Automated scale reduction of nonlinear QSP models with an example of a bone biology system

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Quantitative systems pharmacology (QSP) models

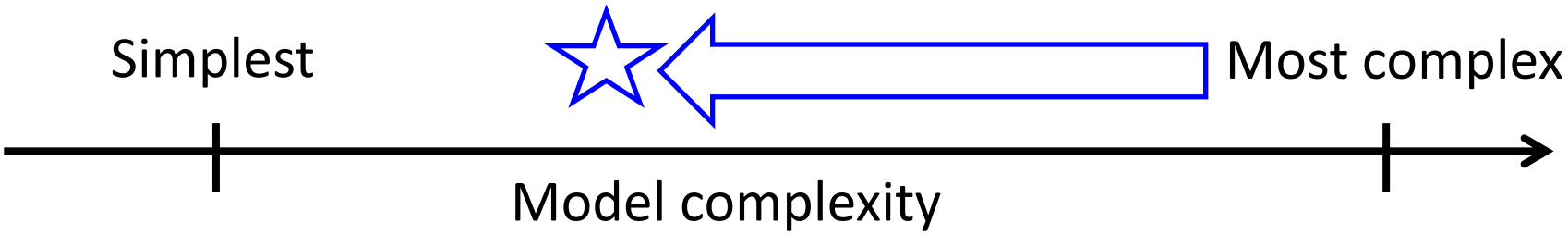
- increasingly used in drug development to:
  - provide a deeper understanding of the mechanism of action of drugs
  - identify appropriate disease targets
  - …
- mathematically complex and may need to be simplified by reducing the scale (size) of the QSP model

Cucurull-Sanchez et al, Drug Discov Today 2012; 17(13-14):665-70
Ribba et al, CPT Pharmacometrics Syst Pharmacol [Epub ahead of print]

Why scale reduction?

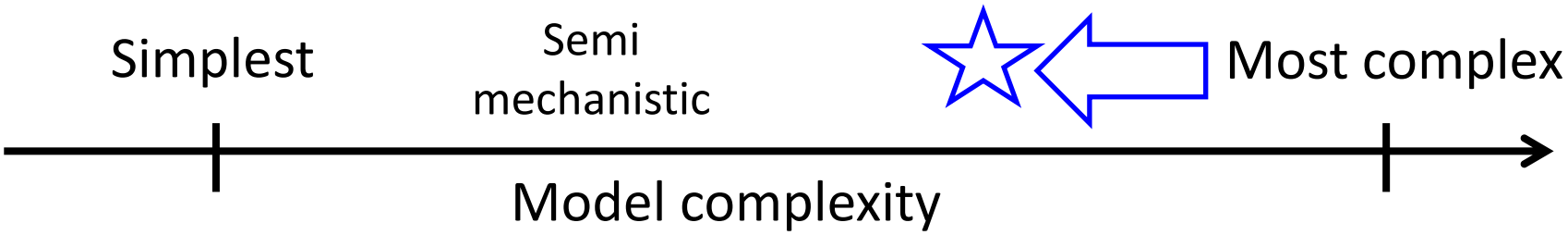
- Semi-mechanistic models can be obtained as a structural model for data-driven (e.g. population) analyses

May have better predictability and extrapolatability than empirical approach

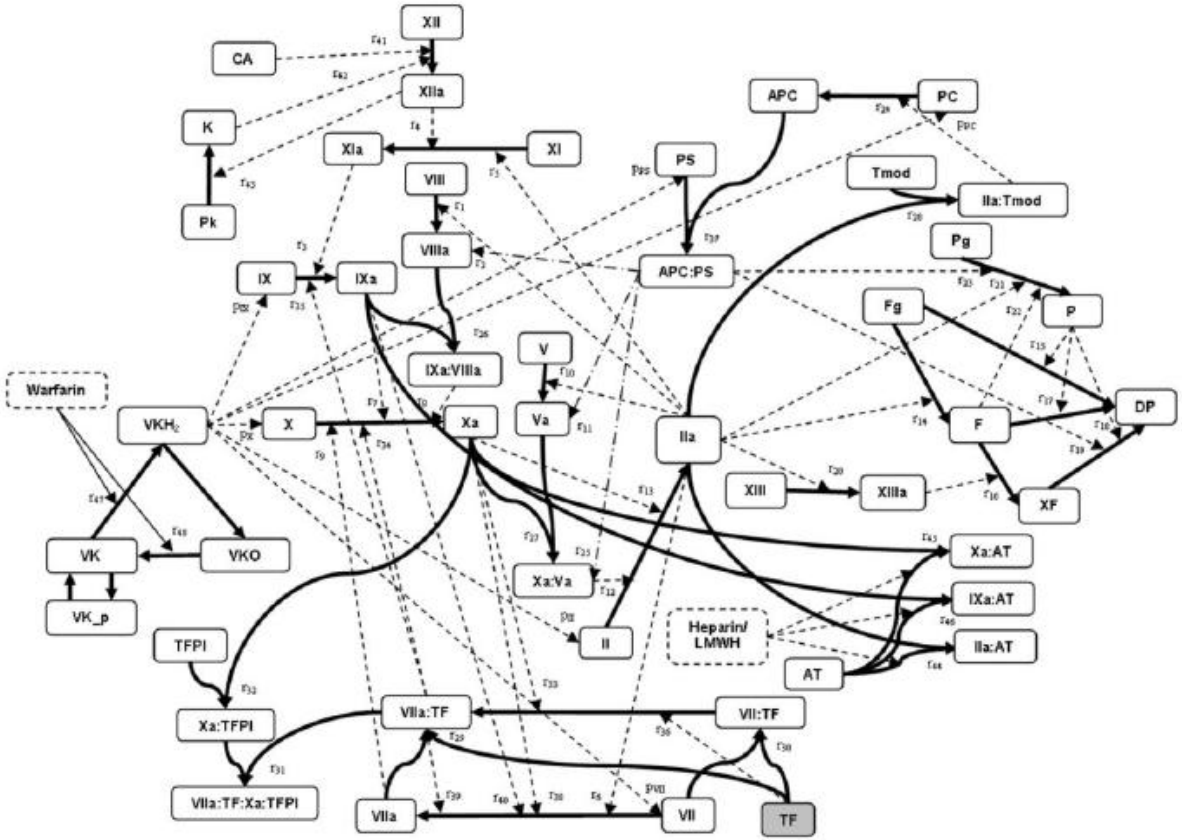


Why scale reduction?

- Semi-mechanistic models can be obtained as a structural model for data-driven (e.g. population) analyses
- Minimal QSP models can be obtained for the same aim of using original QSP models but to more focus on a particular subsystem of interest



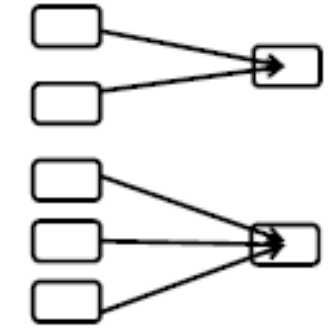
QSP model for coagulation network



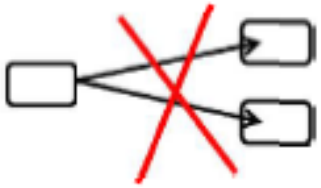
Wajima *et al* Clin Pharmacol Ther 2009

Proper lumping as an existing reduction technique

- A special case of lumping that merges some of the states to only one state



original lumped



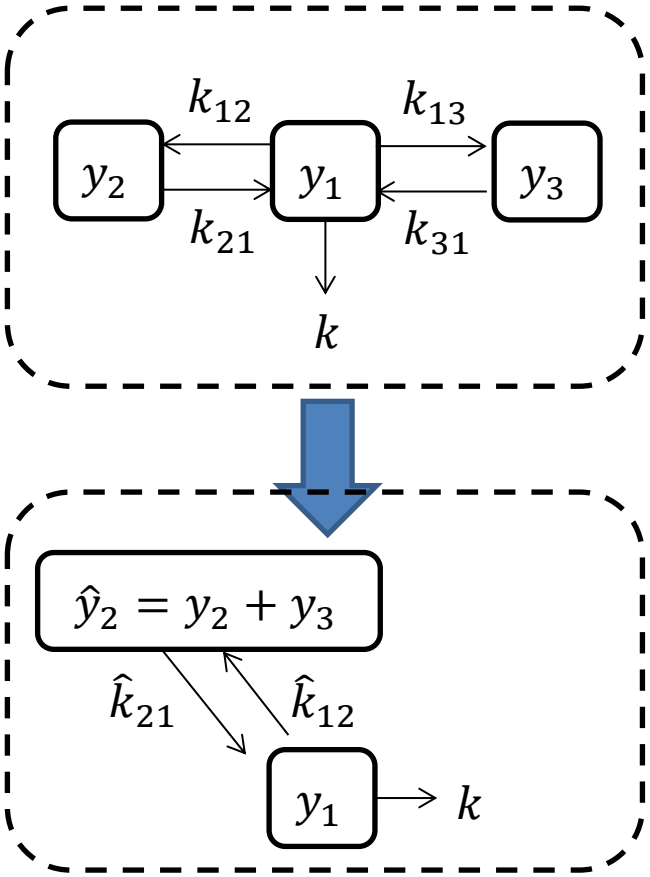
original lumped

- Reduced states after proper lumping are able to retain the physiological meaning as in the original system

An example of proper lumping

Original model (3-compartment) $\frac{d\boldsymbol{y}}{dt} = \boldsymbol{K} \cdot \boldsymbol{y}$

$$\begin{pmatrix} \frac{dy_1}{dt} \\ \frac{dy_2}{dt} \\ \frac{dy_3}{dt} \end{pmatrix} = \begin{pmatrix} -(k + k_{12} + k_{13}) & k_{21} & k_{31} \\ k_{12} & -k_{21} & 0 \\ k_{13} & 0 & -k_{31} \end{pmatrix} \begin{pmatrix} y_1 \\ y_2 \\ y_3 \end{pmatrix}$$



Lumped model (2-compartment) $\frac{d\hat{\boldsymbol{y}}}{dt} = \hat{\boldsymbol{K}} \cdot \hat{\boldsymbol{y}}$

$$\begin{pmatrix} \frac{dy_1}{dt} \\ \frac{d\hat{y}_2}{dt} \end{pmatrix} = \begin{pmatrix} -(k + \hat{k}_{12}) & \hat{k}_{21} \\ \hat{k}_{12} & -\hat{k}_{21} \end{pmatrix} \begin{pmatrix} y_1 \\ \hat{y}_2 \end{pmatrix}$$

How are lumped parameters ($\hat{K}$) derived?

