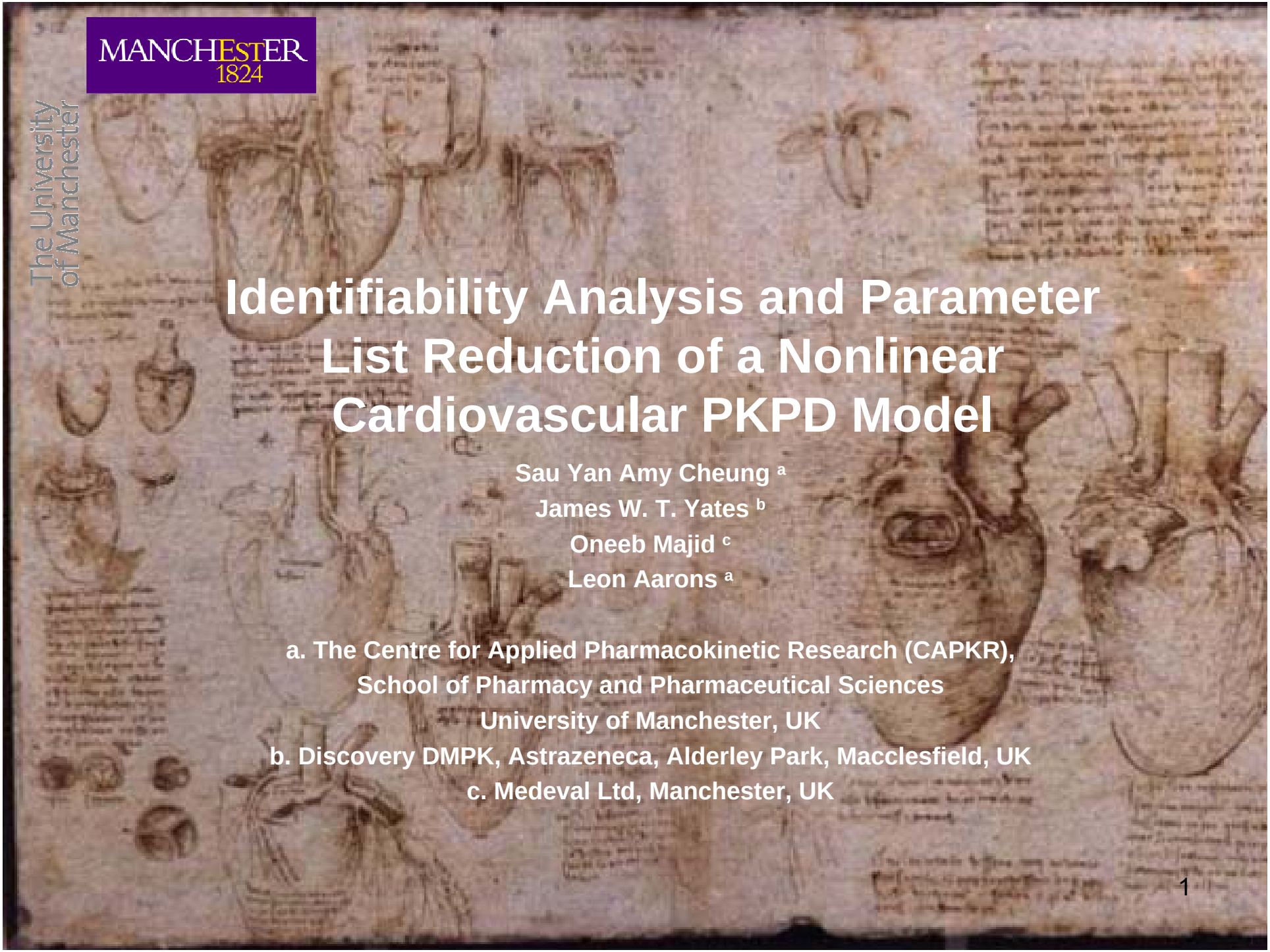

Identifiability Analysis and Parameter List Reduction of a Nonlinear Cardiovascular PKPD Model

