Simplification of multi-scale systems models for data-driven analyses : our progress over the last 5 years

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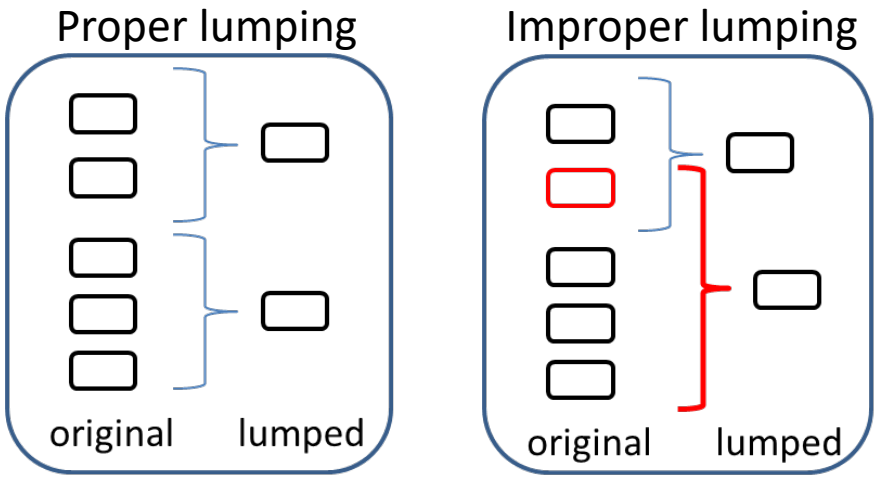
Bridging pharmacometrics and multi-scale systems models

- Has resulted in models that are often not suitable for parameter estimation.
  - Time consuming and numerically unstable
- Proper lumping is one of the ways to reduce the order of such complicated models.
  - A special case of lumping that merges some of the states to only one state
  - Reduced states after proper lumping are able to retain the physiological meaning as in the original system
  - Simplified models can be directly used as a structural model for data-driven analyses



In PAGE 2013 (5 years ago)…

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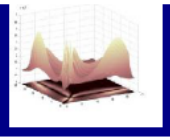

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Simplification of a multi-scale systems coagulation model with an application to modelling PKPD data

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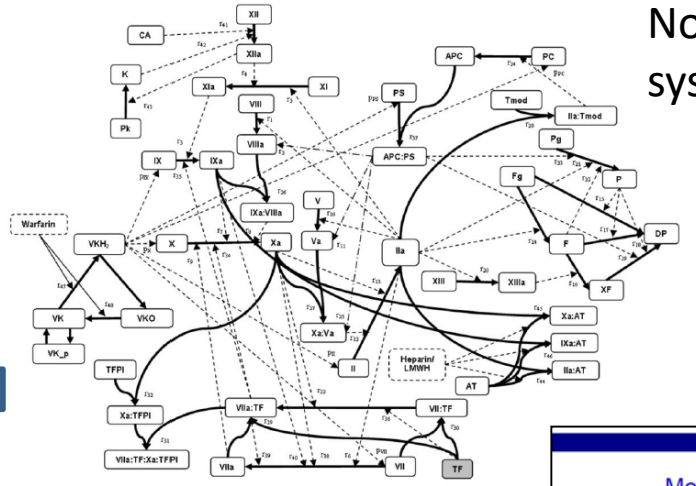
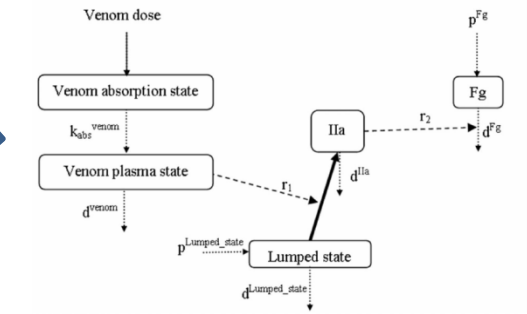
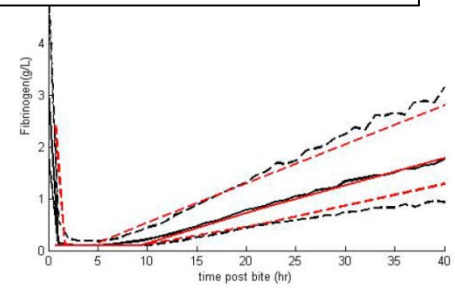


Nonlinear 62-state system



Modelling venom-fibrinogen data

- Use of a full population approach to analyse the data using NONMEM v7.2



https://www.page-meeting.org/pdf_assets/2343-PAGE_Oral_Gulati_2013_vFinal.pdf

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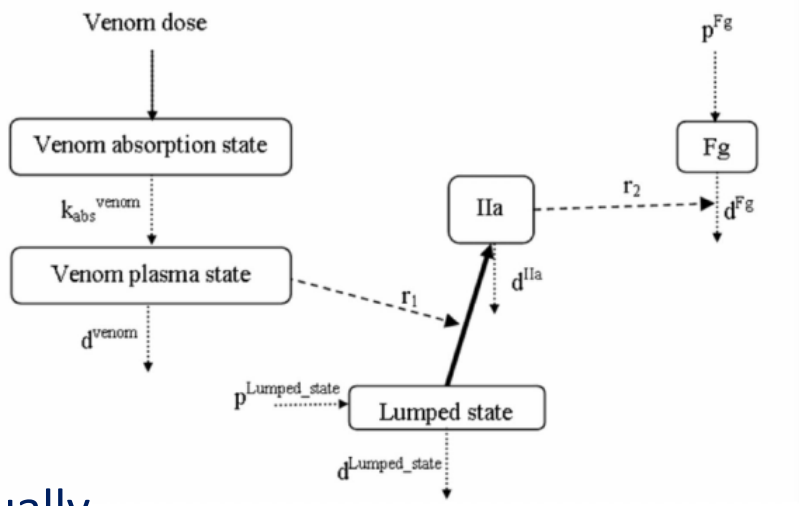
Difficulty with lumping coagulation model in 2013

- Model structure was able to be visualized.