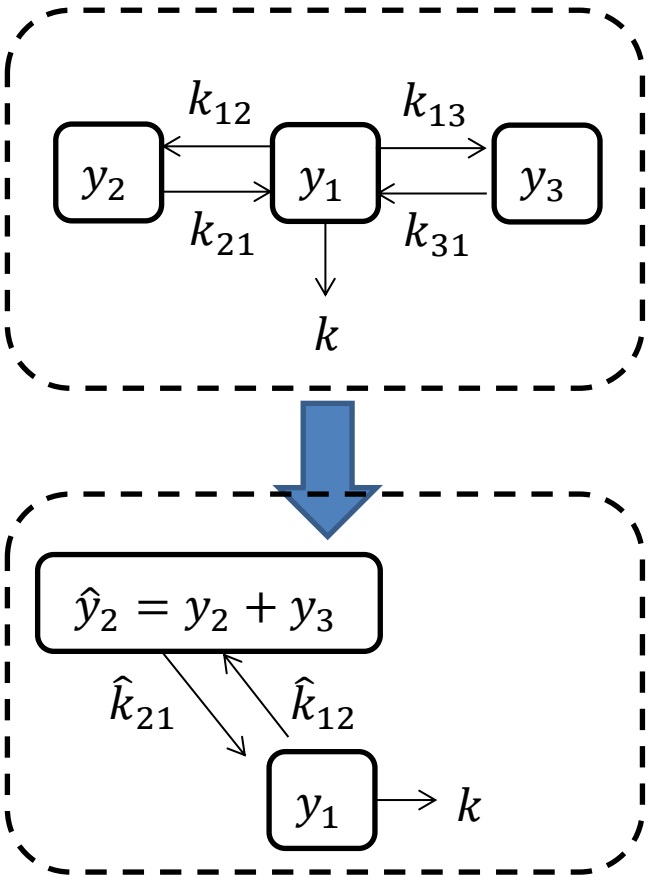
By a lumping formula using lumping matrix (L),

$$\hat{K} = L \cdot K \cdot L^{+} \quad (1)$$

(L^{+}: pseudo inverse of L)

where

$$\hat{y} = L \cdot y = \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 1 \end{pmatrix} \cdot \begin{pmatrix} y_1 \\ y_2 \\ y_3 \end{pmatrix} \quad (2)$$



Lumped model (2-compartment) $\frac{d\hat{y}}{dt} = \hat{K} \cdot \hat{y}$

$$\begin{pmatrix} \frac{dy_1}{dt} \\ \frac{d\hat{y}_2}{dt} \end{pmatrix} = \begin{pmatrix} -(k + \hat{k}_{12}) & \hat{k}_{21} \\ \hat{k}_{12} & -\hat{k}_{21} \end{pmatrix} \begin{pmatrix} y_1 \\ \hat{y}_2 \end{pmatrix}$$

Important feature of proper lumping

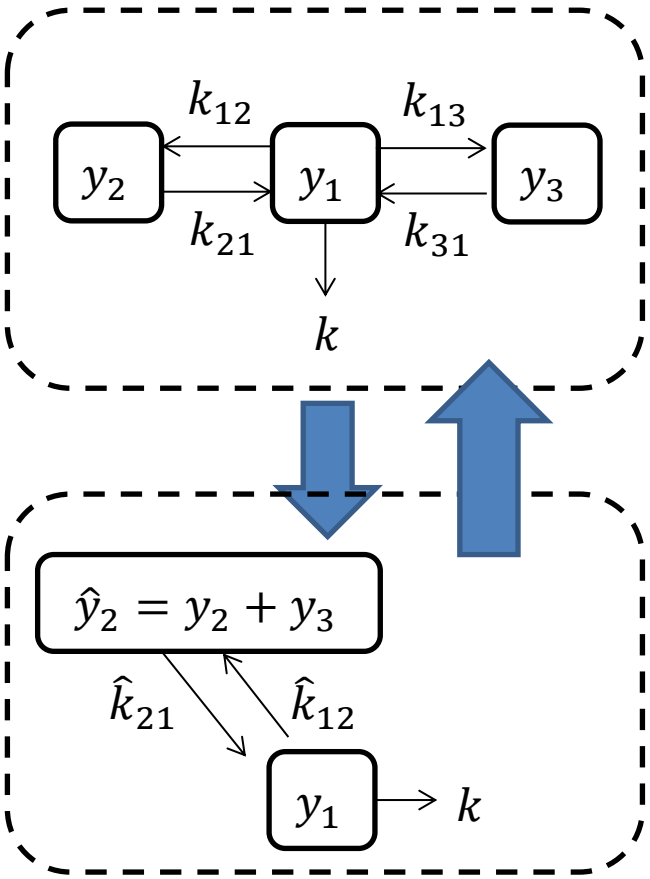
By a lumping formula using lumping matrix ($\boldsymbol{L}$),

$$\hat{\boldsymbol{K}} = \boldsymbol{L} \cdot \boldsymbol{K} \cdot \boldsymbol{L}^{+} \qquad (1)$$

($\boldsymbol{L}^{+}$: pseudo inverse of $\boldsymbol{L}$)

where

$$\hat{\boldsymbol{y}} = \boldsymbol{L} \cdot \boldsymbol{y} \quad \leftrightarrow \quad \boldsymbol{y} = \boldsymbol{L}^{+} \cdot \hat{\boldsymbol{y}} \qquad (2)$$



Lumped model (2-compartment) $\dfrac{d\hat{\boldsymbol{y}}}{dt} = \hat{\boldsymbol{K}} \cdot \hat{\boldsymbol{y}}$

$$\begin{pmatrix} \frac{dy_1}{dt} \\ \frac{d\hat{y}_2}{dt} \end{pmatrix} = \begin{pmatrix} -(k + \hat{k}_{12}) & \hat{k}_{21} \\ \hat{k}_{12} & -\hat{k}_{21} \end{pmatrix} \begin{pmatrix} y_1 \\ \hat{y}_2 \end{pmatrix}$$

How are lumped parameters ($\widehat{\boldsymbol{K}}$) derived?

By a lumping formula using lumping matrix ($\boldsymbol{L}$),

$$\widehat{\boldsymbol{K}} = \boldsymbol{L} \cdot \boldsymbol{K} \cdot \boldsymbol{L}^{+}$$

$$= \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 1 \end{pmatrix} \cdot \begin{pmatrix} -(k + k_{12} + k_{13}) & k_{21} & k_{31} \\ k_{12} & -k_{21} & 0 \\ k_{13} & 0 & -k_{31} \end{pmatrix} \cdot \begin{pmatrix} 1 & 0 \\ 0 & 1/2 \\ 0 & 1/2 \end{pmatrix}$$

$$= \begin{pmatrix} -(k + k_{12} + k_{13}) & \dfrac{k_{21} + k_{31}}{2} \\ k_{12} + k_{13} & -\dfrac{k_{21} + k_{31}}{2} \end{pmatrix}$$

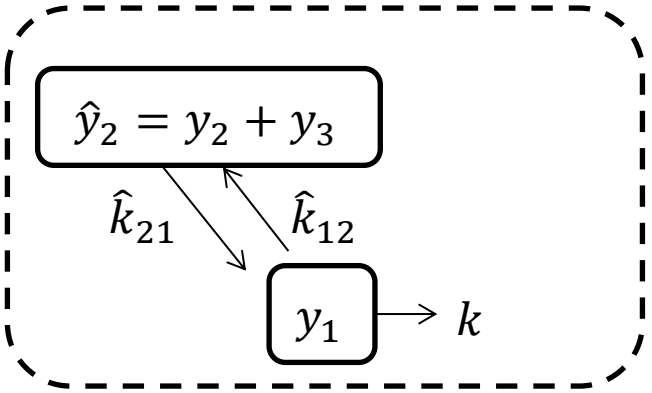
✓

$$\hat{k}_{12} = k_{12} + k_{13}$$

$$\hat{k}_{21} = \frac{k_{21} + k_{31}}{2}$$

Lumped model

$$\begin{pmatrix} \dfrac{dy_1}{dt} \\ \dfrac{d\hat{y}_2}{dt} \end{pmatrix} = \begin{pmatrix} -(k + \hat{k}_{12}) & \hat{k}_{21} \\ \hat{k}_{12} & -\hat{k}_{21} \end{pmatrix} \begin{pmatrix} y_1 \\ \hat{y}_2 \end{pmatrix}$$



Any issues on scale reduction?

- Proper lumping can be fully applied for only linear ODEs which are uncommon in QSP models
  - Lumped parameters ($\widehat{\boldsymbol{K}}$) cannot be derived for nonlinear ODEs since the original parameters ($\boldsymbol{K}$) include responses ($\boldsymbol{y}$) which are unknown before solving ODEs

    e.g. Michaelis-Menten function

- No comprehensive criteria for choosing a final reduced model
  - Impede automating the process

Contents of talk

1. Simplification of a nonlinear QSP model by inductively linearizing the system followed by automated lumping based on a composite criterion

   – with an example of a systems bone biology model consisting of 28 states

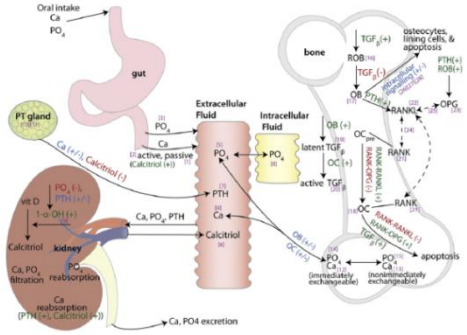
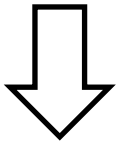


Figure 1 of Peterson and Riggs, 2010

2. The reduced model will then be utilized to extrapolate long-term bone mineral density responses

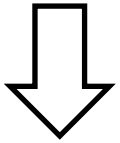
Process to get a final reduced model

Original nonlinear bone biology model



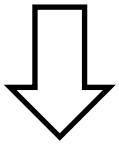
Inductive approximation

Linearized bone biology model



Proper lumping using a composite criterion

Reduced bone biology model

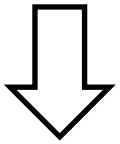


Identifiability analyses

Final reduced bone biology model

Process to get a final reduced model

Original nonlinear bone biology model



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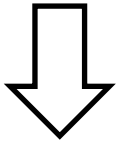
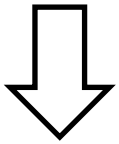
Linearized bone biology model