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Overview

- Background
- Cardiovascular PKPD model
- Structural identifiability analysis (SIA)
- Similarity transformation approach
- Result
- Parameter list reduction (reparameterisation)
- The new model
- New and old model comparison
- Conclusion
- Remarks

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

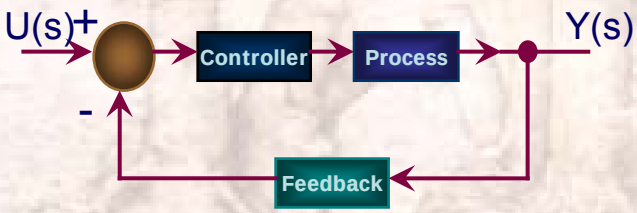
- Predict qualitative and quantitative changes in mean arterial pressure and cardiac output after drug administration

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

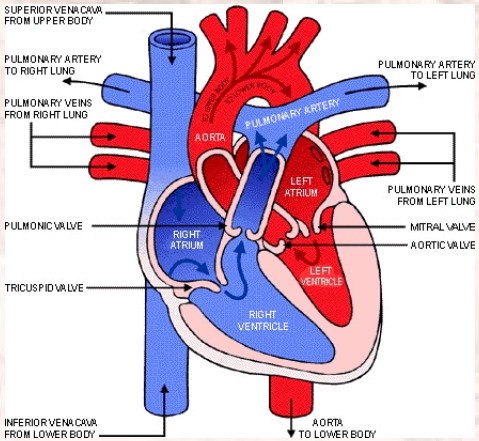
- Lack of identifiability

$$CO = HR \cdot SV$$

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



Closed loop feedback control system



Heart model

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

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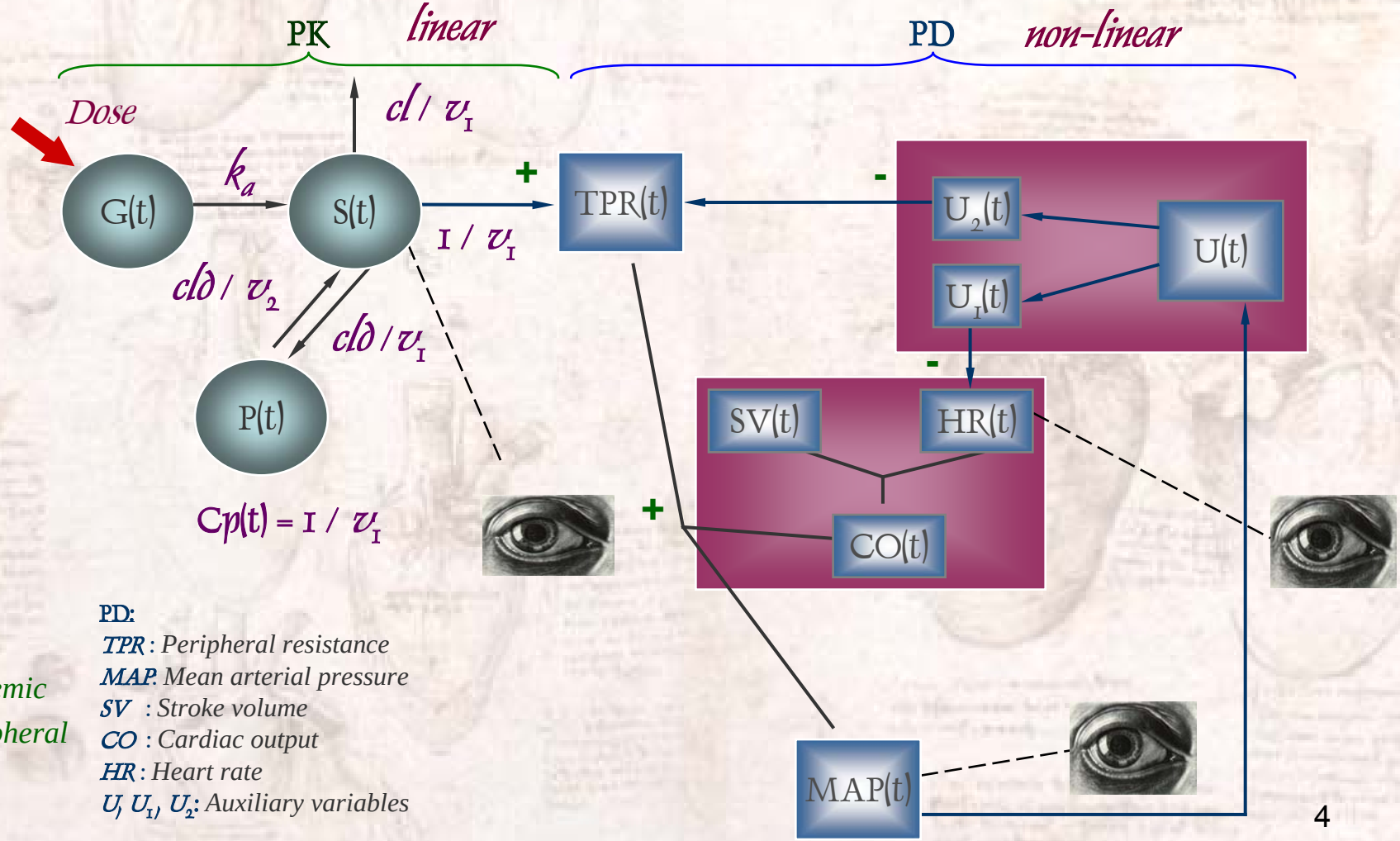
PKPD Model



