Parameter Identification

Re-parameterisation and Numerical techniques to explore issues

James Yates, iMED Oncology DMPK, Modelling and Simulation

Identifiability issues
Sources and order they should be considered

Model Structure

Experiment – inputs (single or repeat dose, challenge test)

Experiment – time points
Experiment – measurement noise

Structural identifiability has consequences for experimental design

Feedback Control Mathematical Model

- Describes the dynamics of cardiovascular drug action

- Main (physiologically based) features of:
    1. Cardiovascular pathophysiology
    2. Limited number of hemodynamic variables

- Developed based on assumption of:
    1. Hemodynamic relationship
    2. Regulation of the Arterial Pressure (feedback control mechanism)
    3. The dynamics of the drug

- Predict qualitative and quantitative changes in mean arterial pressure and cardiac output after drug administration

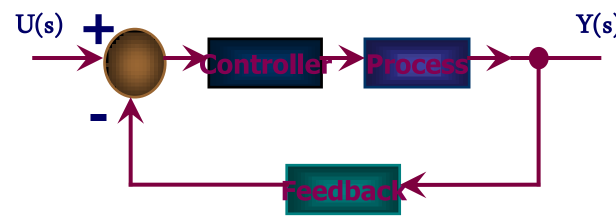
- A non-linear overly simplified model but too complex for parameter estimation

- Lack of identifiability

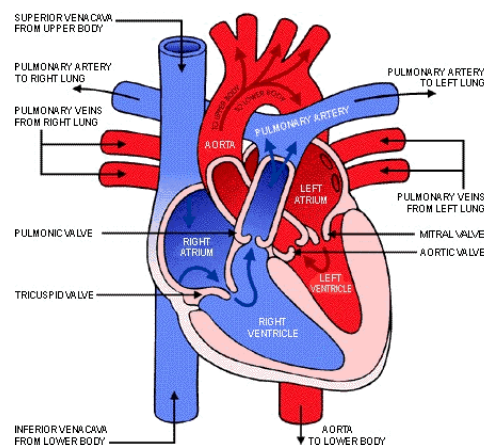
Analysis performed by Amy Cheung

$$CO = HR \cdot SV$$

$$MAP - RAP = TPR \cdot CO$$



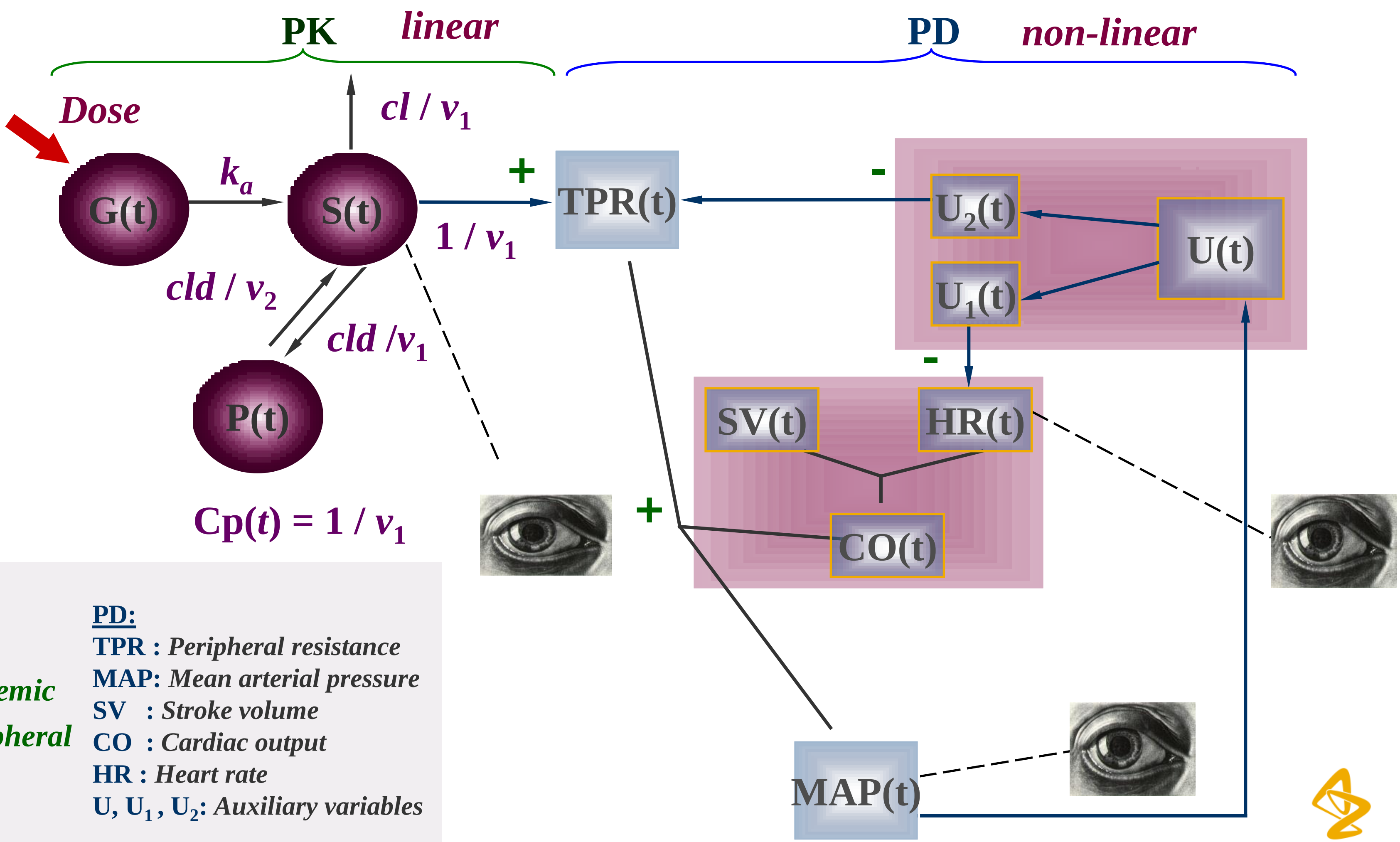
Closed loop feedback control system



Heart model

Francheteau, P., et al., J Pharmacokinet Biopharm. 21:489-414 (1993)

PKPD Model



PK:
G : *Gut*
S : *Systemic*
P : *Peripheral*

PD:
TPR : *Peripheral resistance*
MAP: *Mean arterial pressure*
SV : *Stroke volume*
CO : *Cardiac output*
HR : *Heart rate*
U, U_1, U_2: *Auxiliary variables*