Proper lumping using a composite criterion

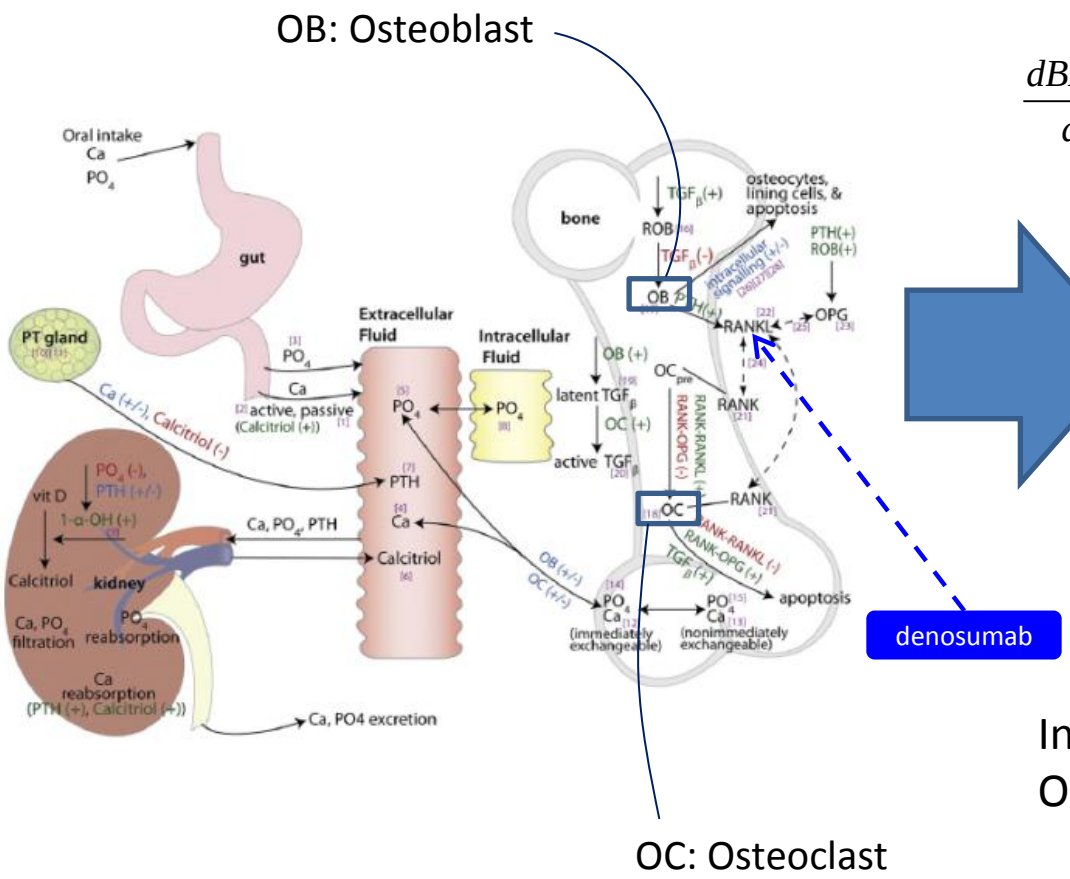
Reduced bone biology model



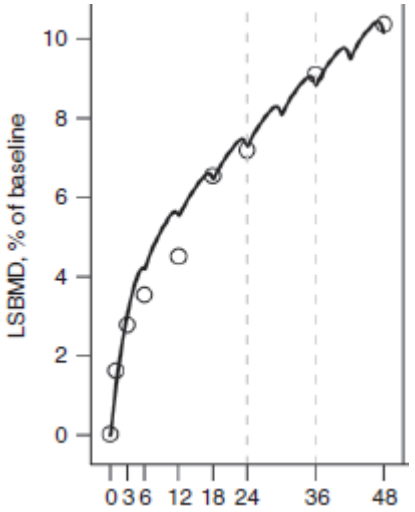
Identifiability analyses

Final reduced bone biology model

Original nonlinear bone biology model



$$\frac{dBMD}{dt} = R_{in} \cdot \left(\frac{OB}{OB_0}\right)^{\gamma_{OB}} - k_{out} \cdot \left(\frac{OC}{OC_0}\right)^{\gamma_{OC}} \cdot BMD$$



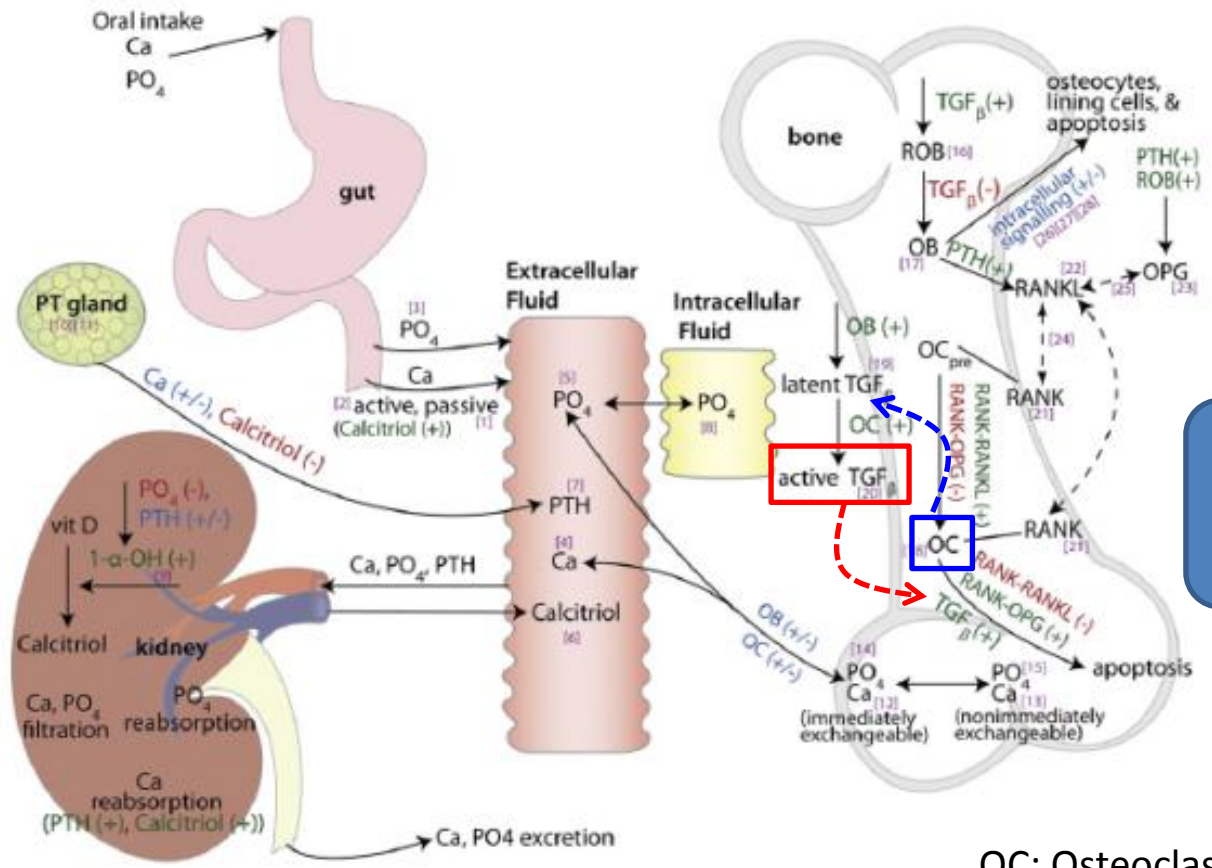
Input: denosumab (RANKL inhibitor)
Output: bone mineral density (BMD)

Peterson MC et al., Bone. 2010; 46:49-63
Peterson MC et al, CPT Pharmacometrics Syst Pharmacol. 2012; 1:e14

otago pharmacometrics

UNIVERSITY of OTAGO
Te Whare Wānanga o Otāgo
NEW ZEALAND

Original **nonlinear** bone biology model



Nonlinear feedback

OC: Osteoclast

Peterson MC et al., Bone. 2010; 46:49-63

Inductive approximation

- generates solutions to nonlinear systems via iteration

Original nonlinear

$$\frac{d\boldsymbol{y}}{dt} = \boldsymbol{f}(t, \boldsymbol{y}) + \boldsymbol{A}(t, \boldsymbol{y})\boldsymbol{y}$$

"Unknown" before solving the ODE

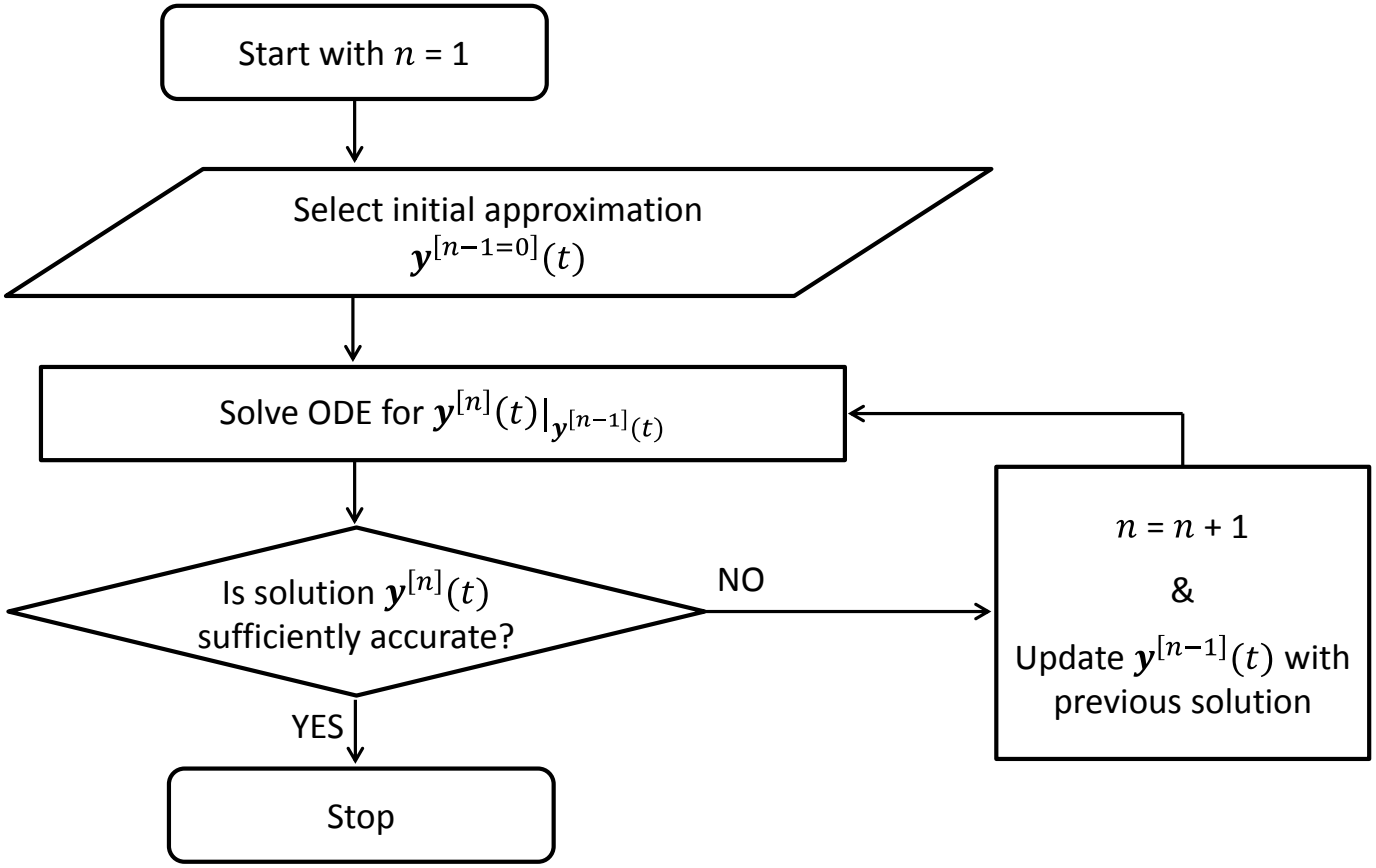
Inductively linearize starting with $y^{[0]} = y_{initial}$

Linearized via *n*-times iteration

$$\frac{d\boldsymbol{y}^{[n]}}{dt} = \boldsymbol{f}(t, \boldsymbol{y}^{[n-1]}) + \boldsymbol{A}(t, \boldsymbol{y}^{[n-1]})\boldsymbol{y}^{[n]}$$

