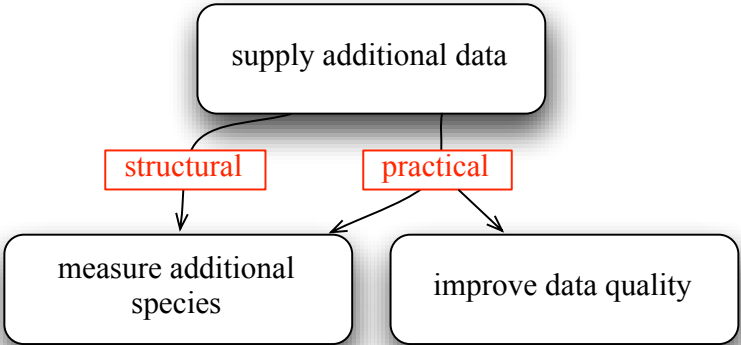
# Experimental Design vs. Model Reduction

(a) scenario 1

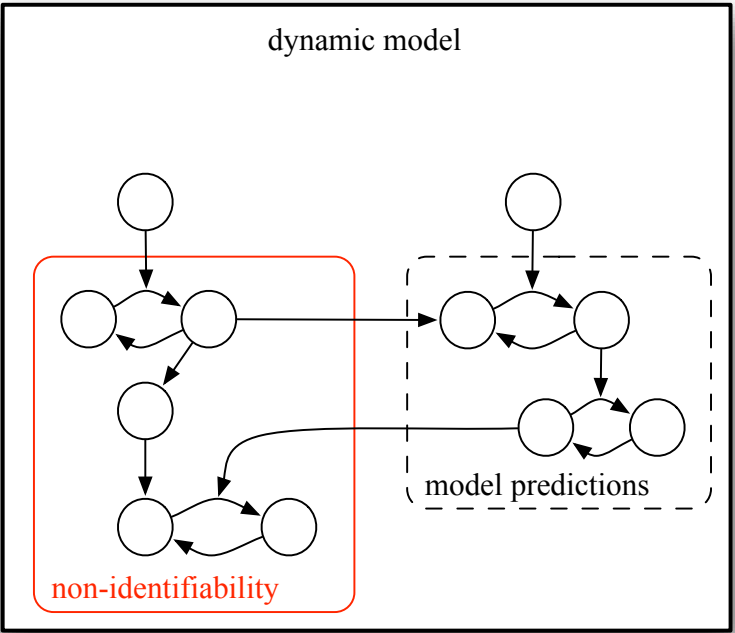


model predictions affected by non-identifiability  
→ model predictions not reliable

experimental design:

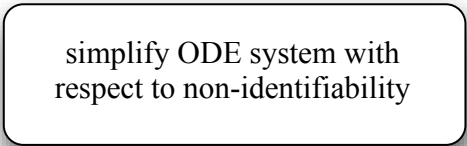


(b) scenario 2



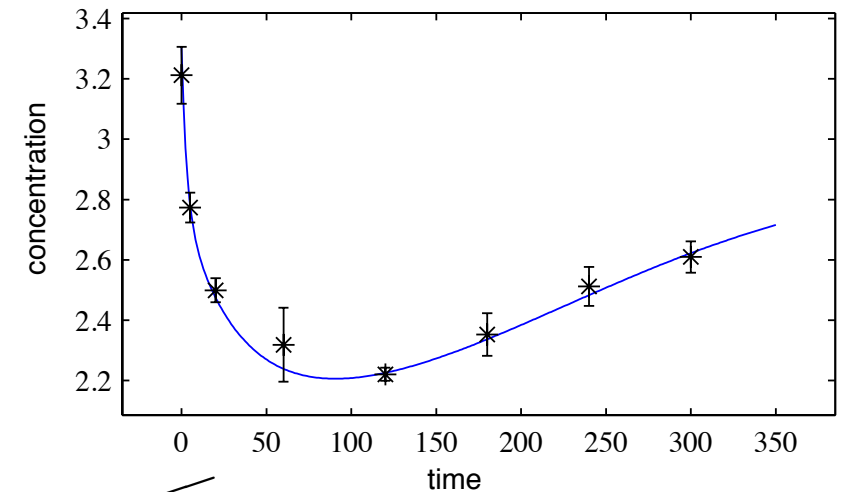
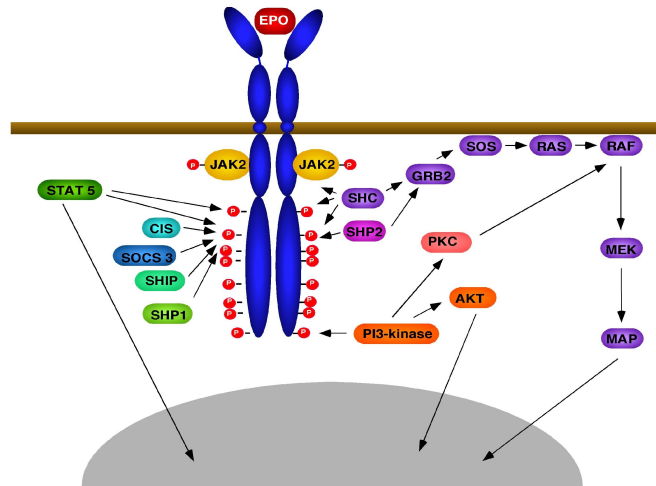
model predictions not or only negligibly affected  
by non-identifiability

model reduction:



# 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