- But
  - The model (equations) had to be reconstructed manually
  - Parameter values and initial values of the reduced model had to be heuristically determined by trial and error
- Therefore the lumping process could not be automated.

https://www.page-meeting.org/pdf_assets/2343-PAGE_Oral_Gulati_2013_vFinal.pdf

Proper lumping and linear vs nonlinear

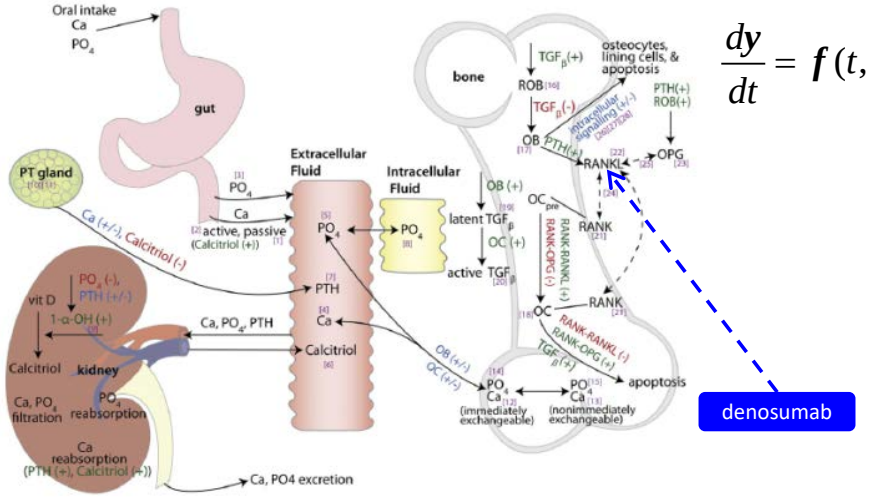
Linear system	Nonlinear system
Lumping formula gives equations and parameter values of the reduced model	Lumping formula does not give equations and parameter values of the reduced model 

Adapted from https://www.page-meeting.org/pdf_assets/2343-PAGE_Oral_Gulati_2013_vFinal.pdf

Aims

- to systematically simplify a nonlinear systems model
  - Use a bone biology model as an illustrative example

Nonlinear 28-state system



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

- to assess the performance of the simplified model by predicting improvement in long-term bone mineral density (BMD) responses from denosumab, a RANKL inhibitor

Extrapolation from short/middle-term data to long-term responses

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

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Systematic simplification of systems models

Original nonlinear systems model

⇩

1. ***Linearise*** *using inductive approximation*

Hasegawa et al, JPKPD 2018; 45:35-47

Linearised systems model

⇩

2. ***Automatic proper lumping*** *using a composite criterion*

Hasegawa et al, AAPSJ 2017; 20:2

Reduced model

⇩

3. *Finalisation of the reduced model*
   - ***Unlinearise*** *the model*
   - ***Identifiability*** *analyses*

Final reduced model

1. **Linearise** the model using inductive (iterative) approximation

Original nonlinear

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

"*Unknown*" before solving the ODE

Linearised via ***n*-times** iteration

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

"*Known*" quantity (just a number at any *t*)

Hasegawa C et al, JPKPD 2018; 45:35-47

Example of linearisation using Michaelis-Menten process

PK model with Michaelis-Menten elimination

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

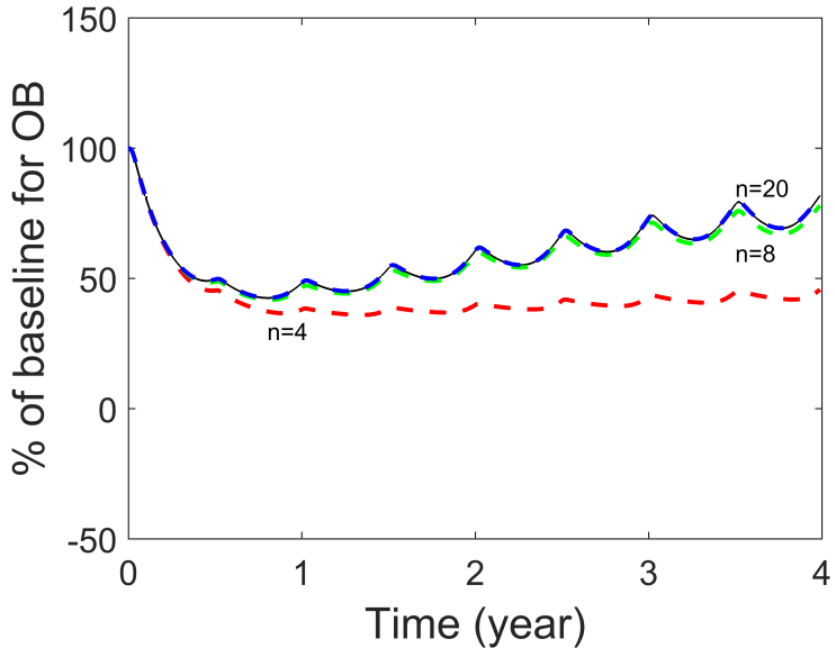
$$\frac{dC^{[n]}}{dt} = f(k_a, Dose, t) - \underbrace{\frac{V_{max}}{K_m + C^{[n-1]}}}_{\checkmark} \cdot C^{[n]}$$