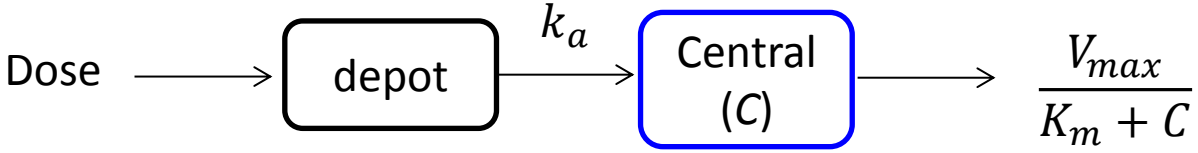
"Known" quantity (just a number)

Flow chart to apply for the inductive linearization



Hasegawa C et al., J Pharmacokinet Pharmacodyn. 2017 [Epub ahead of print]

An example of inductive approximation

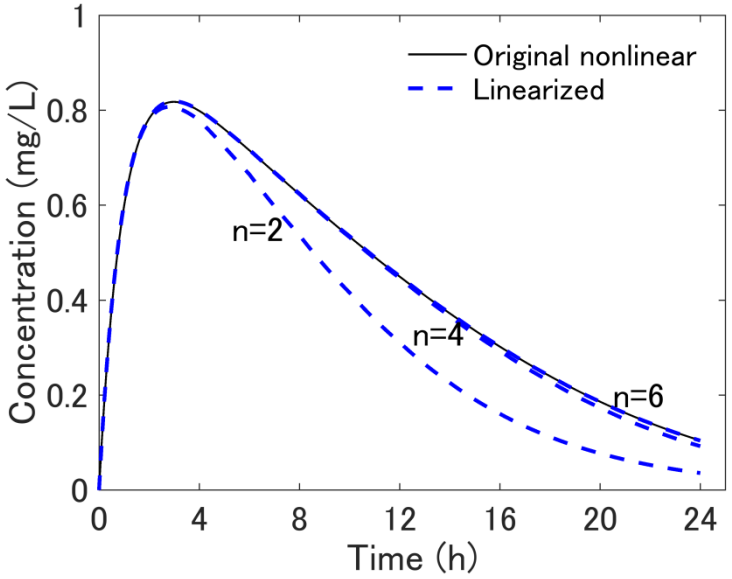


Original nonlinear

$$\frac{dC}{dt} = f(k_a, Dose, t) - \frac{V_{max}}{K_m + C} \cdot C$$

Linearised

$$\frac{dC^{[n]}}{dt} = f(k_a, Dose, t) - \frac{V_{max}}{K_m + C^{[n-1]}} \cdot C^{[n]}$$

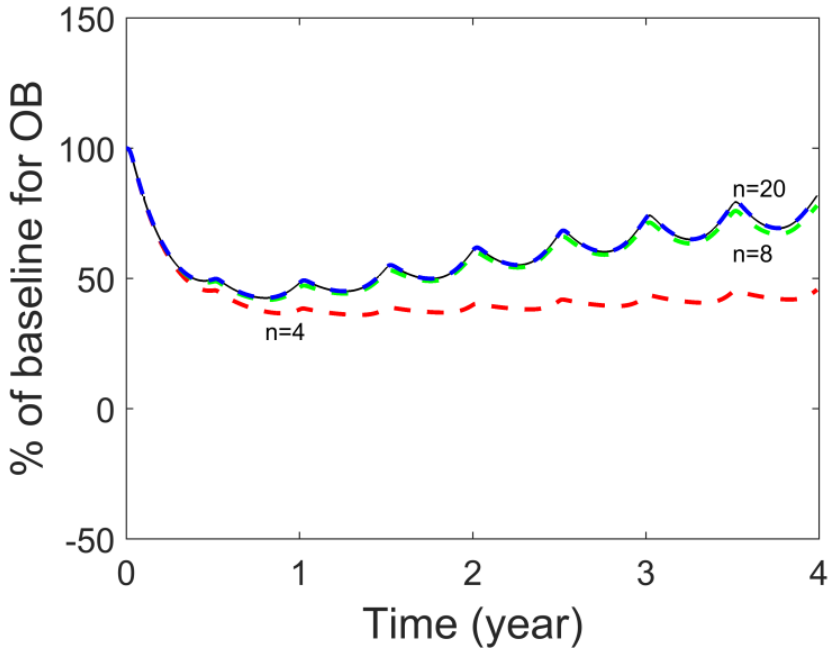


n: number of iterations in inductive linearization

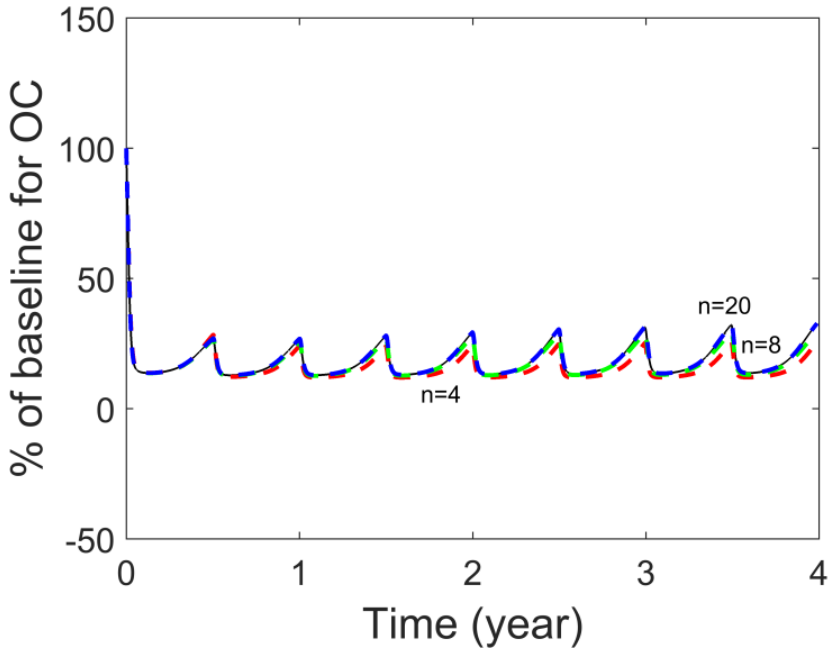
Hasegawa C et al., J Pharmacokinet Pharmacodyn. 2017 [Epub ahead of print]

Linearization results for bone biology model after dosing denosumab every 6 months (Q6W)

OB (osteoblast)

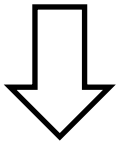


OC (osteoclast)



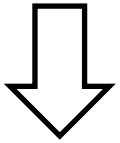
Process to get a final reduced model

Original nonlinear bone biology model



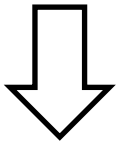
Inductive approximation

Linearized bone biology model



Proper lumping using a composite criterion

Reduced bone biology model



Identifiability analyses

Final reduced bone biology model

Composite criterion (*CC*)

$$CC = \alpha \cdot T_1(m) + (1 - \alpha) \cdot T_2(m)$$

Performance

Penalty for complexity

α: weighting factor

$(m_0 \leq m \leq M)$

Hasegawa C et al., AAPS J. 2017; 20:2

Composite criterion (*CC*)

$$CC = \alpha \cdot T_1(m) + (1 - \alpha) \cdot T_2(m)$$

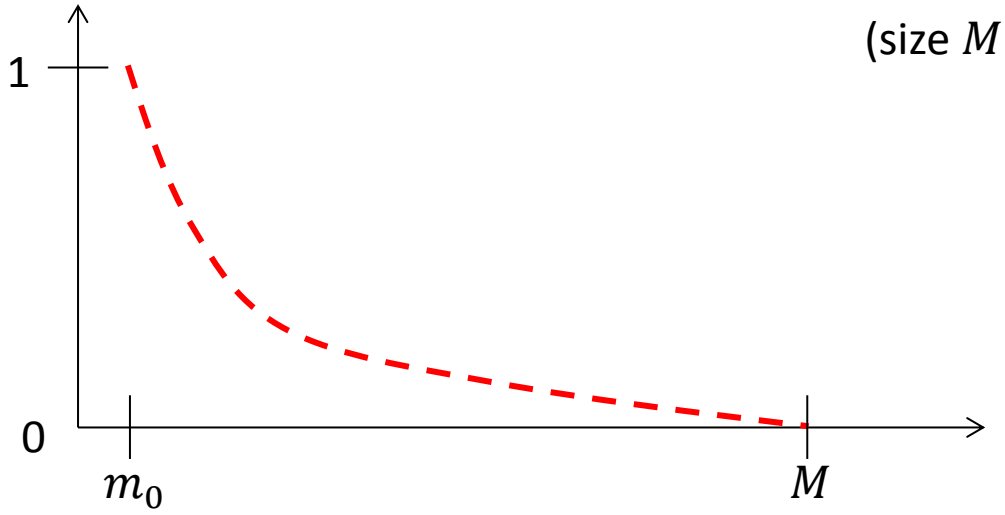
Performance

α: weighting factor

$(m_0 \leq m \leq M)$

$$T_1(m) = \frac{SS(m) - SS(M)}{SS(m_0) - SS(M)}$$

SS: sum of squared differences between predictions from the original (size M) and reduced (size m) models



Composite criterion (*CC*)

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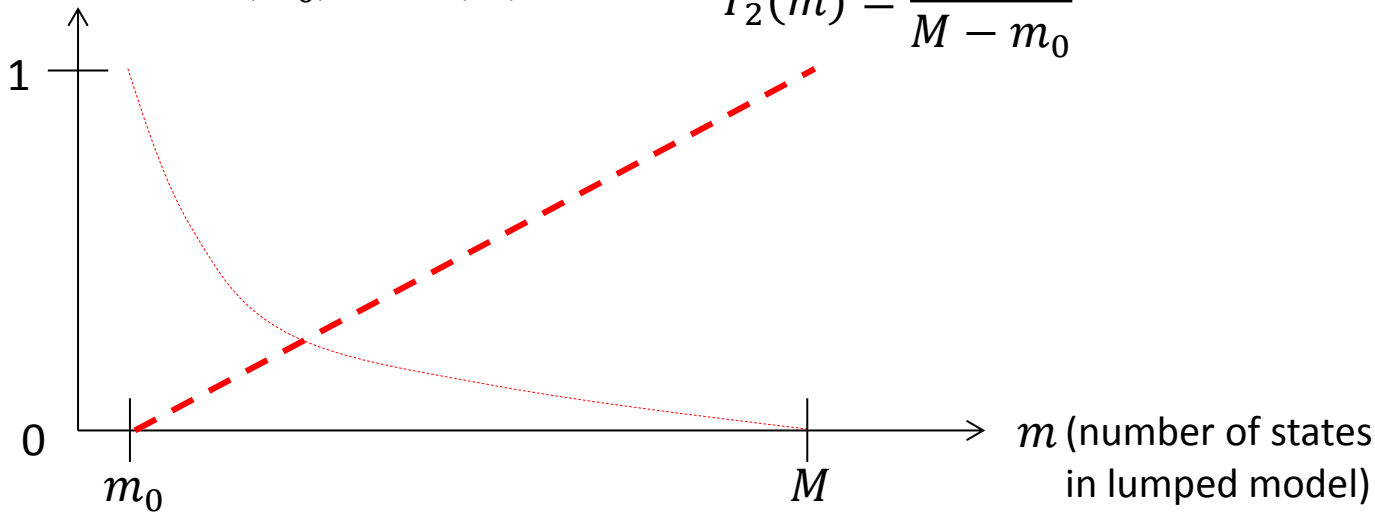
$$T_2(m) = \frac{m - m_0}{M - m_0}$$