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:

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

Unknown parameters:

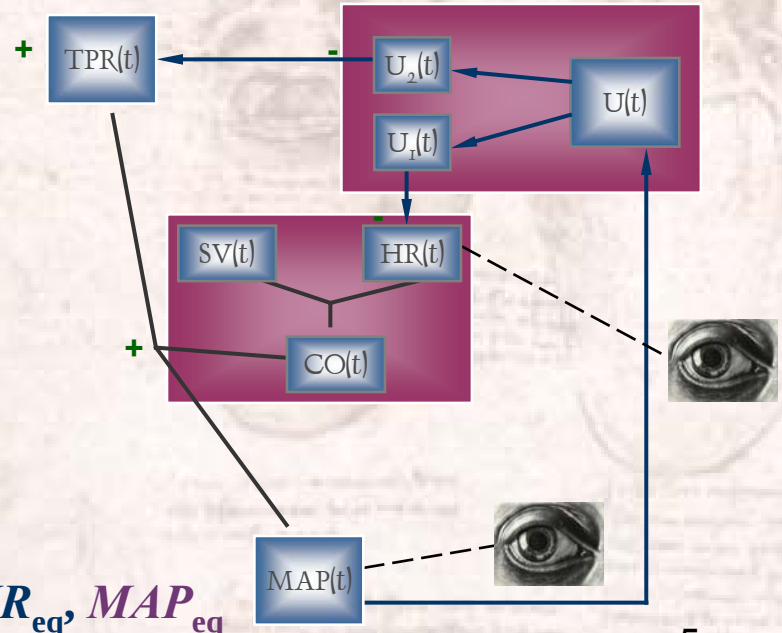
$\alpha, \beta, \tau, \tau_1, \tau_2, ac, bc, E_{max}, EC_{50}, TPR_{eq}, HR_{eq}, MAP_{eq}$

Observation of:

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

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

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



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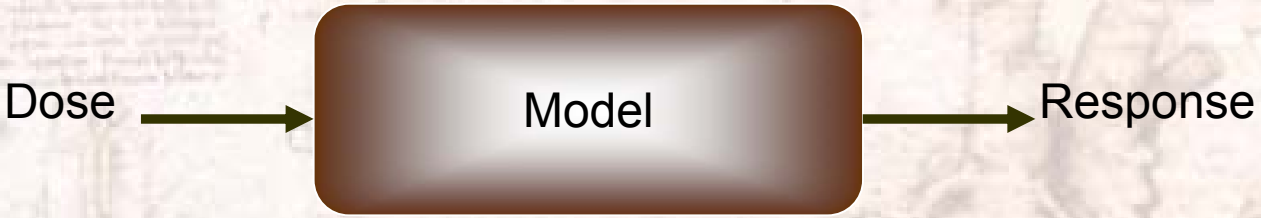
Motivation

- 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

Structural Identifiability Analysis (SIA)

SIA (*Bellman, Cobelli, DiStefano III and Godfrey*)



Aim: Identify whether the internal structure can be 'uniquely identified by the experiment'

Prior or Post check for:

- Experimental design
- System identification
- Parameter estimation

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SIA of Parameters and Model

- A *uniquely globally identifiable model*
  → a unique set of parameter values can be determined by the experiment.

- A *locally identifiable model*
  → there exists a finite sets of distinct parameter values, which produce the same i/p – o/p.

- An *unidentifiable model*
  → 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:

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

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

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

with

$$t \in [0, t_1], \quad x(t, p) \in \mathbb{R}^n, \quad y(t, p) \in \mathbb{R}^m \text{ and } p \in \Omega \in \mathbb{R}^q$$

STA of Nonlinear systems

Assuming full controllability and observability of the system.

We seek:

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

from $\tilde{x}, \tilde{p}$ **to** x, p **such that:**

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

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

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

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

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

where

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

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

STA to nonlinear polynomial systems

In general, for nonlinear ODEs

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

but if:

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

Then, it is sufficient to consider:

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

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 (f)

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:

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

Unknown parameters:

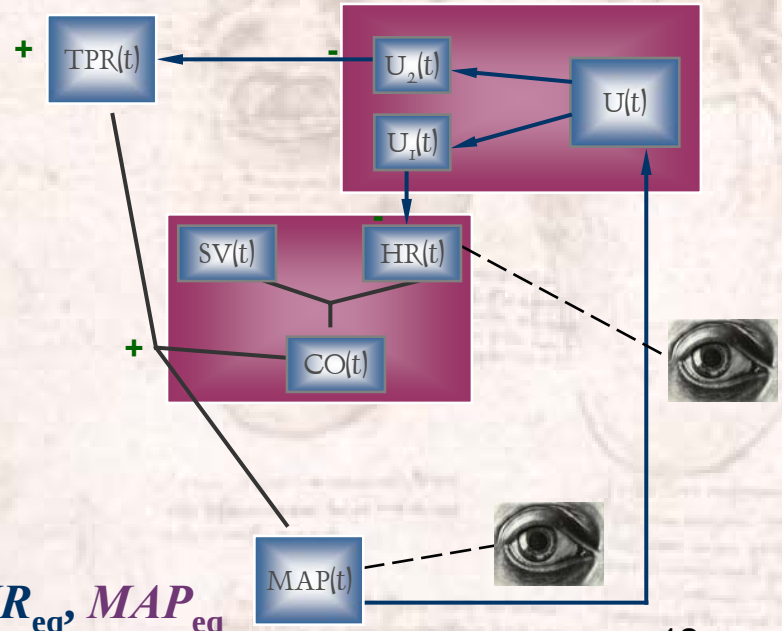
$\alpha, \beta, \tau, \tau_1, \tau_2, ac, bc, E_{max}, EC_{50}, TPR_{eq}, HR_{eq}, MAP_{eq}$

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 (f)