PD Model

$E_{\max}$ model:

$$E(t) = \frac{E_{\max} \cdot Cp(t)}{EC_{50} + Cp(t)}$$

PD model differential equations:

$$\frac{dHR(t)}{dt} = \frac{1}{\tau_1}\left(HR_{eq}\left(1-\alpha \cdot U(t)\right)\right) - HR(t)$$

$$\frac{dTPR(t)}{dt} = \frac{1}{\tau_2}\left(TPR_{eq}\left(1-\beta \cdot U(t)\right) + E(t) - TPR(t)\right) - \frac{dE(t)}{dt}$$

$$\frac{dU(t)}{dt} = \frac{1}{\tau}\left(ac\left(MAP(t) - MAP_{eq}\right) + bc \cdot \frac{dMAP(t)}{dt} - U(t)\right)$$

Initial condition:

$$HR(0) = HR_{eq},\ TPR(0) = TPR_{eq},\ MAP(0) = MAP_{eq},$$
$$Cp(0) = 0, CO(0) = q, U(0) = 0,\ U_1(0) = 0, U_2(0) = 0$$

Unknown parameters:

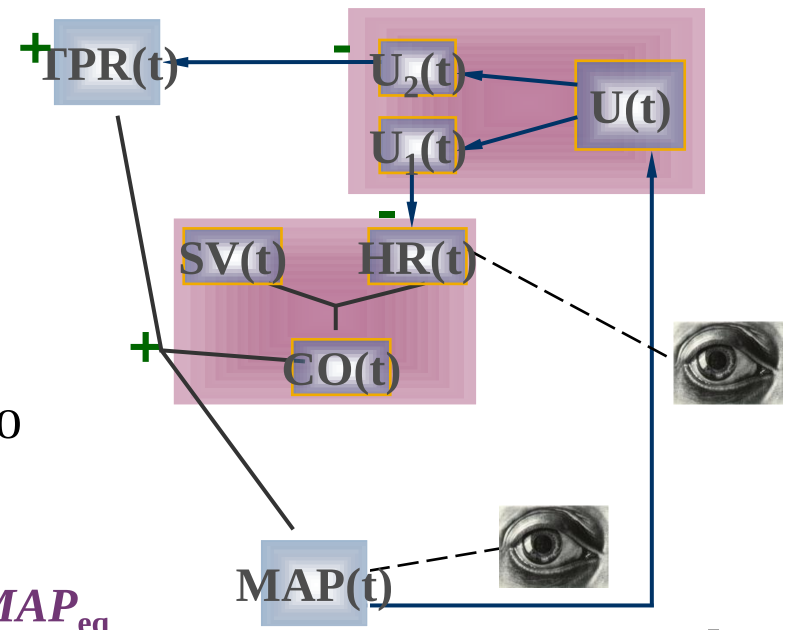
$$\alpha, \beta, \tau, \tau_1, \tau_2,\ ac,\ bc,\ E_{\max},\ EC_{50},\ TPR_{eq},\ HR_{eq},\ MAP_{eq}$$

Observation of:

$$MAP(t) = RAP + SV \cdot TPR(t) \cdot HR(t)$$

$$Cp(t) = \frac{S(t)}{v_1}$$

$$HR(t) = \frac{CO(t)}{SV}$$



Motivation: Findings in the original paper

- The parameters bc, τ and τ_1 were difficult to estimate.

- In the sensitivity analysis, these parameters were showed to have little influence on the outcomes measured.

Suggested unidentifiability of those parameters and model

SIA of Parameters and Model

- A *uniquely globally identifiable model*

  $\longrightarrow$ a unique set of parameter values can be determined by the experiment.

- A *locally identifiable model*

  $\longrightarrow$ there exists a finite sets of distinct parameter values, which produce the same i/p – o/p.

- An *unidentifiable model*

  $\longrightarrow$ there exists an infinite sets of parameter values, which produce the same observed behaviour.

Nonlinear System

A nonlinear system, is expressed in the form below:

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

$$y(t,p) = h(x(t,p),p)$$

$$x(0,p) = x_0(p)$$

Similarity Transformation of Nonlinear systems

Assumed full controllability and observability of the system.

We seek:

$$\lambda\left(\tilde{x}_1,\, \tilde{x}_2,\, \tilde{x}_3\right) = \left(\lambda_1,\, \lambda_2,\, \lambda_3\right)$$

$$(i) \qquad rank\,\frac{\partial \lambda(\tilde{x})}{\partial \tilde{x}} = n$$

$$(ii) \qquad \lambda\left(x_0(\tilde{p})\right) = x_0(p)$$

$$(iii) \qquad f\left(\lambda(\tilde{x}), p\right) = \frac{\partial \lambda(\tilde{x})}{\partial \tilde{x}} \cdot f(\tilde{x}, \tilde{p})$$

$$(iv) \qquad g\left(\lambda(\tilde{x}), p\right) = \frac{\partial \lambda(\tilde{x})}{\partial \tilde{x}} \cdot g(\tilde{x}, \tilde{p})$$

$$(v) \qquad h\left(\lambda(\tilde{x}), p\right) = h(\tilde{x}, \tilde{p})$$

$$\frac{\partial \lambda}{\partial \tilde{x}} = \begin{bmatrix} \frac{\partial \lambda_1}{\partial \tilde{x}_1} & \cdots & \frac{\partial \lambda_1}{\partial \tilde{x}_n} \\ \vdots & \ddots & \vdots \\ \frac{\partial \lambda_n}{\partial \tilde{x}_1} & \cdots & \frac{\partial \lambda_n}{\partial \tilde{x}_n} \end{bmatrix}$$

Chappell, C., et al., Math. Biosci. 102:41-73 (1990)

Similarity transformation of nonlinear polynomial systems

In general, for nonlinear ODEs

$$f\left(\lambda(\tilde{x}), p\right) = \frac{\partial \lambda(\tilde{x})}{\partial \tilde{x}} \cdot f\left(\tilde{x}, \tilde{p}\right) \quad \cdots\cdots\cdots (iii)$$

but if:

1. f is polynomial in x
2. *The observation function is linear*

Then, it is sufficient to consider (for general inputs):

$$\lambda\left(\tilde{x}\right) = \Lambda \cdot \tilde{x}$$

So,

$$\tilde{f}\left(\Lambda \cdot \tilde{x}, p\right) = \Lambda \cdot \tilde{f}\left(\tilde{x}, \tilde{p}\right)$$

Chappell, C., et al., Math. Biosci. 102:41-73 (1990)

Original model equations

E_{max} model:

$$E(t)=\frac{E_{max}\cdot Cp(t)}{EC_{50}+Cp(t)}$$

PD model differential equations:

$$\frac{dHR(t)}{dt}=\frac{1}{\tau_1}\left(HR_{eq}\left(1-\alpha\cdot U(t)\right)\right)-HR(t)$$

$$\frac{dTPR(t)}{dt}=\frac{1}{\tau_2}\left(TPR_{eq}\left(1-\beta\cdot U(t)\right)+E(t)-TPR(t)\right)-\frac{dE(t)}{dt}$$

$$\frac{dU(t)}{dt}=\frac{1}{\tau}\left(ac\left(MAP(t)-MAP_{eq}\right)+bc\cdot\frac{dMAP(t)}{dt}-U(t)\right)$$