Hasegawa C et al, JPKPD 2018; 45:35-47

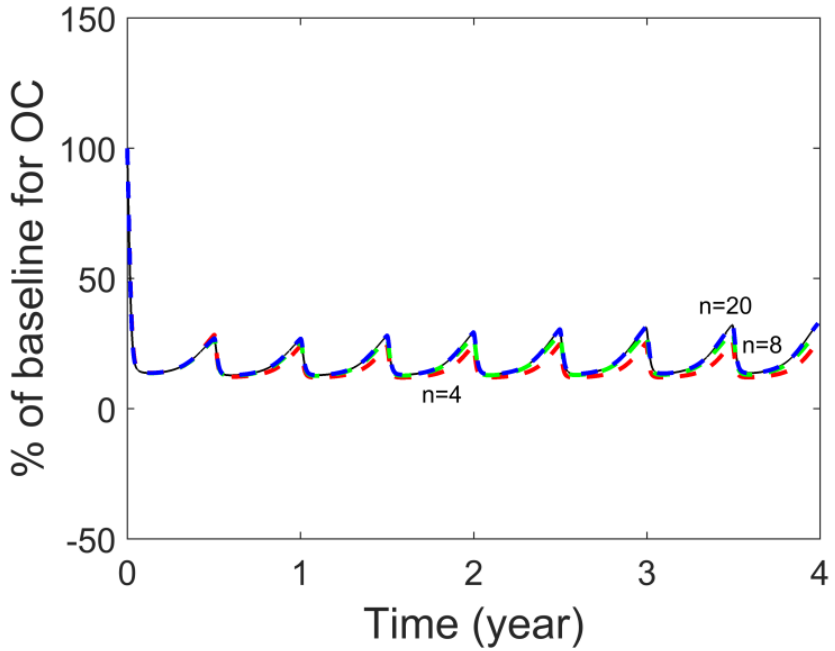
Linearisation results in bone biology model after dosing denosumab every 6 months (Q6W)

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

OB (osteoblast)



OC (osteoclast)



Sufficiently accurate at n=20

2. Automatic proper lumping using a composite criterion

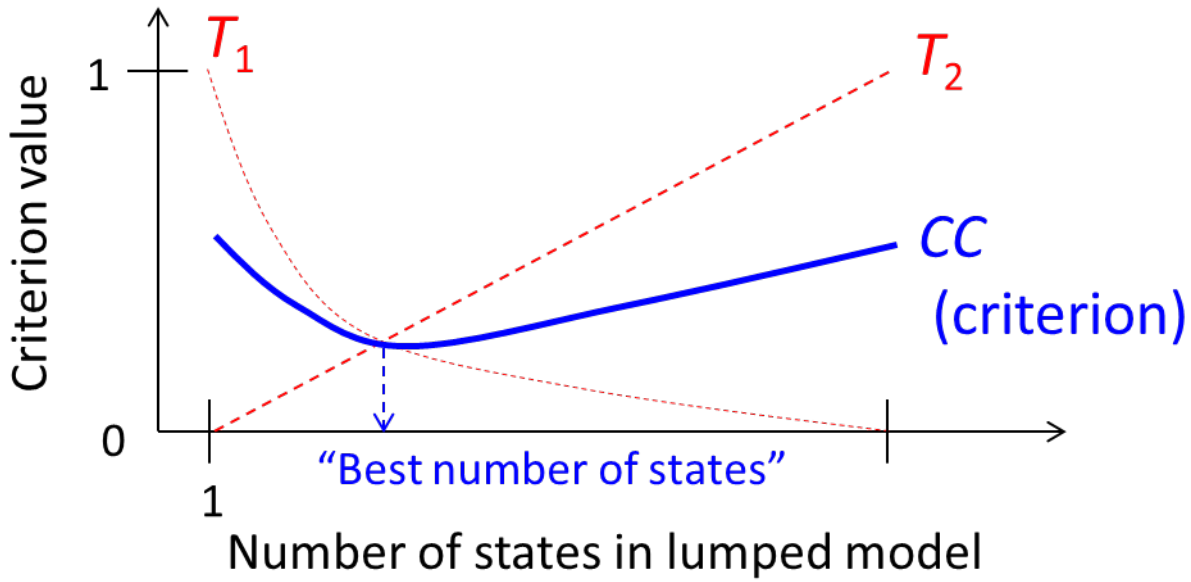
- The criterion (*CC*) consists of opposing two indices.