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

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

$$\dot{MAP}(t) = sv.\left(TPR(t)\cdot\dot{HR}(t) + \dot{TPR}(t)\cdot HR(t)\right)$$

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

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

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

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

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

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

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

This gives that:

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

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Results

- A total of 593 simultaneous equations generate by the theorem of the model to solve for 12 unknown parameters.
- The process was divided into 11 sessions in the analysis
- The following relations which describe the relation between $\tilde{p} = p$ are as follow (obtained with assistance of *MATHEMATICA*):

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

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

- The Λ matrix obtained is:

PK model

PD model

$$\Lambda = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{bc}{\tilde{bc}} \end{bmatrix}$$

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

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

$$\Lambda^{8\times 8} \neq I^{8\times 8}$$

Parameter list Reduction

Step 1:

Consider the Taylor series expansion on the similarity transformation of the defining conditions in state variables:

$$\begin{aligned} F(\tilde{x}, p, \tilde{p}) &= 0 & \hat{F}(\tilde{x}, p, \tilde{p}) &= 0 \\ G(\tilde{x}, p, \tilde{p}) &= 0 \quad \Rightarrow & \hat{G}(\tilde{x}, p, \tilde{p}) &= 0 \\ H(\tilde{x}, p, \tilde{p}) &= 0 & \hat{H}(\tilde{x}, p, \tilde{p}) &= 0 \end{aligned}$$

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,… n_{p-q}} span the null space of . Consider any function $\varphi(p)$-> *R* which satisfied the condition

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

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

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

is a locally identifiable reparameterisation of the system

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

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Parameter list reduced Cardiac Model

The possible solutions obtain 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:

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

$$\dot{MAP}(t) = sv.\left(TPR(t) \cdot \dot{HR}(t) + \dot{TPR}(t) \cdot HR(t)\right)$$

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

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

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

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

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:

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

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

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

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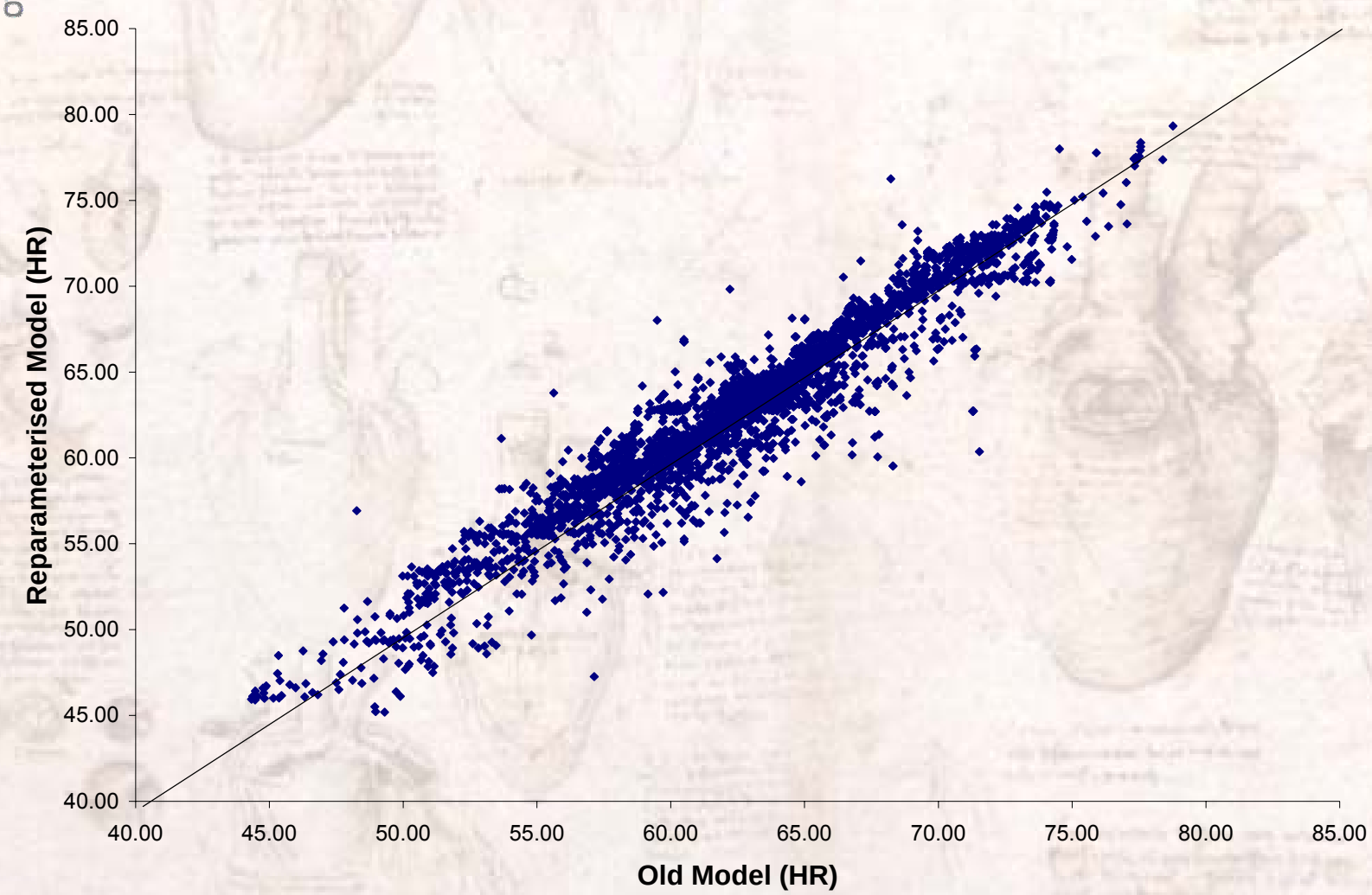
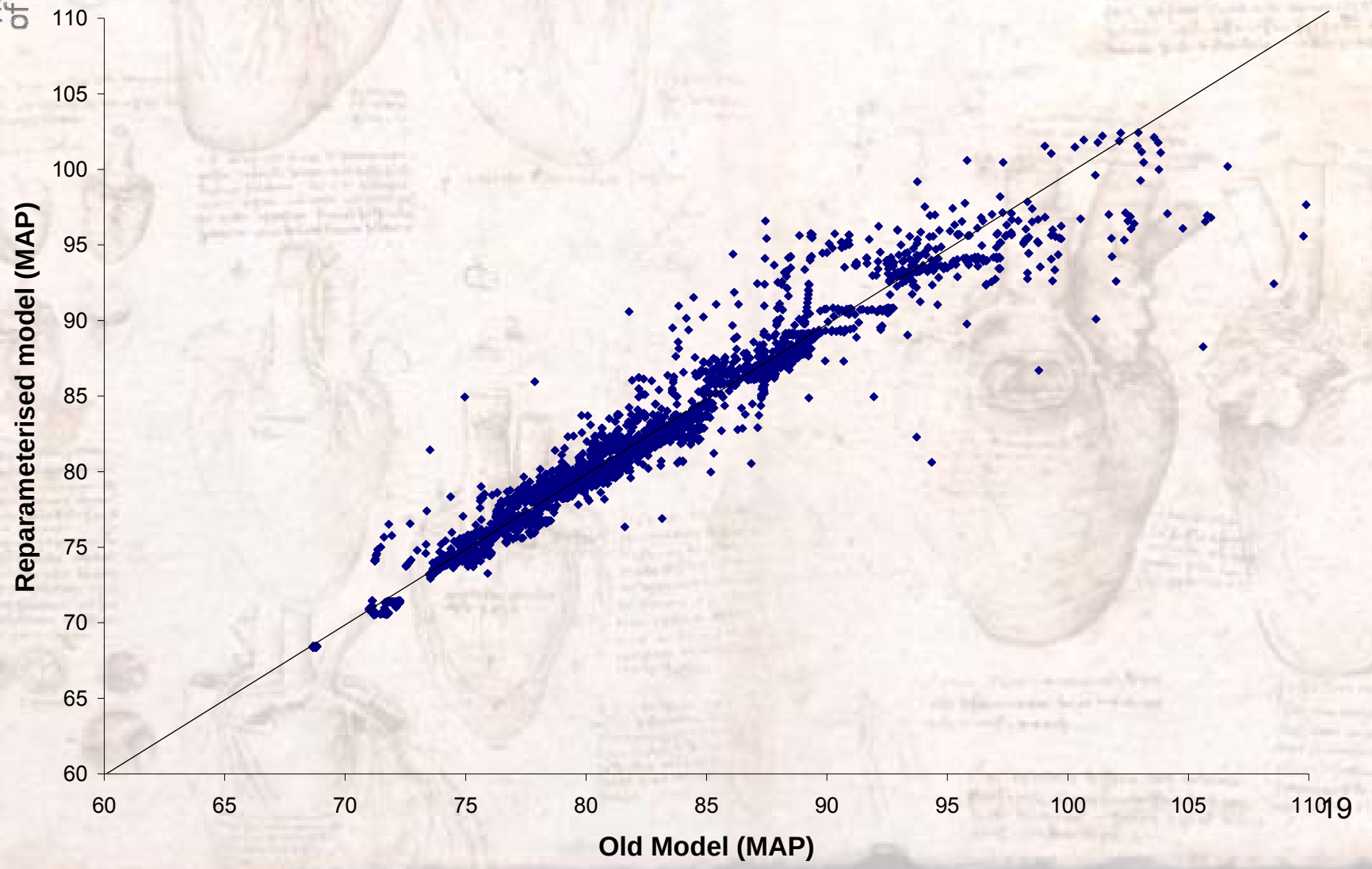
Model Comparison