Initial condition:

$$HR(0)=HR_{eq},\ TPR(0)=TPR_{eq},\ MAP(0)=MAP_{eq},$$
$$Cp(0)=0, CO(0)=q, U(0)=0,\ U_1(0)=0,\ U_2(0)=0$$

Unknown parameters:

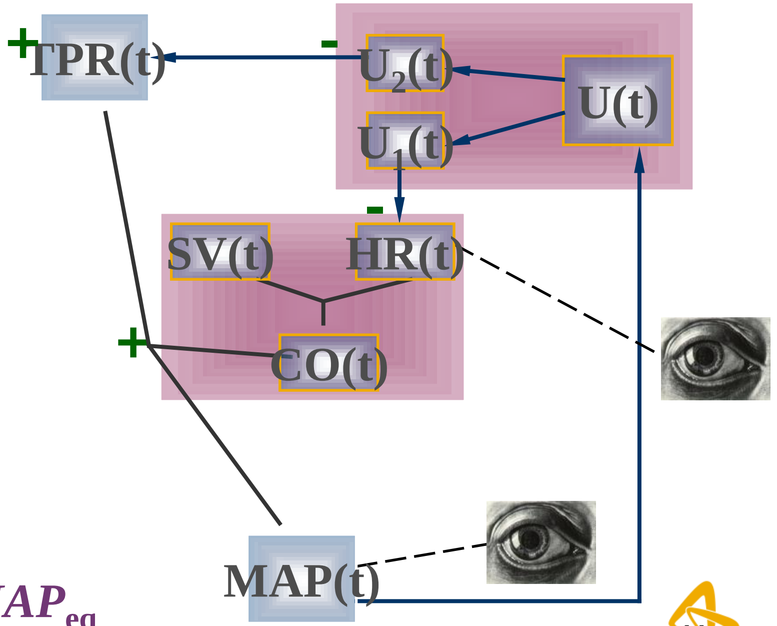
$\alpha,\beta,\tau,\tau_1,\tau_2$, ac, bc, E_{max}, EC_{50}, TPR_{eq}, HR_{eq}, MAP_{eq}

Observation of:

$$MAP(t)=RAP+SV\cdot TPR(t)\cdot HR(t)$$

$$Cp(t)=\frac{S(t)}{v_1}$$

$$HR(t)=\frac{CO(t)}{SV}$$



Cardiac Model: polynomial form

Cardiac PK/PD model rewritten to have polynomial form and linear observation

$$obs = \begin{bmatrix} \frac{S(t)}{v_1} & MAP(t) & sv.HR(t) \end{bmatrix}$$

$$\boxed{\dot{A}(t) = \frac{-S(t)\cdot A(t)^2}{v_1}}$$

$$M\dot{A}P(t) = sv.\left(TPR(t)\cdot \dot{H}R(t) + T\dot{P}R(t)\cdot HR(t)\right)$$

$$\dot{H}R(t) = \frac{1}{\tau_1}\left[HR_{eq}\cdot\left(1-\alpha\cdot U_1\right)\right] - HR(t)$$

$$\boxed{T\dot{P}R(t) = \frac{1}{\tau_2}\left[TPR_{eq}\cdot\left(1-\beta\cdot U_2\right) + E_{\max}\cdot\frac{S(t)}{v_1}\cdot A(t) - TPR(t)\right] - E_{\max}\cdot EC_{50}\cdot\frac{\dot{S}(t)}{v_1}A(t)^2}$$

$$\dot{U}(t) = \frac{1}{\tau}\left[ac\left(MAP(t) - MAP_{eq}\right) + bc\cdot M\dot{A}P(t) - U(t)\right]$$

$$x(0) = \begin{bmatrix} dose \\ 0 \\ 0 \\ \dfrac{1}{EC_{50} + \dfrac{dose}{v_1}} \\ RAP + sv.TPR_{eq}.hHR_{eq} \\ HR_{eq} \\ TPR_{eq} \\ 0 \end{bmatrix}$$

States A and MAP are added to remove a rational polynomial and a nonlinear observation respectively. They are based upon the following definitions:

$$A(t) = \frac{1}{EC_{50} + \frac{S(t)}{v_1}}$$ **and** $$MAP(t) = sv\cdot TPR(t)\cdot HR(t)$$

This gives that:

$$E(t) = E_{\max}\cdot\frac{S(t)}{v_1}\cdot A(t)$$

Results

$$\tilde{HR}_{eq} = HR_{eq},\quad \tilde{TPR}_{eq} = TPR_{eq},\quad \tilde{MAP}_{eq} = MAP_{eq},\quad \tilde{E}_{max} = E_{max},\quad \tilde{EC}_{50} = EC_{50},$$

$$\tilde{\tau} = \tau,\quad \tilde{\tau}_1 = \tau_1,\quad \tilde{\tau}_2 = \tau_2,\quad \tilde{ac} = \frac{ac \cdot \tilde{bc}}{bc},\quad \tilde{\alpha} = \frac{bc \cdot \alpha}{\tilde{bc}},\quad \tilde{\beta} = \frac{bc \cdot \beta}{\tilde{bc}}$$

- The Λ matrix obtained is:

PK MODEL

PD MODEL

$$\Lambda = \underbrace{\begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{bc}{\tilde{bc}} \end{bmatrix}}_{\Lambda^{8\times8} \neq I^{8\times8}}$$

$$\frac{dU(t)}{dt} = \frac{1}{\tau}\left(ac\left(MAP(t) - MAP_{eq} \right) + bc \cdot \frac{dMAP(t)}{dt} - U(t) \right)$$

$$\lambda_{8,8} : \frac{\tilde{\alpha}}{\alpha}, \frac{\tilde{\beta}}{\beta}, \frac{bc}{\tilde{bc}}, \frac{ac}{\tilde{ac}}$$

Reparameterisation

Step 1:

Consider the Taylor series expansion on the similarity transformation of the defining conditions (on inputs, ODE observations) in state variables:

$$\hat{F}\left(\tilde{x}, p, \tilde{p}\right) = 0$$
$$\hat{G}\left(\tilde{x}, p, \tilde{p}\right) = 0$$
$$\hat{H}\left(\tilde{x}, p, \tilde{p}\right) = 0$$

Step 2:

Consider the Jacobian matrix of the partial derivatives of the Taylor series coefficients:

$$J(p) = \begin{bmatrix} \frac{\partial \hat{F}_1^{(0)}}{\partial p_1}(p,\tilde{p}) & \frac{\partial \hat{F}_1^{(0)}}{\partial p_2}(p,\tilde{p}) & \cdots & \frac{\partial \hat{F}_1^{(0)}}{\partial p_p}(p,\tilde{p}) \\ \frac{\partial \hat{F}_1^{(1)}}{\partial p_1}(p,\tilde{p}) & \frac{\partial \hat{F}_1^{(1)}}{\partial p_2}(p,\tilde{p}) & \cdots & \frac{\partial \hat{F}_1^{(1)}}{\partial p_p}(p,\tilde{p}) \\ \vdots & \vdots & & \vdots \\ \frac{\partial \hat{G}_1^{(0)}}{\partial p_1}(p,\tilde{p}) & \frac{\partial \hat{G}_1^{(0)}}{\partial p_2}(p,\tilde{p}) & \cdots & \frac{\partial \hat{G}_1^{(0)}}{\partial p_p}(p,\tilde{p}) \\ \frac{\partial \hat{G}_1^{(1)}}{\partial p_1}(p,\tilde{p}) & \frac{\partial \hat{G}_1^{(1)}}{\partial p_2}(p,\tilde{p}) & \cdots & \frac{\partial \hat{G}_1^{(1)}}{\partial p_p}(p,\tilde{p}) \\ \vdots & \vdots & & \vdots \\ \frac{\partial \hat{H}_1^{(0)}}{\partial p_1}(p,\tilde{p}) & \frac{\partial \hat{H}_1^{(0)}}{\partial p_2}(p,\tilde{p}) & \cdots & \frac{\partial \hat{H}_1^{(0)}}{\partial p_p}(p,\tilde{p}) \\ \frac{\partial \hat{H}_1^{(0)}}{\partial p_1}(p,\tilde{p}) & \frac{\partial \hat{H}_1^{(0)}}{\partial p_2}(p,\tilde{p}) & \cdots & \frac{\partial \hat{H}_1^{(0)}}{\partial p_p}(p,\tilde{p}) \\ \vdots & \vdots & & \vdots \end{bmatrix}$$

Step 3:

Substitution of the results from the structural identifiability analysis is then applied to the row-reduced form of $J(p)$. Suppose that rank $J(p)= q<p$, then there exist $(p-q)$ redundant parameters and a locally identifiable reparameterisation with q parameters.

Step 4:

If $J(p)$ with rank $J(p)=q$. Let $N=\{n_1, n_2,\ldots n_{p-q}\}$ span the null space of . Consider any function $\varphi(p) \to R$ which satisfied the condition

$$n_i \cdot \nabla \varphi = 0, \;\; i = 1, \ldots, p-q$$

Then $\varphi(p)$ is a locally identifiable parameter of the system and

$$\varphi\left(p_1, \ldots, p_p\right) = \left(\varphi_1, \ldots, \varphi_q\right)$$

is a locally identifiable reparameterisation of the system

Chappell, C., et al., Math. Biosci. 102:41-73 (1990)

Reparameterised Cardiac Model

The possible solutions obtained from step 4 are as follow:

$$\varphi(p_1) = \alpha \cdot bc, \quad \varphi(p_2) = \beta \cdot bc, \quad \varphi(p_3) = \frac{ac}{bc}$$

A new model with globally identifiable parameters:

$$obs = \begin{bmatrix} \frac{S(t)}{v_1} & MAP(t) & sv.HR(t) \end{bmatrix}$$

$$\dot{A}(t) = \frac{-S(t) \cdot A(t)^2}{v_1}$$

$$M\dot{A}P(t) = sv.\left(TPR(t) \cdot \dot{H}R(t) + T\dot{P}R(t) \cdot HR(t)\right)$$

$$\dot{H}R(t) = \frac{1}{\varphi_5}\left[\varphi_3 \cdot (1 - \varphi_9 \cdot U)\right] - HR(t)$$

$$T\dot{P}R(t) = \frac{1}{\varphi_6}\left[\varphi_2 \cdot (1 - \varphi_{10} \cdot U) + \varphi_8 \cdot \frac{S(t)}{v_1} \cdot A(t) - TPR(t)\right] - \varphi_7 \cdot \varphi_8 \cdot \frac{\dot{S}(t)}{v_1} A(t)^2$$

$$\dot{U}(t) = \frac{1}{\varphi_4}\left[\varphi_{11}\left(MAP(t) - \varphi_1\right) + M\dot{A}P(t) - U(t)\right]$$

$$x(0) = \begin{bmatrix} dose \\ 0 \\ 0 \\ \dfrac{1}{\varphi_7 + \dfrac{dose}{v_1}} \\ RAP + sv.\varphi_2.\varphi_3 \\ \varphi_3 \\ \varphi_2 \\ 0 \end{bmatrix}$$

$$A(t) = \frac{1}{\varphi_7 + \frac{S(t)}{v_1}}, \qquad MAP(t) = sv \cdot TPR(t) \cdot HR(t), \qquad E(t) = \varphi_8 \cdot \frac{S(t)}{v_1} \cdot A(t)$$

where

$$\varphi_1 = MAP_{eq}, \varphi_2 = TPR_{eq}, \varphi_3 = HR_{eq}, \varphi_4 = \tau, \varphi_5 = \tau_1, \varphi_6 = \tau_2,$$

$$\varphi_7 = EC_{50}, \varphi_8 = E_{\max}, \varphi_9 = \alpha \cdot bc, \varphi_{10} = \beta \cdot bc, \varphi_{11} = \frac{ac}{bc}$$

This gives that:

$$\varphi(p) = (\varphi_1, \varphi_2, \varphi_3, \varphi_4, \varphi_5, \varphi_6, \varphi_7, \varphi_8, \varphi_9, \varphi_{10}, \varphi_{11})$$

Conclusion

- Structural identifiability analysis has been performed on a nonlinear PK PD model.
- The unidentifiable parameters are: α,β, ac and bc and hence model is unidentifiable
- Unidentifiable problem is solved by reparameterisation of the polynomial model
- The model was found to be rank deficient by one
- Core PD parameters such as Emax and EC50 can still be uniquely estimated
- Reparameterised model is globally identifiable

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Structural identifiability analysis and reparameterisation (parameter reduction) of a cardiovascular feedback model

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Bootstrap Algorithm

- **Non-parametric – Based upon data only**
- **Is valid for nonlinear models**
- **Can measure prediction error**
- **(Still fit log-transformed parameters)**
- **Basic algorithm:**
    1. **Generate new data set randomly**
    2. **Fit model to this new data set**
    3. **Repeat x100-1000**
    4. **Do stats on the resulting list of estimates**