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

Performance | Penalty for complexity

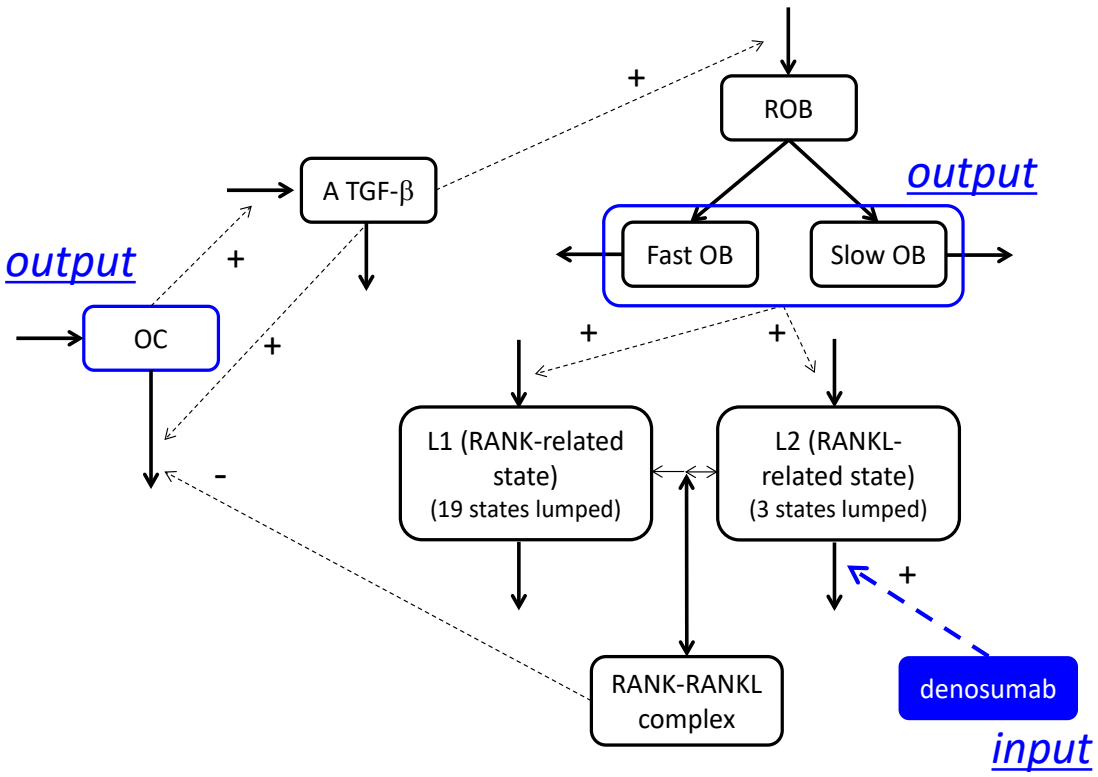
α: weighting factor

m: number of states in lumped model (x-axis)



Lumping results in bone biology model

- 8-state model provided the smallest criterion value



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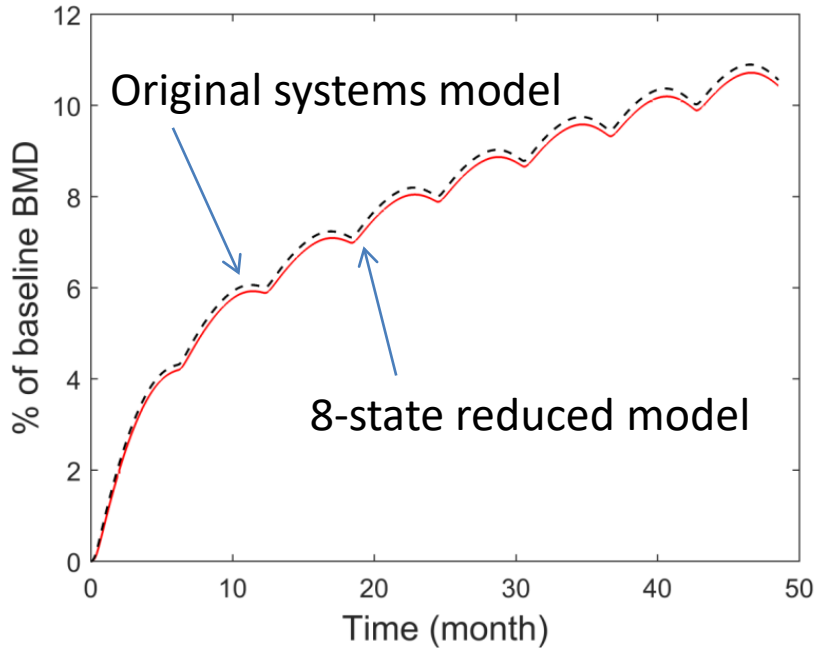