Hasegawa C et al., AAPS J. 2017; 20:2

Composite criterion (*CC*)

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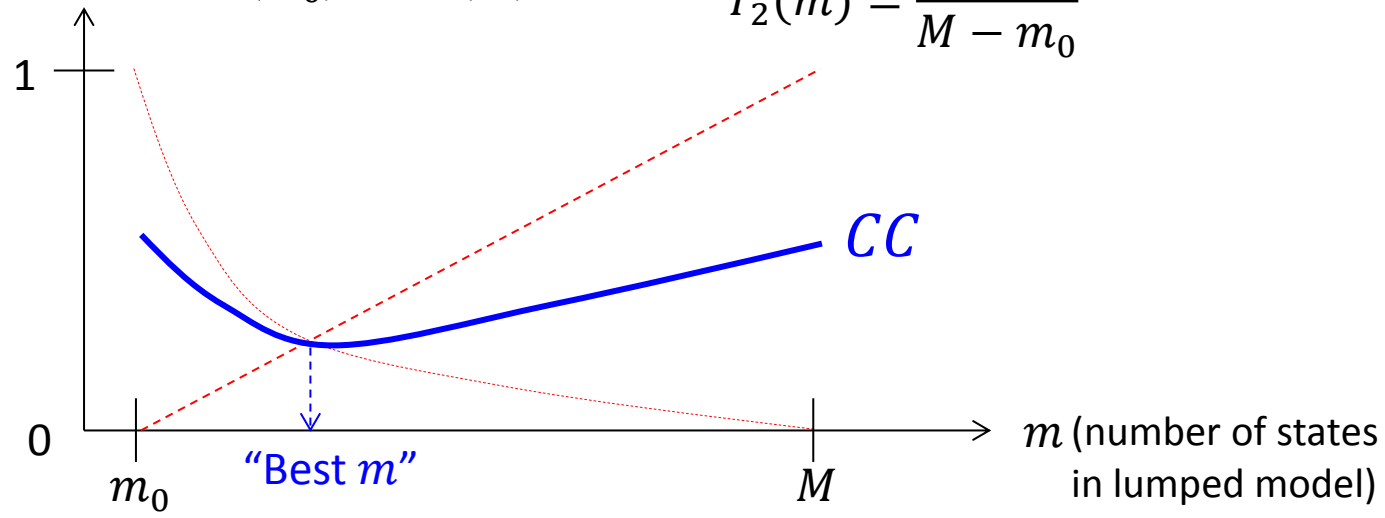


Hasegawa C et al., AAPS J. 2017; 20:2

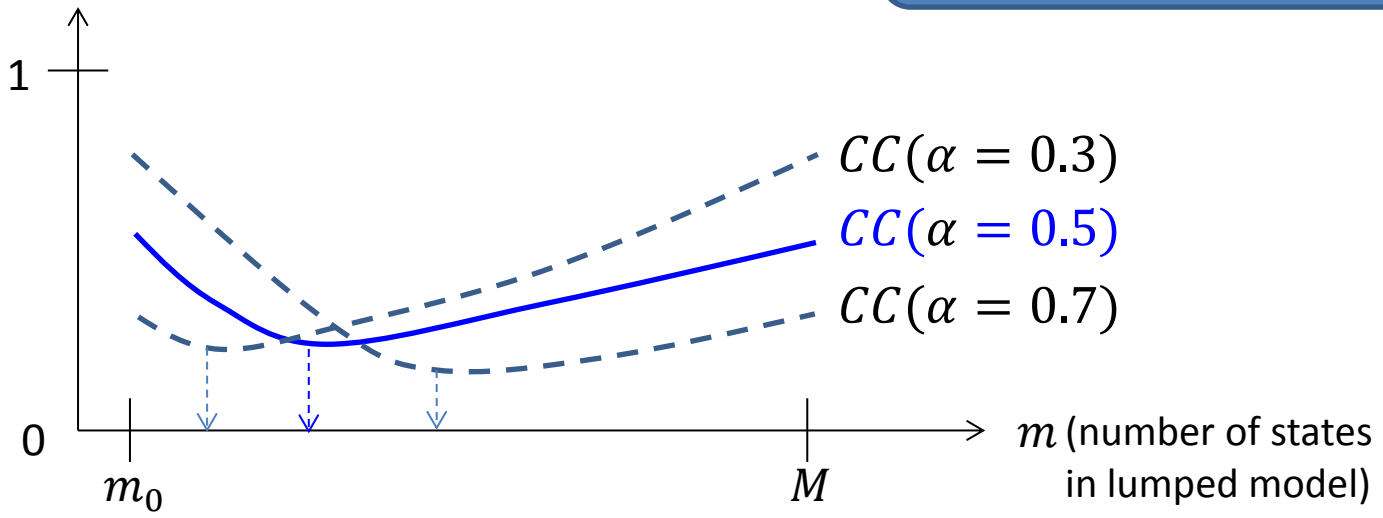
How to determine a weighting factor?

$$CC = \alpha \cdot T_1(m) + (1-\alpha) \cdot T_2(m)$$

α: weighting factor

$0 \leq \alpha \leq 1$

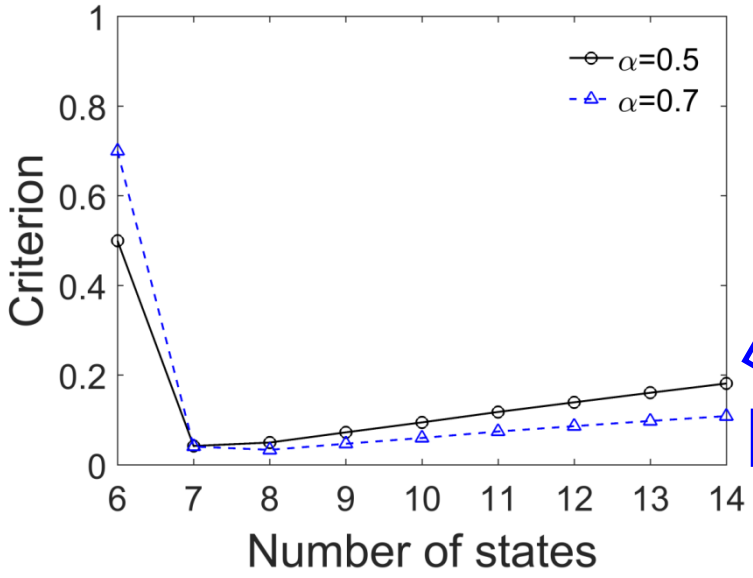
Chosen based on VPC with parameter value uncertainty



Hasegawa C et al., AAPS J. 2017; 20:2

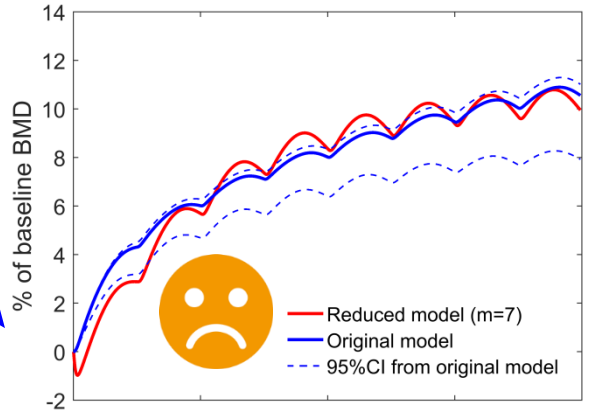
Scale reduction results for bone biology model

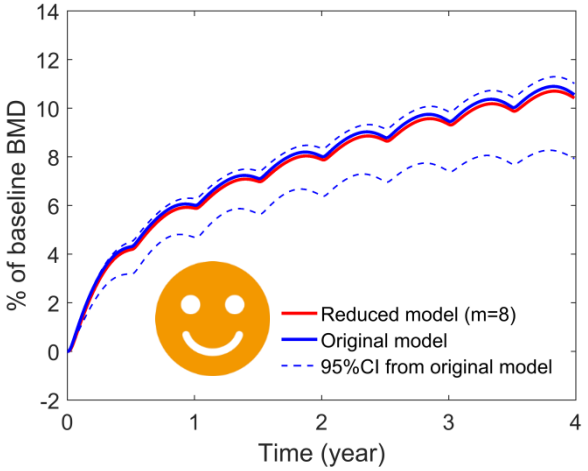
BMD: bone mineral density



7-state

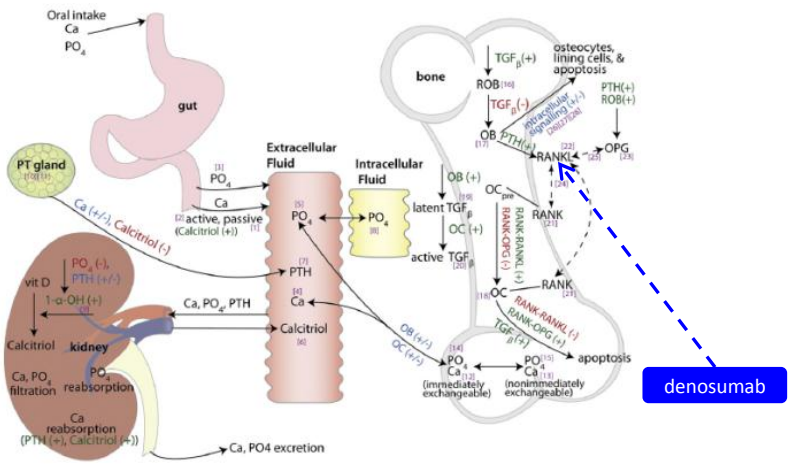
8-state





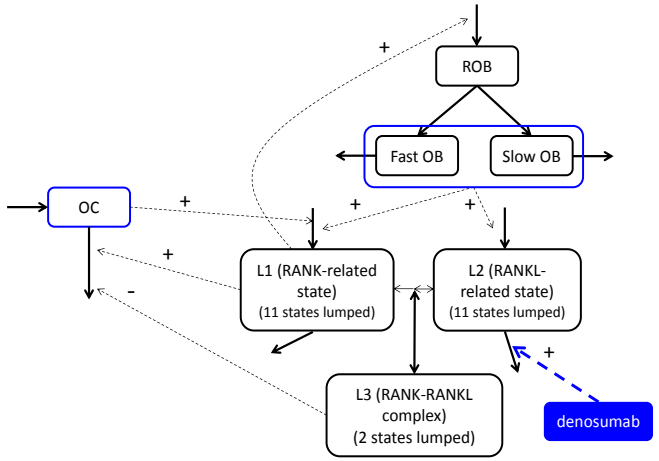
Schematic representation of reduced models