Bootstrap Algorithm

- Uncertainty in Parameter estimates
  - We could keep repeating the study and look at what variation of estimates we get
- Bootstrap Uncertainty
  - Generate “new studies” by sampling from existing data
- Can sample on Observed Data or Residuals

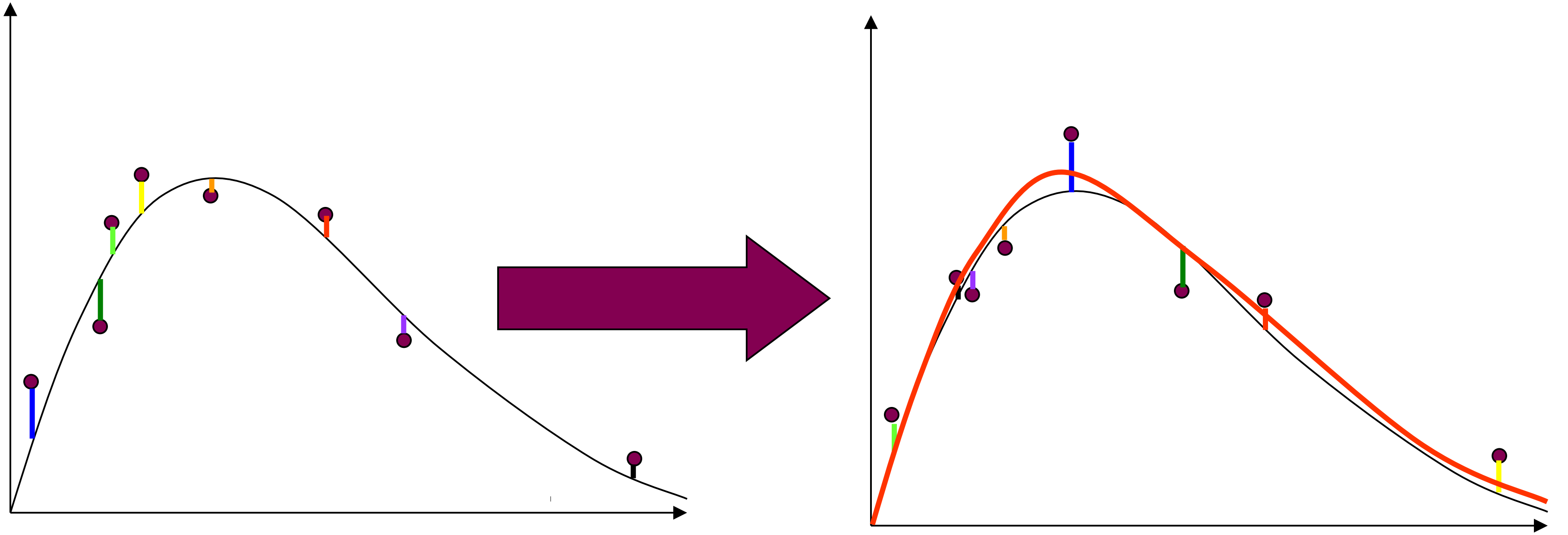
Bootstrap Algorithm - Observed

Here we sample the data set with replacement to obtain a new data with the same number of observations

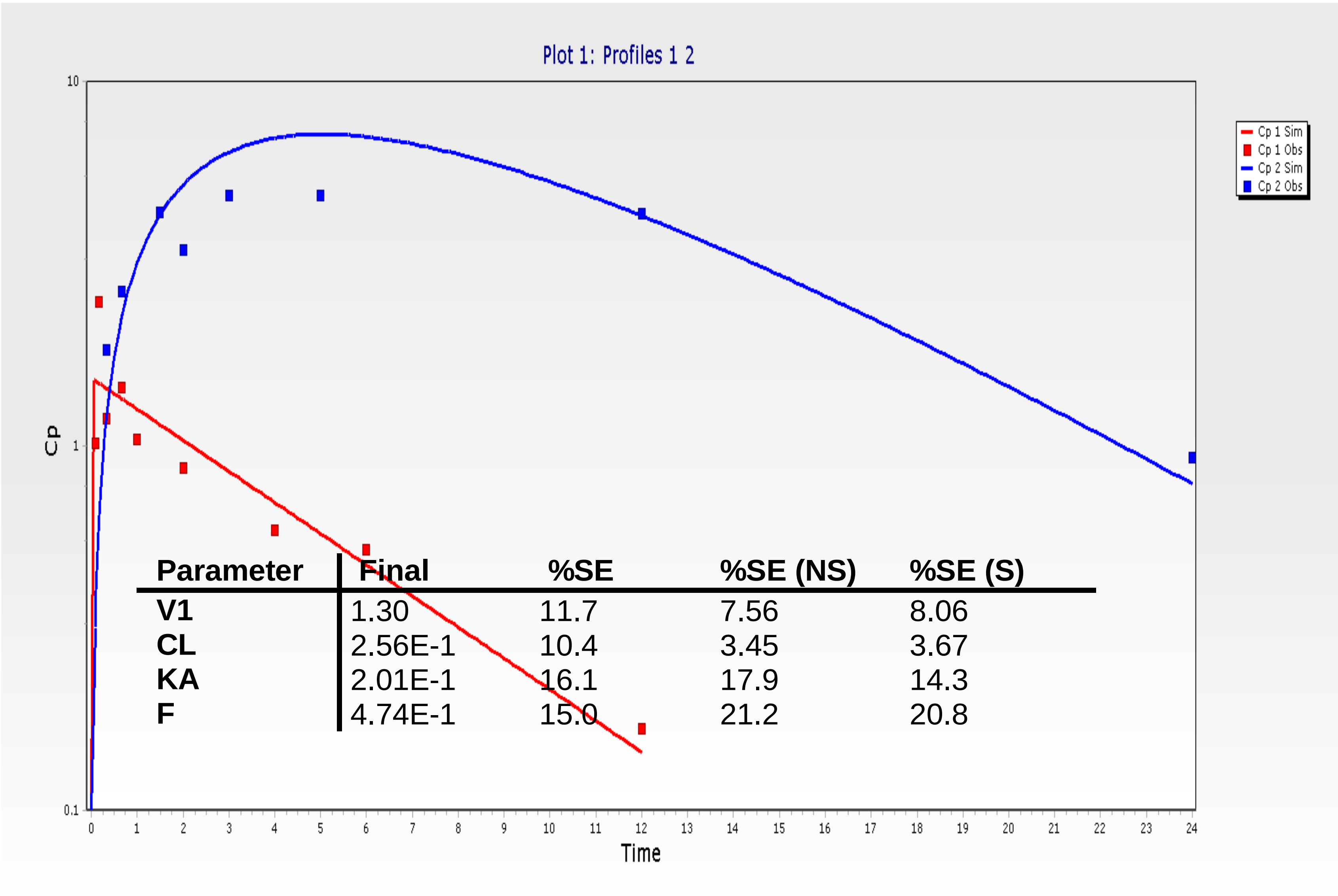
T	C
1	0.1
2	0.6
3	0.5
4	0.2
5	0.07
6	0.01