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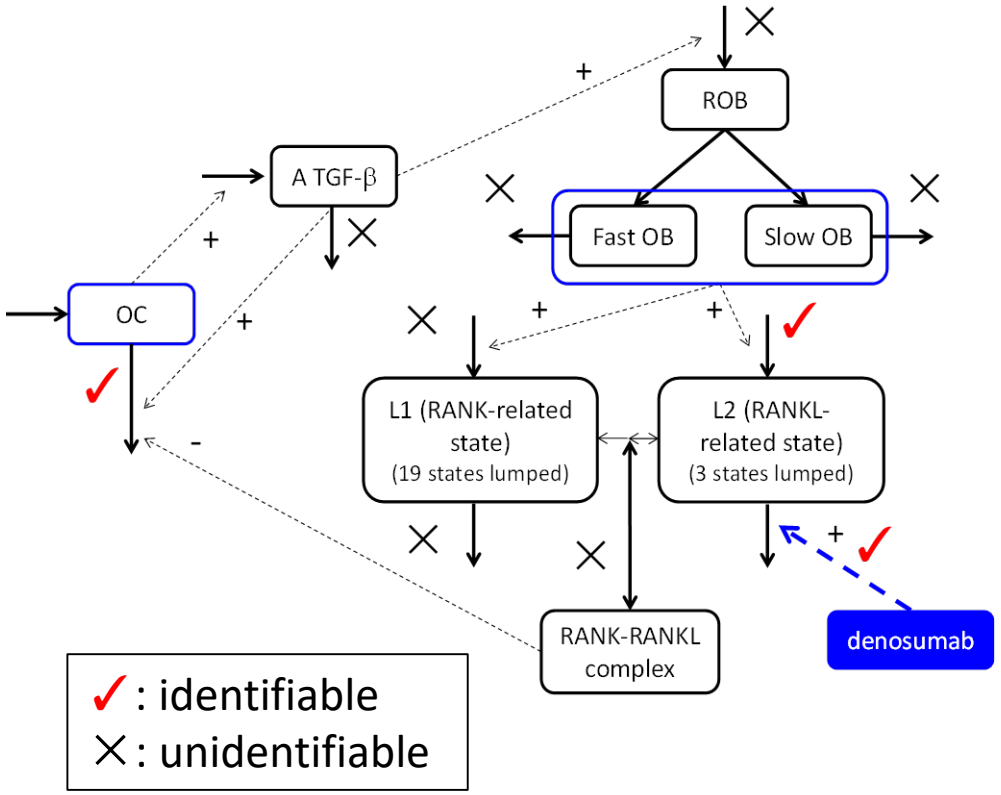
3. Finalisation of the reduced model

- Unlinearise the model (for unlumped states)
  - to transform back to the original form
- Identifiability analyses
  - to identify estimable parameters using an information approach (popt_i, MATLAB)

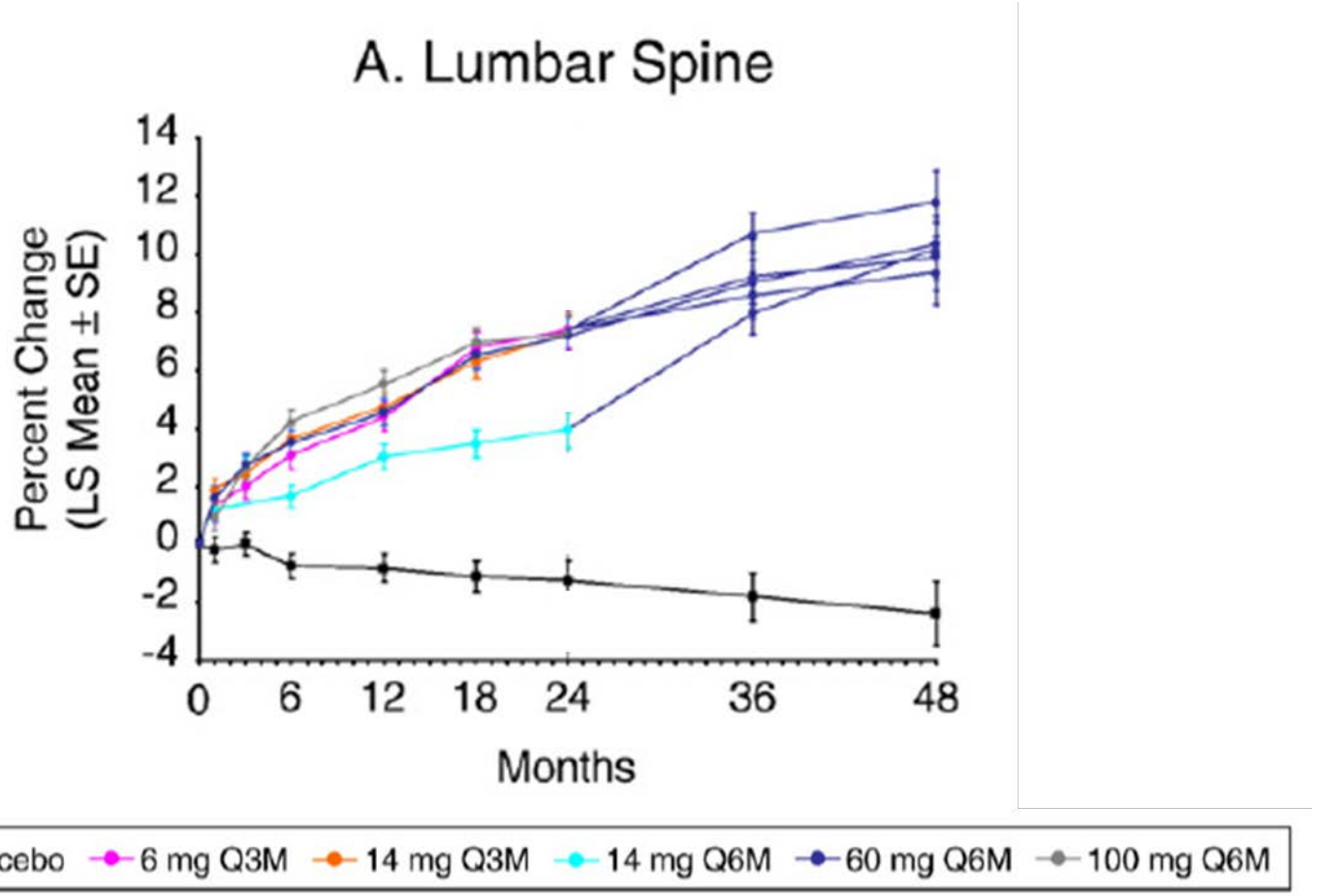
Shivva V et al., CPT Pharmacomet Syst Pharmacol. 2013; 2:e49