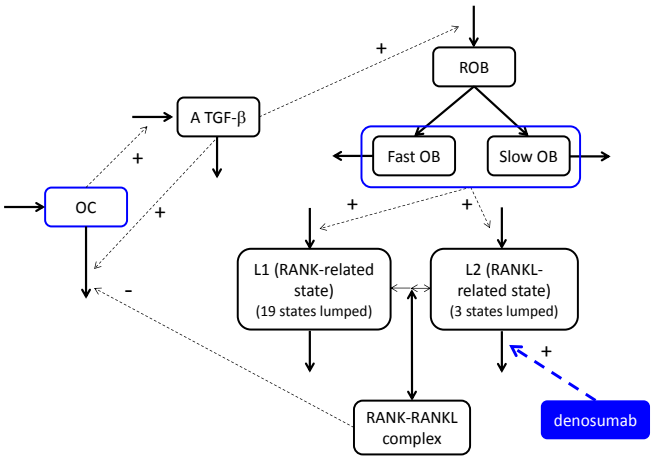
Original 28-state model



7-state

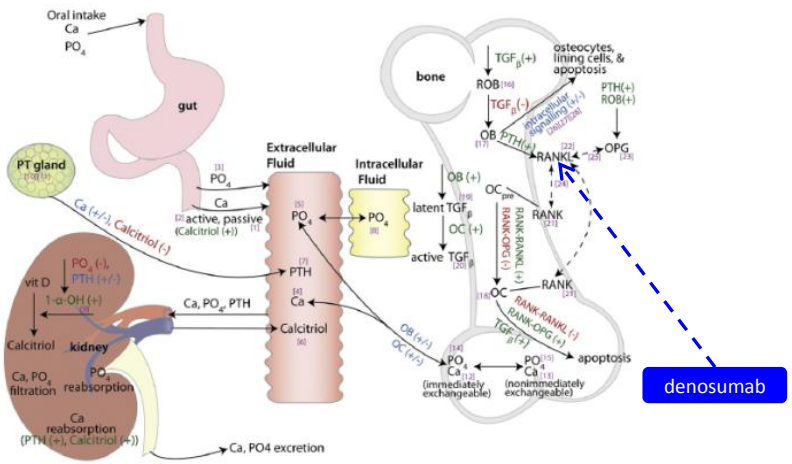
8-state





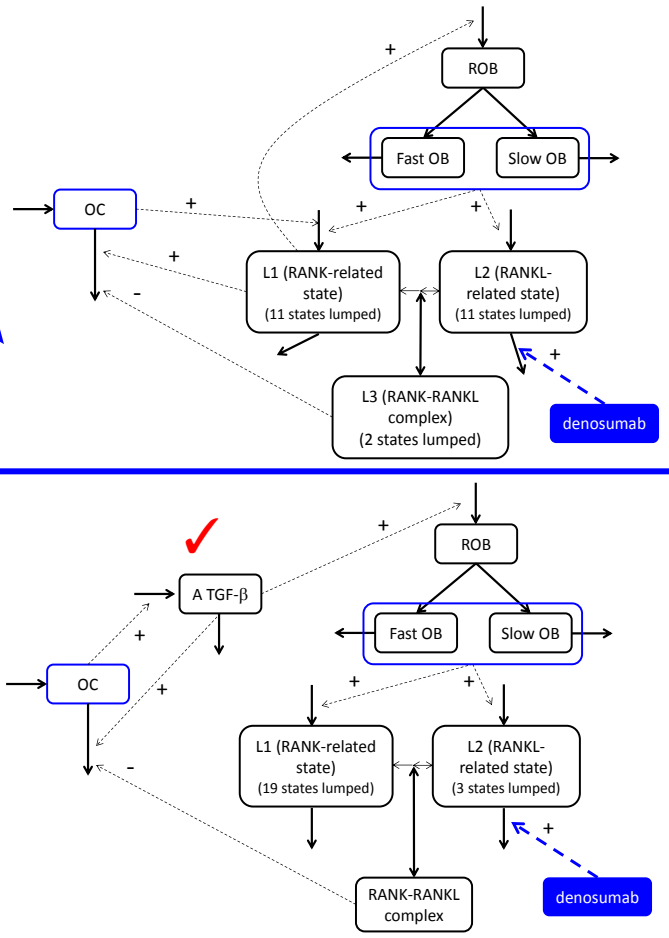
Schematic representation of reduced models

Original 28-state model



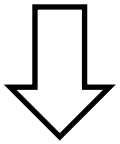
7-state

8-state



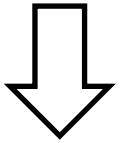
Process to get a final reduced model

Original nonlinear bone biology model



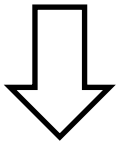
Inductive approximation

Linearized bone biology model



Proper lumping using a composite criterion

Reduced bone biology model



Identifiability analyses

Final reduced bone biology model

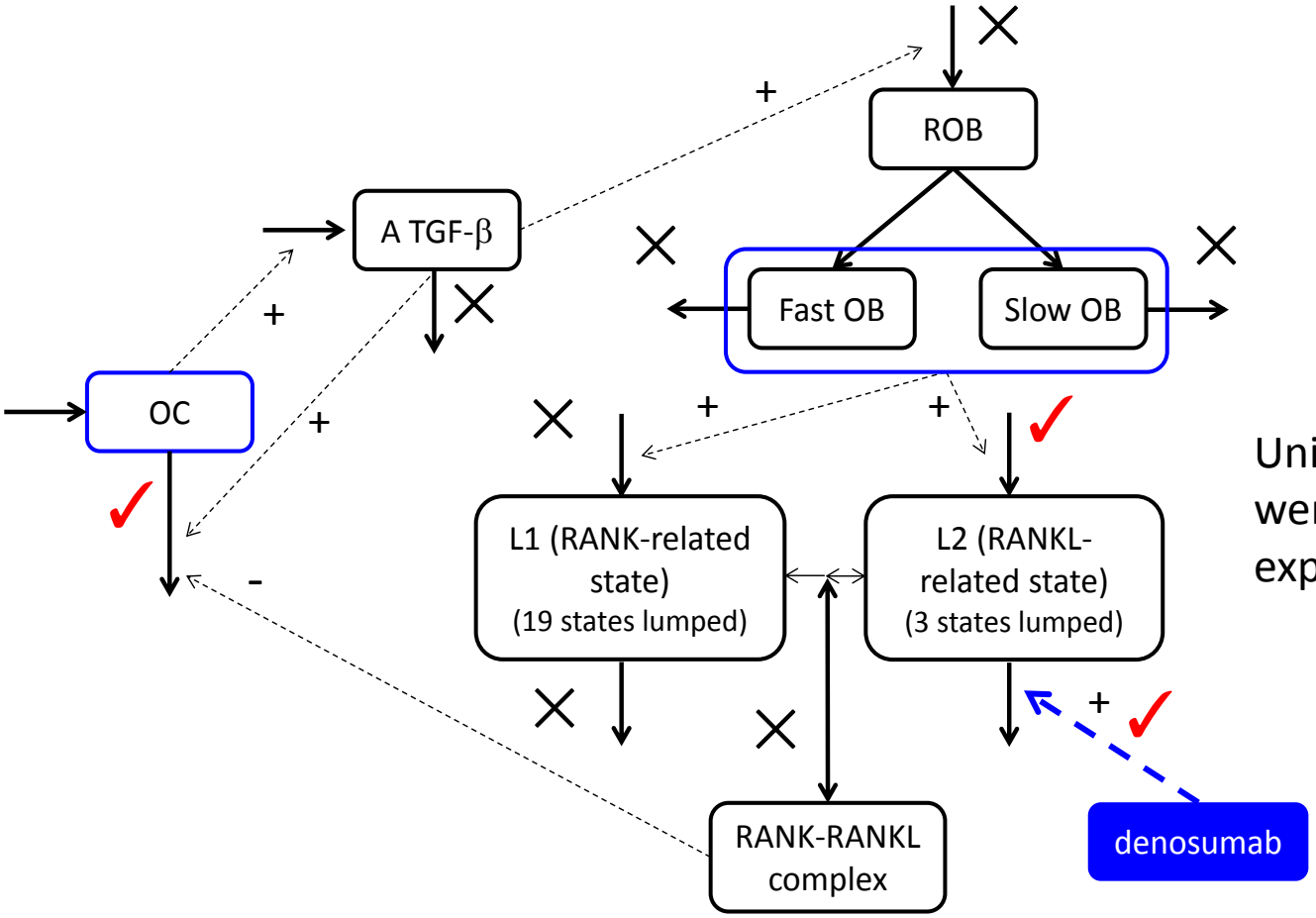
Identifiability analyses

- performed using an information approach which assessed structural and deterministic identifiability.

Shivva V et al., CPT Pharmacomet Syst Pharmacol. 2013; 2:e49

- In addition, an informal heuristic approach was used to assess whether further parameters could be estimated by using a sensitivity analysis.
  - performed through parameter estimation using published BMD data (shown later), in which each parameter was assessed for its influence on the OFV (objective function value) of NONMEM univariately.

Final reduced bone biology model

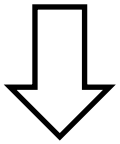


✓ : identifiable
× : unidentifiable

Unidentifiable parameters were fixed for later exploration.