T	C
1	0.1
1	0.1
3	0.5
4	0.2
5	0.07
5	0.07

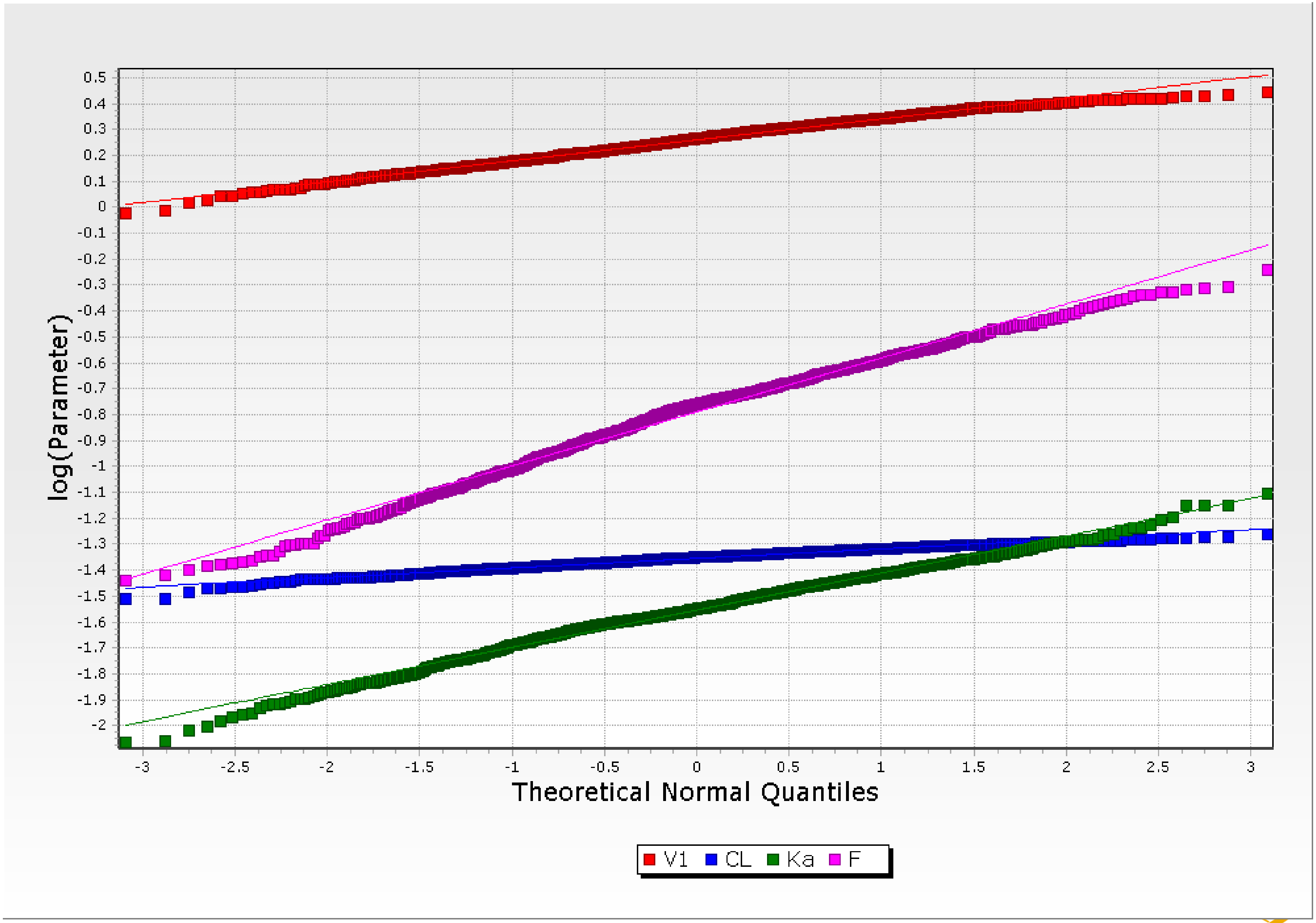
Bootstrap Algorithm - Residuals



Example 1: iv and po dosing



Parameter	Final	%SE	%SE (NS)	%SE (S)
V1	1.30	11.7	7.56	8.06
CL	2.56E-1	10.4	3.45	3.67
KA	2.01E-1	16.1	17.9	14.3
F	4.74E-1	15.0	21.2	20.8