Assess the performance of the final reduced model by predicting improvement in long-term BMD responses

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 (reference)

(i) Direct response model

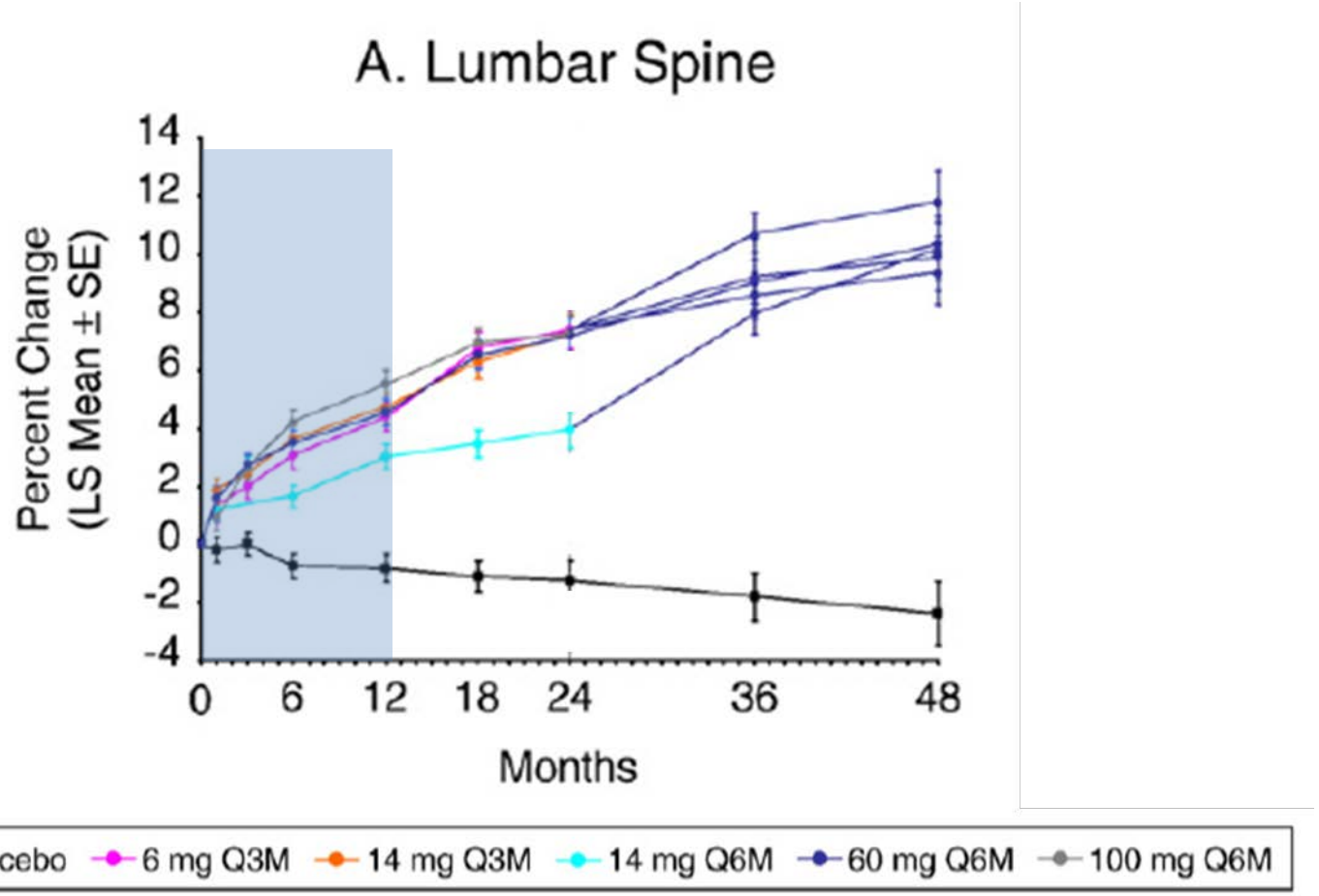
$$\%\Delta BMD = Emax(t) \cdot \frac{C}{C50 + C}$$

$$Emax(t) = Emax \cdot (1 - \exp(-kt))$$

C: denosumab concentration

(ii) Turnover model

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



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

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Extrapolation beyond 1 year

- Reduced model
- Two Empirical models (reference)