- Clinical data set analysed in NONMEM using both models
- Some fixed effects were held constant due to old model unidentifiability (*bc* and τ)
- Corresponding fixed effects for reduced parameterisation were also held constant
- Mixed effect modelling demonstrates that the reduced parameterisation still allows the model to behave as richly as the full parameter list

Model Comparison



Model Comparison



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Conclusion

- Structural identifiability analysis has been performed on a nonlinear PK PD model.
- Model was rewritten into polynomial form (with extra state to ensure linear observation)
- Linear transformation considered
- The unidentifiable parameter are: α, β, ac and *bc* and hence model is unidentifiable
- Unidentifiable problem is solved by parameter list reduction of the polynomial model
- Taylor series of the similarity transformation criteria is calculated
- The model was found to be rank deficient by one
- Core PD parameters such as E_{max} and EC_{50} can still be uniquely estimated
- Parameter list reduced model is globally identifiable
- Model fits obtained using the new and old parameterisations confirm the behaviour of the new model is indistinguishable
- In the parameter estimation, we fixed all the time constant due to data restriction

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Remarks

- Globally (unique) identifiability ≠ good fits to experimental data, and good fit to the model only useful if the parameter vector is unique.
- The techniques do not required physical data for the analysis but instead symbolic algebra obtained from the model description are manipulated to seek for the identifiability status.
- Lack of identifiability does implies that for every parameter estimate, there will be at least one alternative parameter existed that fit the data sets equally well. So infinite number of parameter vectors that give the same fit even for perfect data
- If the a model is unidentifiable, infinite sets of parameter will be found and these will cause difficulties in parameter estimation.
- The analysis is carried out with assistance of symbolic computation software MATHEMATICA.
- Limitation will depends on computational power available and skills of analysis
- Structural identifiability analysis is a necessary theoretical prerequisite to experimental design, system identification and parameter estimation.

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Thank you