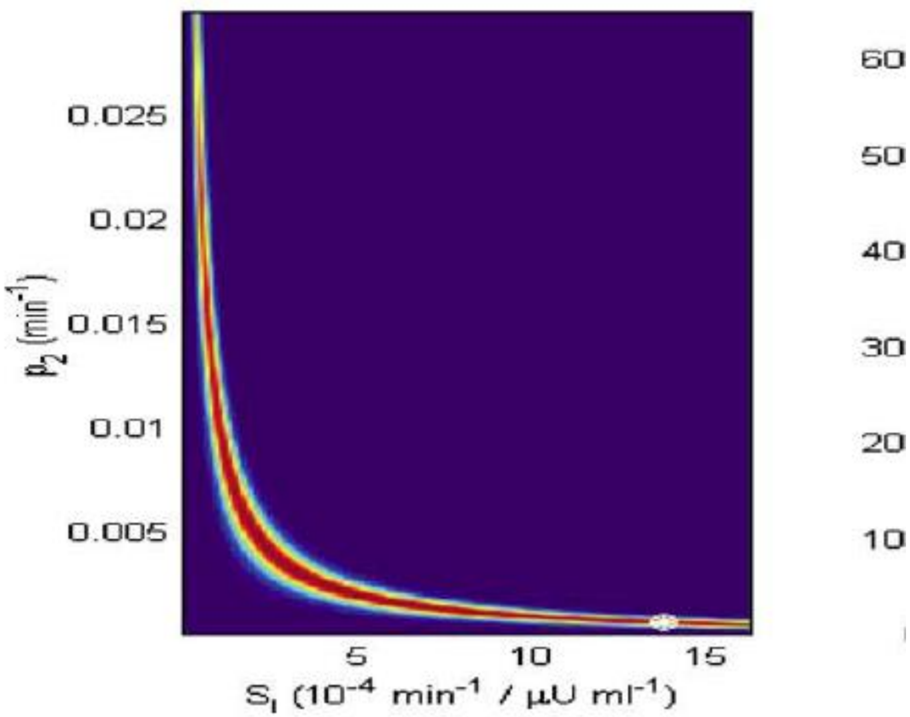


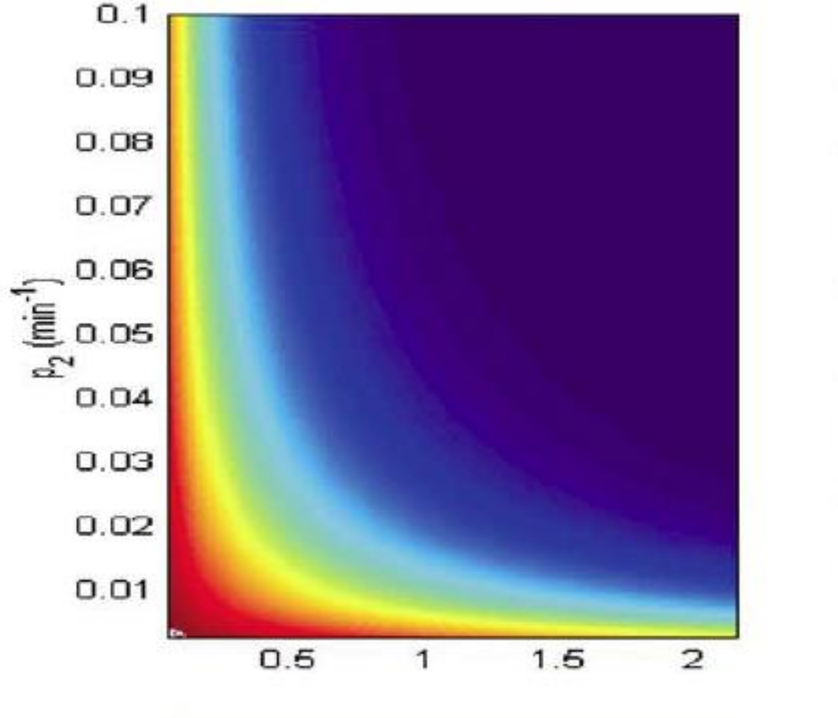
log(Parameter)
0.5
0.4
0.3
0.2
0.1
0
-0.1
-0.2
-0.3
-0.4
-0.5
-0.6
-0.7
-0.8
-0.9
-1
-1.1
-1.2
-1.3
-1.4
-1.5
-1.6
-1.7
-1.8
-1.9
-2
-3
-2.5
-2
-1.5
-1
-0.5
0
0.5
1
1.5
2
2.5
3
Theoretical Normal Quantiles
V1
CL
Ka
F

The bootstrap
Empirical parameter distribution

Useful to get evaluation of SEs for globally identifiable model
Issue – if not identifiable parameters will be observed to vary very little!!
Issue – what happens if model is locally identifiable? Multimodal distribution?

Profile likelihood



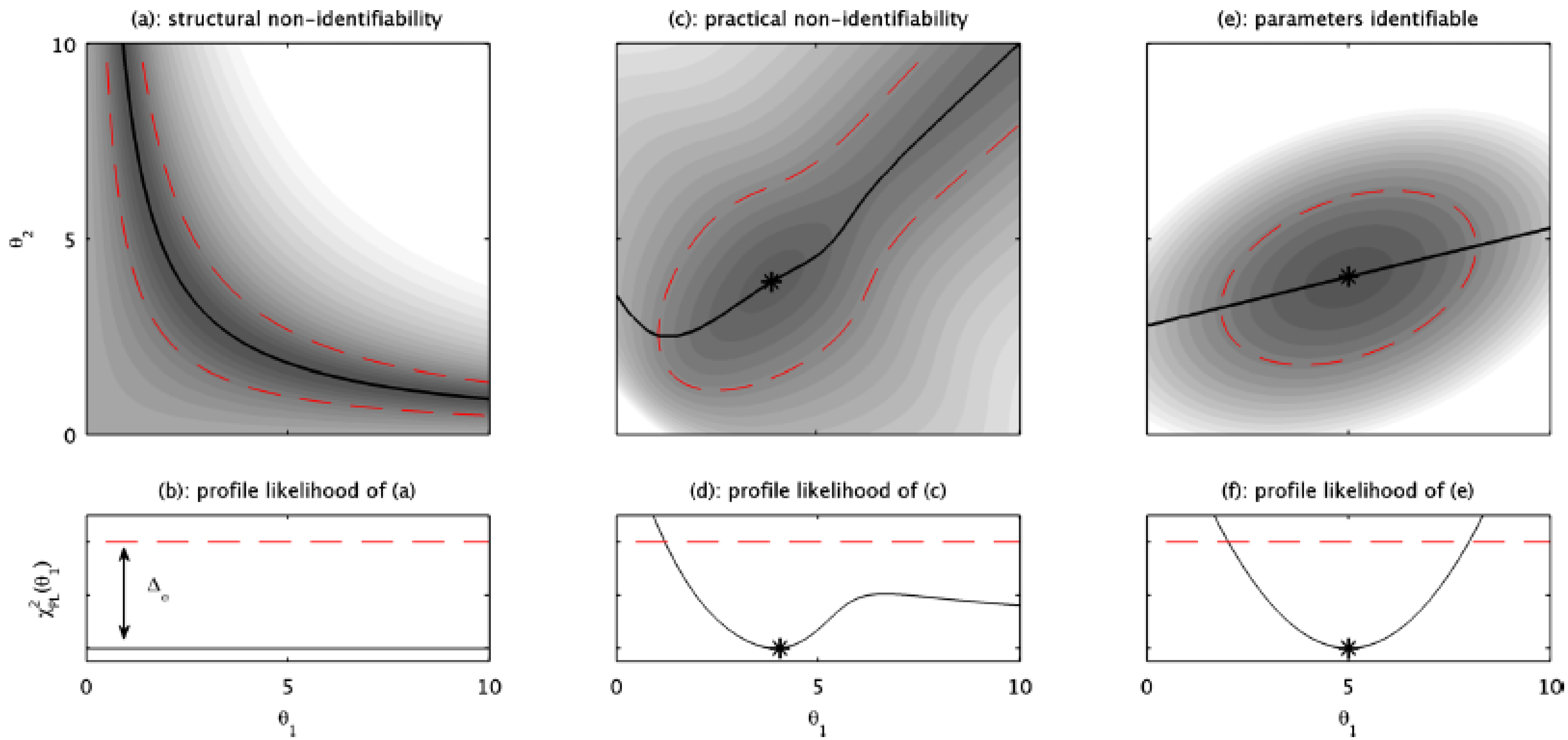


Highly correlated (though nonlinear not something FIM would pick up)

Parameters generally poorly determined

Profile likelihood surface

Is there another minima outside of these pictures?