(i) Direct response model

$$\%\Delta BMD = Emax(t) \cdot \frac{C}{C50 + C}$$

$$Emax(t) = Emax \cdot (1 - \exp(-kt))$$

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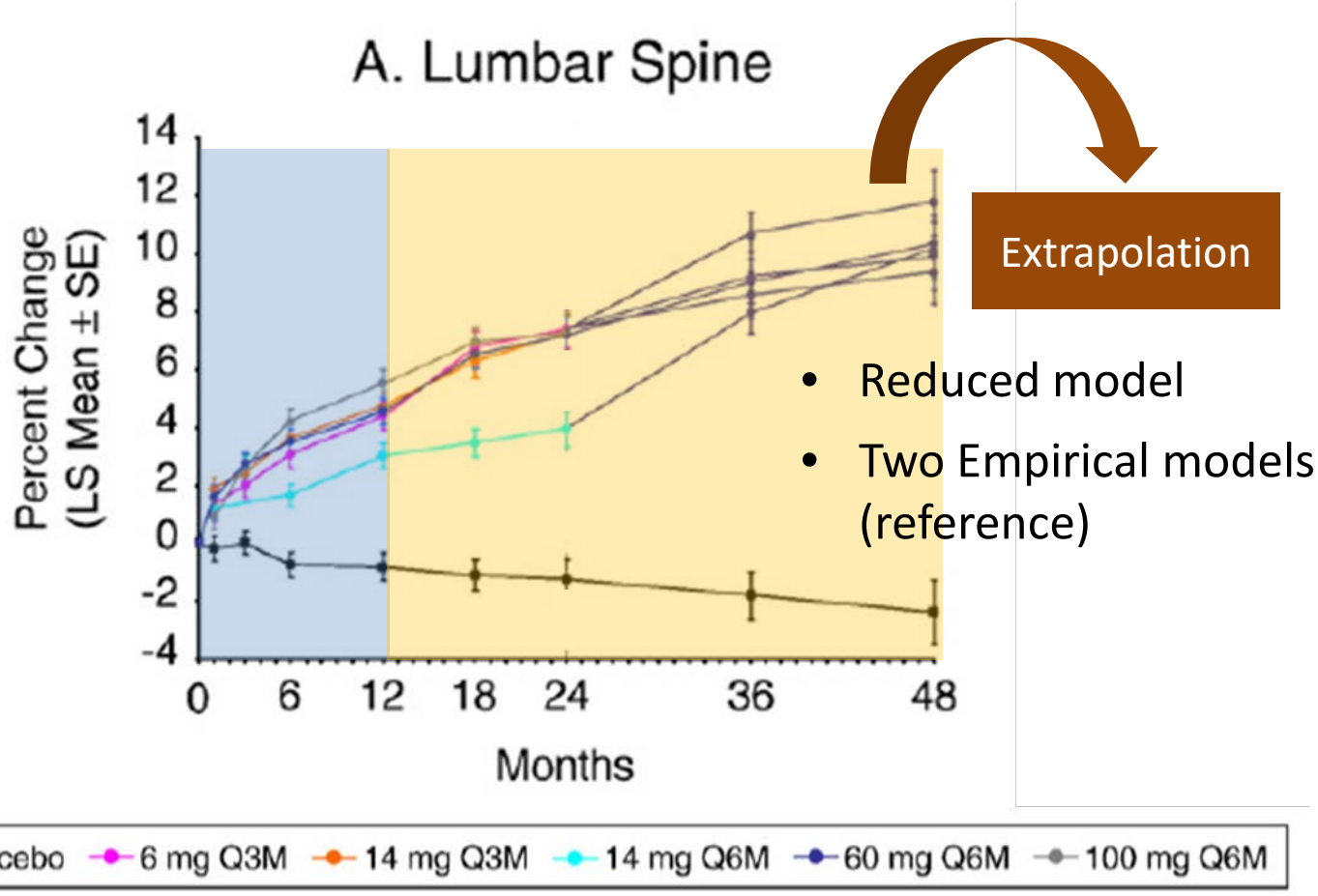

- Reduced model
- Two Empirical models (reference)