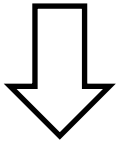
Process to get a final reduced model

Original nonlinear bone biology model



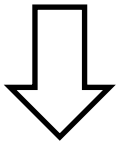
Inductive approximation

Linearized bone biology model



Proper lumping using a composite criterion

Reduced bone biology model



Identifiability analyses

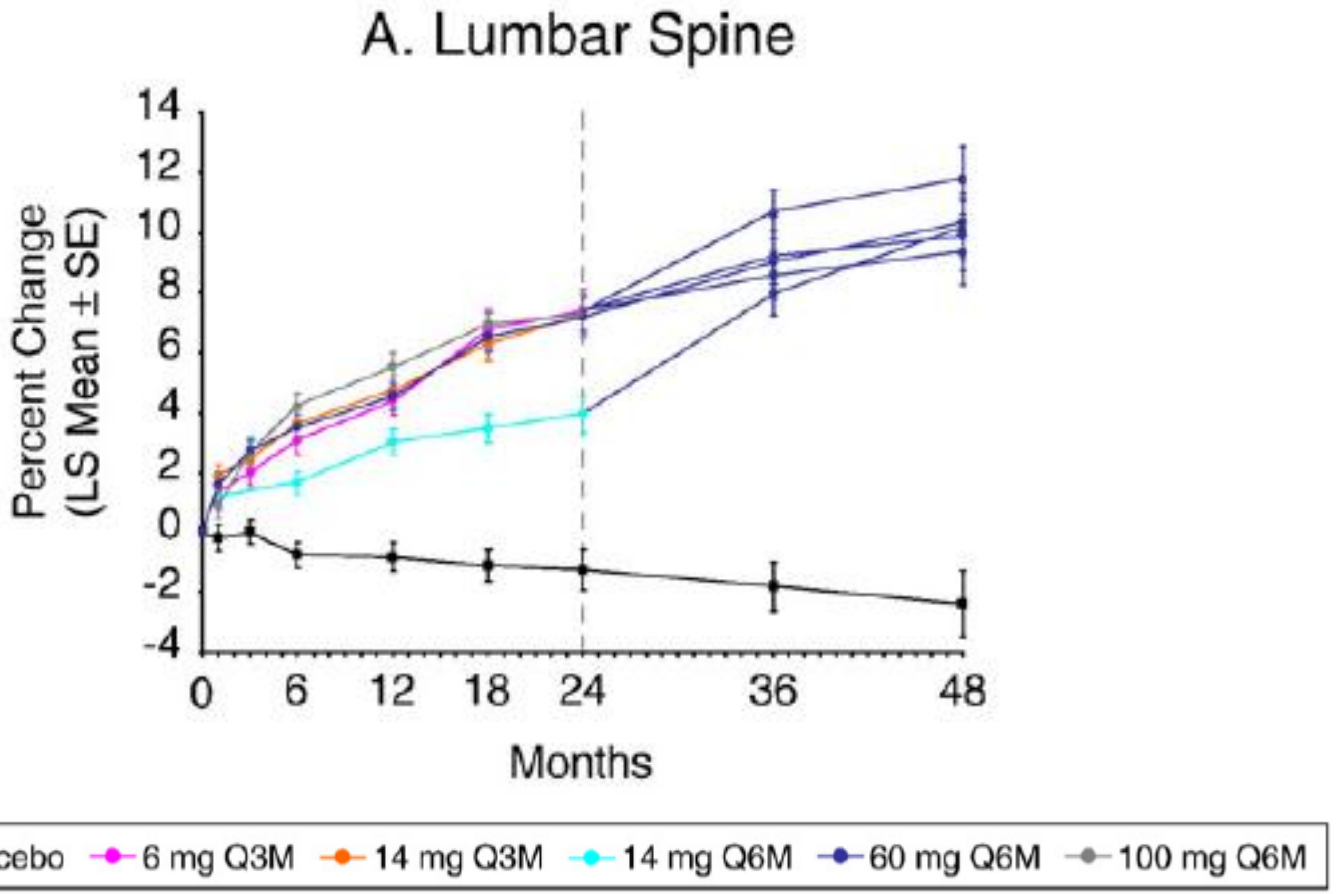
Final reduced bone biology model

Contents of talk

1. Simplification of a nonlinear QSP model by inductively linearizing the system followed by automated lumping based on a composite criterion
   - with an example of a systems bone biology model consisting of 28 states

2. The reduced model will then be utilized to extrapolate long-term bone mineral density responses

The BMD data from denosumab phase 2 study

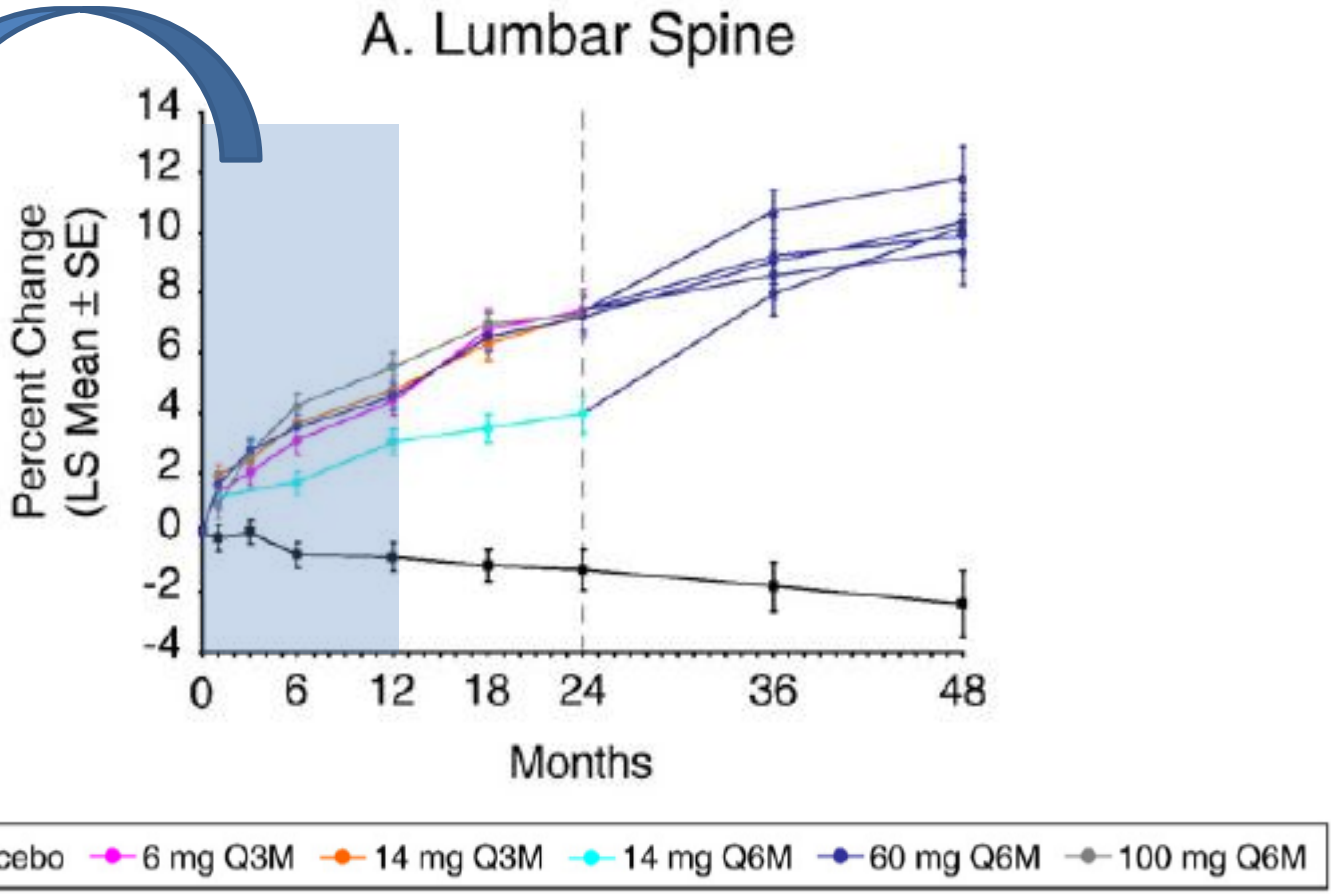


Miller PD et al., Bone. 2008; 43:222-9.

Fitting with 1-year training dataset

Fitting

- Reduced model
- Two Empirical models



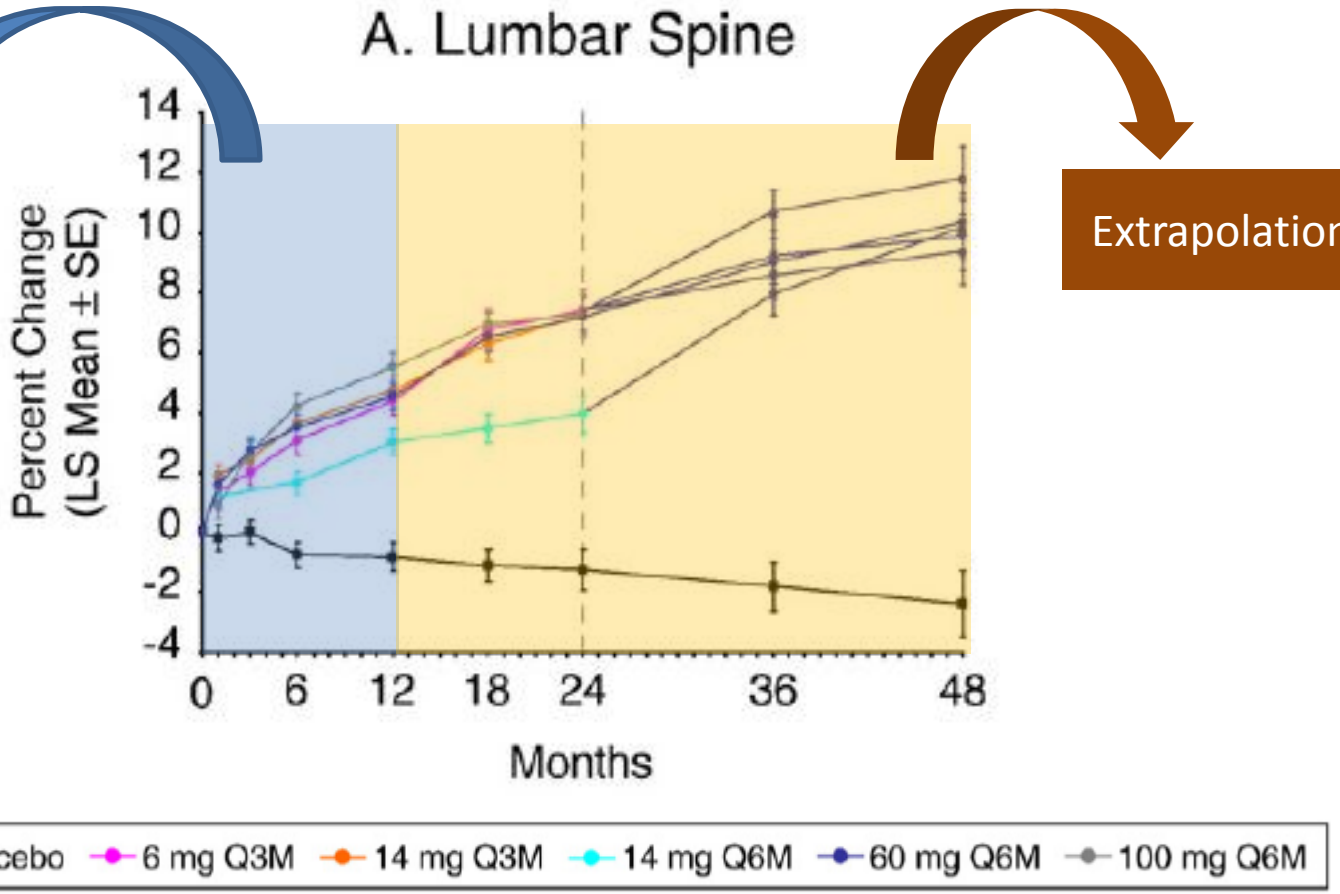
Miller PD et al., Bone. 2008; 43:222-9.

Extrapolation over 1 year

Fitting

Extrapolation

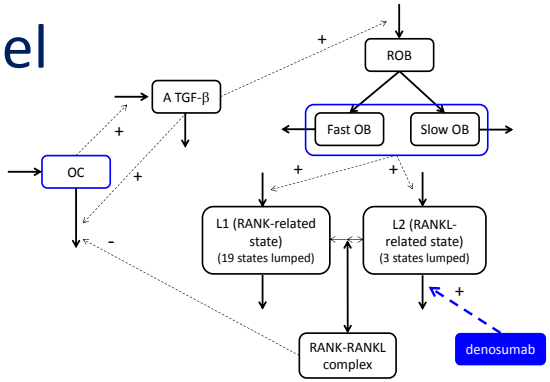
- Reduced model
- Two Empirical models



Miller PD et al., Bone. 2008; 43:222-9.