Identifiability and observability analysis for experimental design in nonlinear dynamical models

A. Raue, V. Becker, U. Klingmüller, and J. Timmer

Citation: Chaos **20**, 045105 (2010); doi: 10.1063/1.3528102

Profile likelihood for one parameter at a time

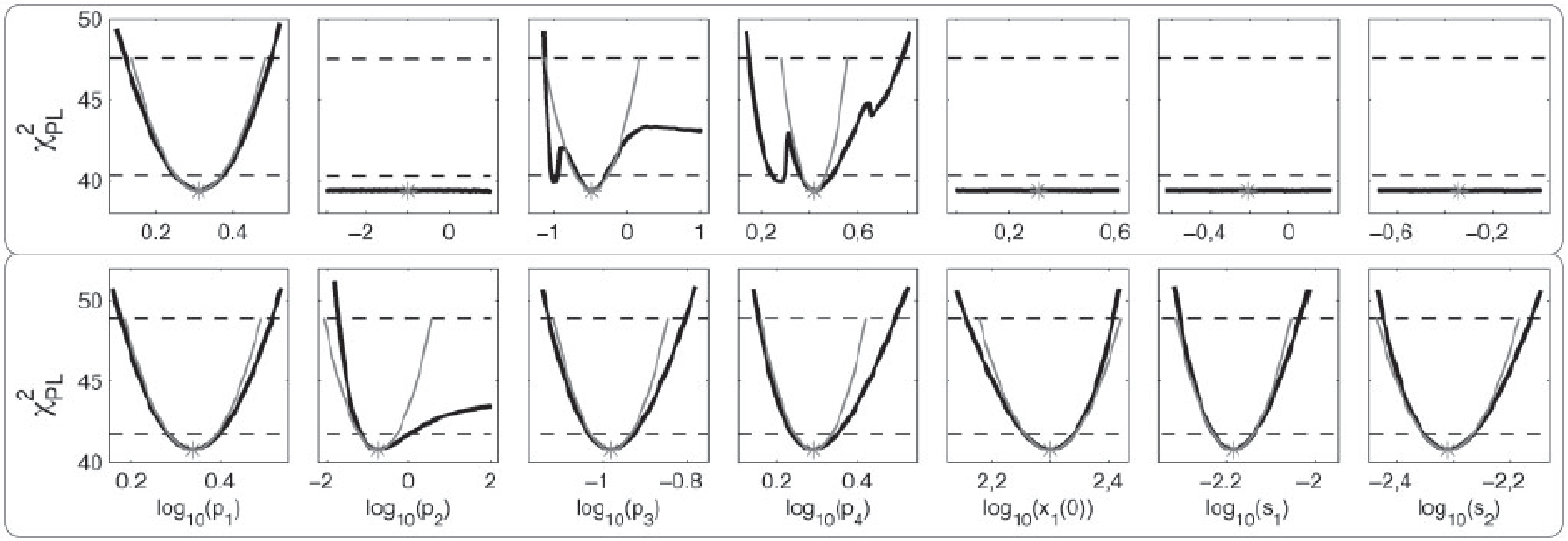


Fig. 3. Black lines display profile likelihood versus parameter. The results for the original dataset are shown in the upper panel. The lower panel shows the alteration of the profile likelihood, after taking into account the additional data. Calibrated parameter values $\hat{\theta}$ are displayed by gray stars, thresholds for simultaneous and pointwise 1-σ confidence intervals by upper, respectively, lower dashed lines. Gray parabolas indicate the quadratic approximation used for asymptotic confidence intervals. They are very flat for the structurally non-identifiable parameters. Discontinuities in the profile likelihood of p_3 and p_4 in the upper panel stem from local minima that govern the profile likelihood in remote regions. Parameter values are given in orders of magnitude.

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Systems biology

Structural and practical identifiability analysis of partially observed dynamical models by exploiting the profile likelihood

A. Raue[1,*], C. Kreutz[1], T. Maiwald[2], J. Bachmann[3], M. Schilling[3], U. Klingmüller[3] and J. Timmer[1,4]

Multistart

Useful for finding good parameter values. Useful at looking at local correlations. Useful for identifiability analysis?

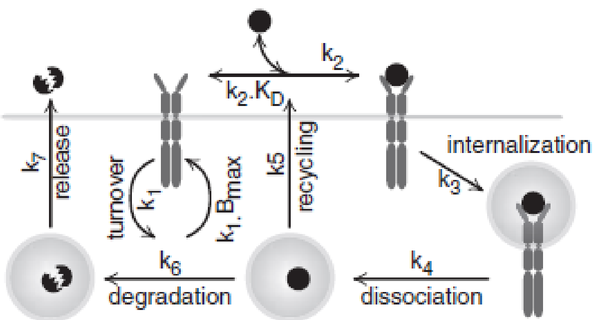

Fig. 4. Non-linear dynamical model for the endocytosis of the erythropoietin receptor (EPO receptor). The EPO receptor is constitutively produced and internalized. EPO reversibly binds to the receptor and thereby induces accelerated endocytosis. Internalized EPO may either be recycled to the cytoplasm or undergo degradation before it is recycled. It is assumed, that the internalized dissociated receptors are degraded and that the degraded receptors do not interfere with the dynamic of the system.

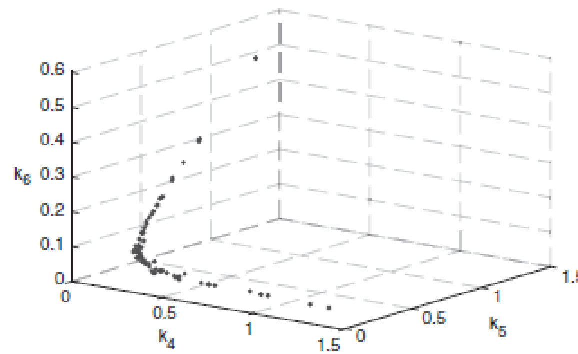

Fig. 5. Scatterplot. Our algorithm for identifiability analysis identifies a three parameter relation between k_4, k_5 and k_6. The parameters lie on a tilted hyperbola in the 3D parameter space. The model's observation functions are invariant under parameter variations along the hyperbola, i.e. all points yield comparable χ^2 values. In order to render the *constrained structure* identifiable, one of the three parameters has to be fixed.

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doi:10.1093/bioinformatics/btm382

Systems biology

Data-based identifiability analysis of non-linear dynamical models

S. Hengl*, C. Kreutz, J. Timmer and T. Maiwald

Parting words

•Structural identifiability provides insight into parameter estimation problem. Could have been done prior to estimation

•Reparameterisation takes “problem” model and “fixes it” whilst retaining mechanism or forcing fixing of parameter values

•Numerical vs Algebraic identifiability

•Large versus infinity

•Reasons for identification issues: model vs experimental design

•“Proof” by simulation is not a proof

Confidentiality Notice