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

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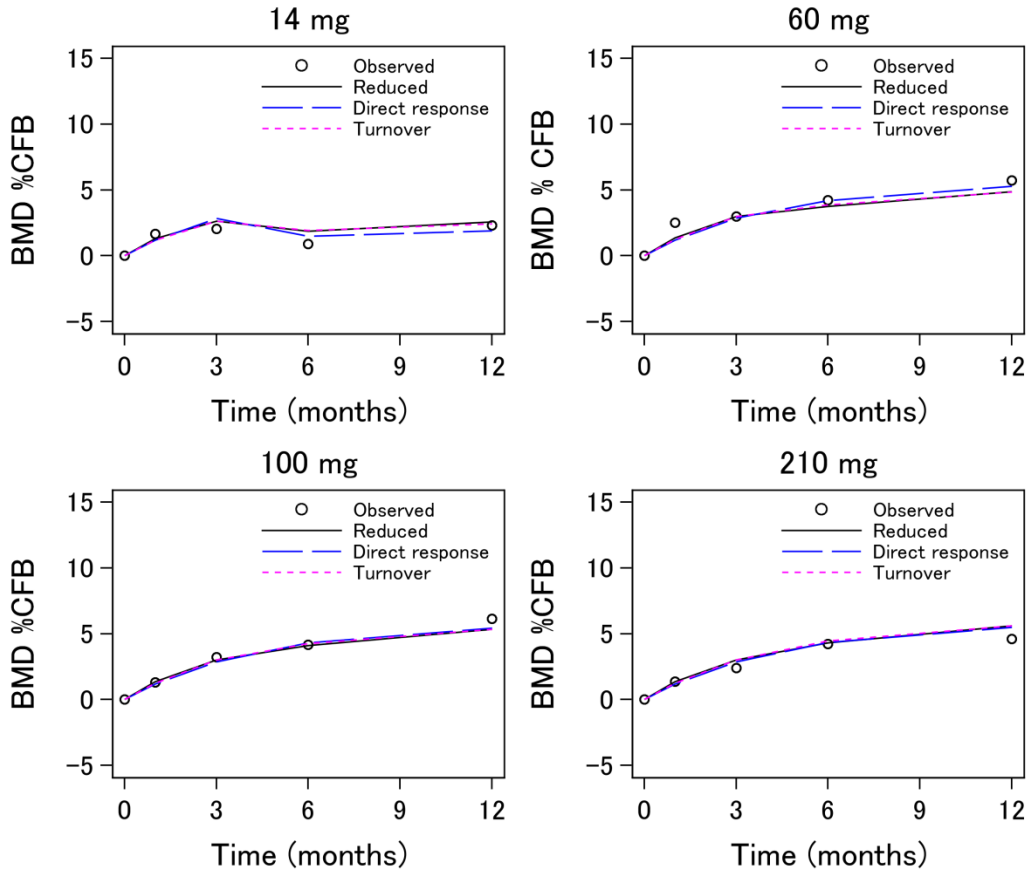
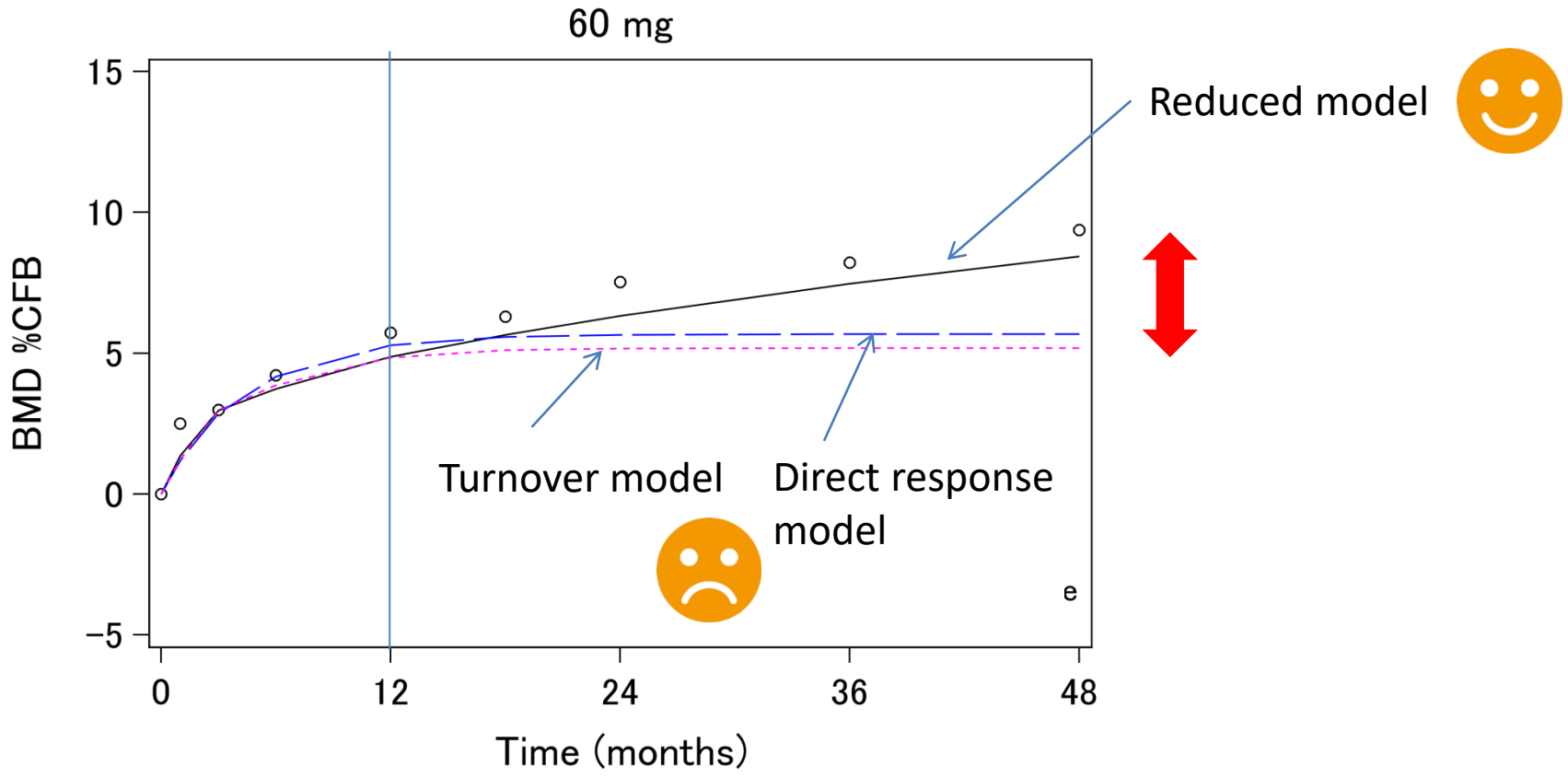
Fitting results **for 1 year**



Similar results from all models

Extrapolation results **beyond 1 year**



Conclusions

- 5 years ago we could lump but could not automatically lump or extract the model.
- In this work we illustrated that the combination of linearisation and lumping can be automated.
- The systematic lumping process was illustrated using a bone biology model.
  - The process is automatic, and can be applied directly to other multiscale models for developing a mechanism-based structural model for data-driven analyses.
  - Other groups are also working on model simplification *Snowden TJ et al., PAGE 27 (2018) Abstr 8647.*
- The reduced model adequately described an increase in responses after long-term dosing which was not able to be emulated by empirical/semi-mechanistic models.

Acknowledgements

- Mark Peterson (Pfizer)
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