Applied three models

- Reduced model



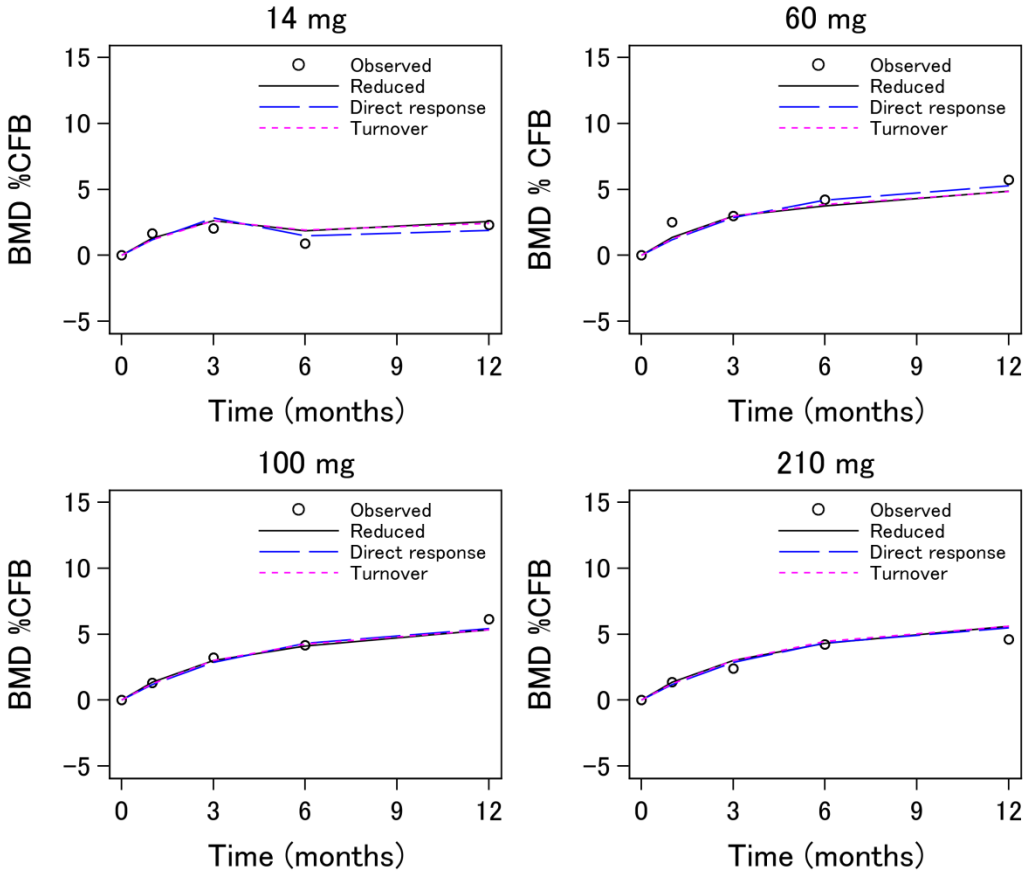
- Two empirical models (Direct response model, Turnover model)

$$\%\Delta BMD = Emax(t) \cdot \frac{C}{C50 + C} \qquad Emax(t) = Emax \cdot (1 - \exp(-kt))$$

C: denosumab concentration

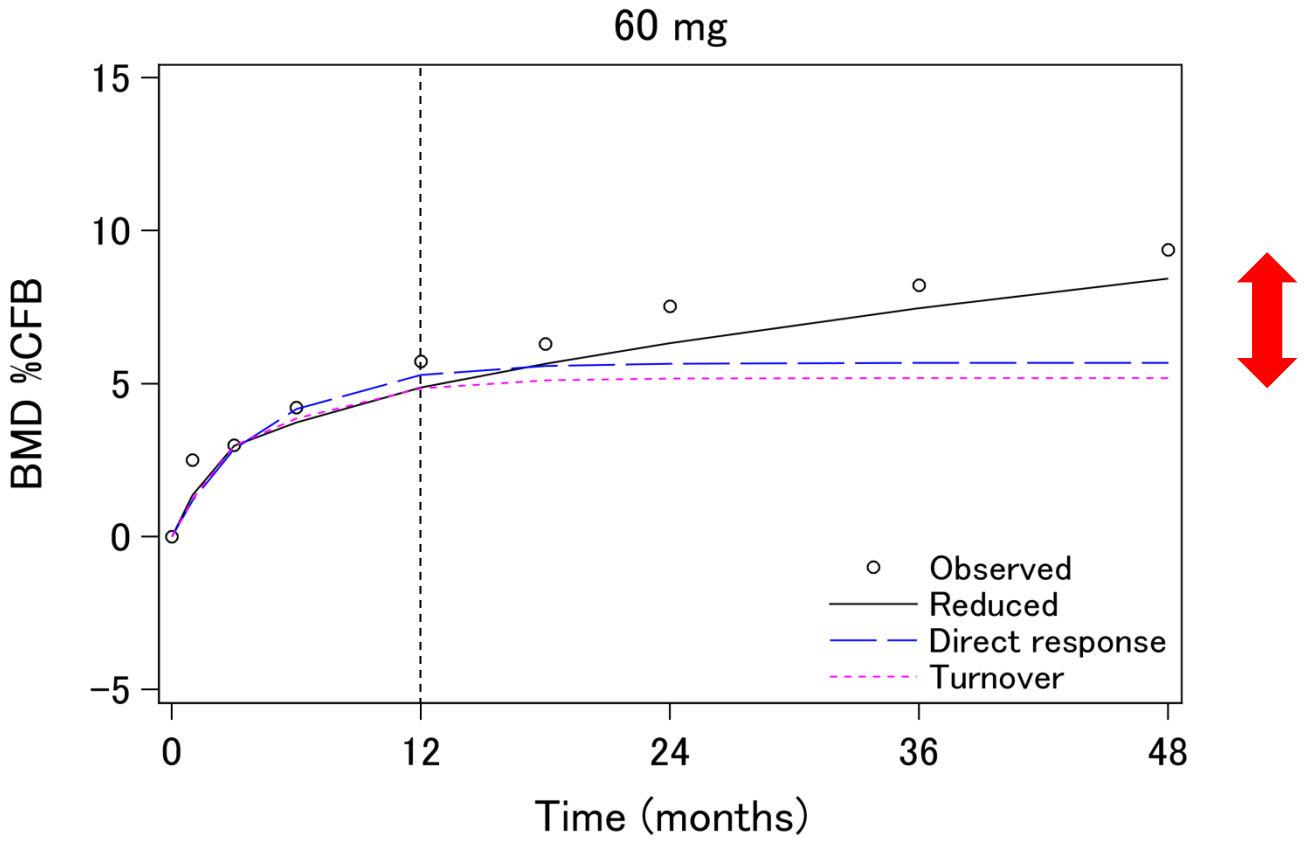
$$\frac{dBMD}{dt} = R_{in} - k_{out} \cdot \left(1 - I_{max} \cdot \frac{C}{C_{50} + C}\right) \cdot BMD$$

Fitting results for 1 year

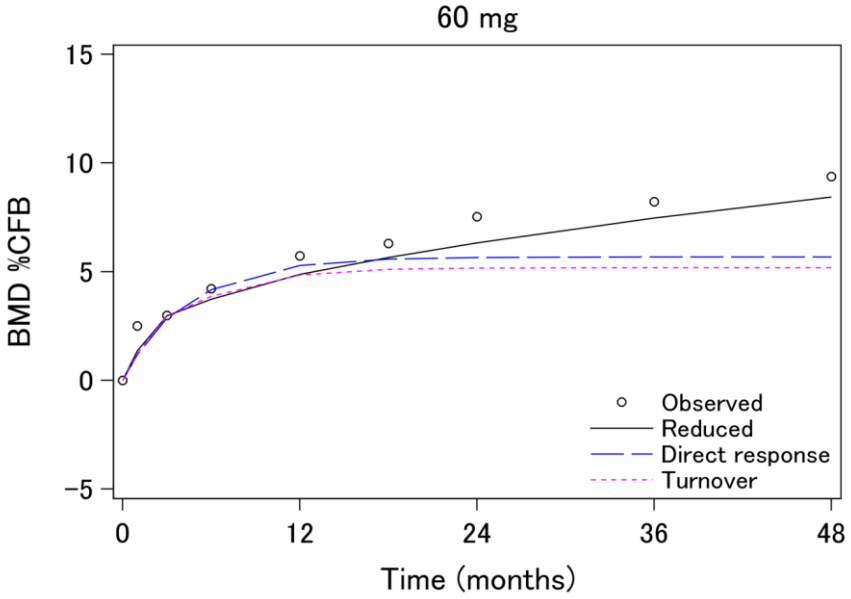


Similar results from all models

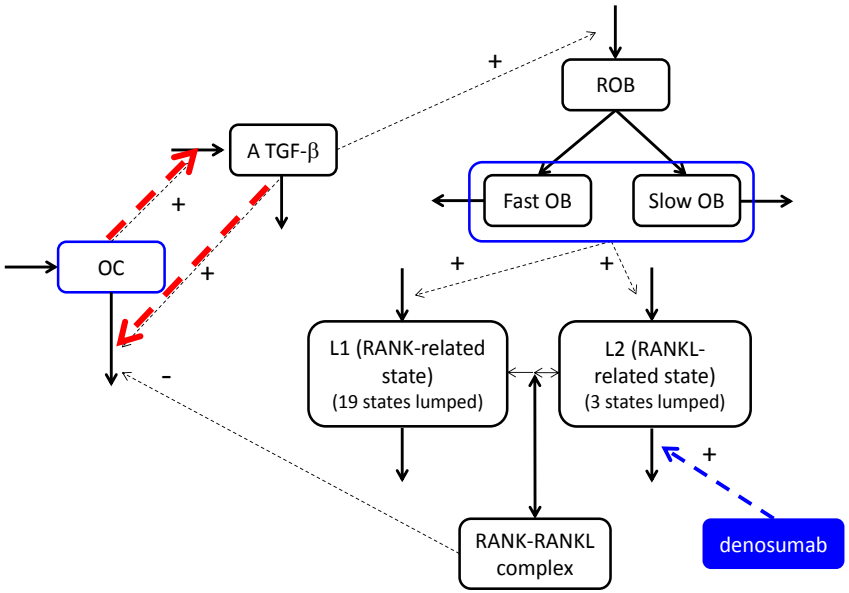
Extrapolation results over 1 year



Why the reduced model can extrapolate?



Reduced model



Conclusions

- A nonlinear bone biology model was successfully reduced by inductively linearizing the system followed by proper lumping.
  - The method shown in this talk is automatic, and can be applied directly to other multiscale models
- The reduced model described an increase in BMD after denosumab dosing while maintaining physiological meaning, and could be used for extrapolating long-term responses.
  - e.g. from phase 2 to phase 3

Acknowledgements

- Prof. Stephen Duffull (Otago Pharmacometrics Group in the School of Pharmacy, University of Otago)
- Mark Peterson (Pfizer)
- Matthew Riggs (Metrum)

Downloads / publications

- Inductive linearization
  - *Hasegawa C et al., J Pharmacokinet Pharmacodyn. 2017 [Epub ahead of print]*
  - Proof for convergence and tutorial paper to be submitted
- Composite criterion and automatic lumping
  - *Hasegawa C et al., AAPS J. 2017; 20:2*
- Automated nonlinear lumping & bone model
  - will be published and released on GitHub
- Identifiability analysis
  - *Shivva V et al., CPT Pharmacomet Syst Pharmacol. 2013; 2:e49*
  - popt_i (http://www.otago.ac.nz/pharmacometrics/otago669687.zip) for download