A comparison of two model reduction methodologies for a QSP bone biology system with denosumab dosing

CERTARA QSP

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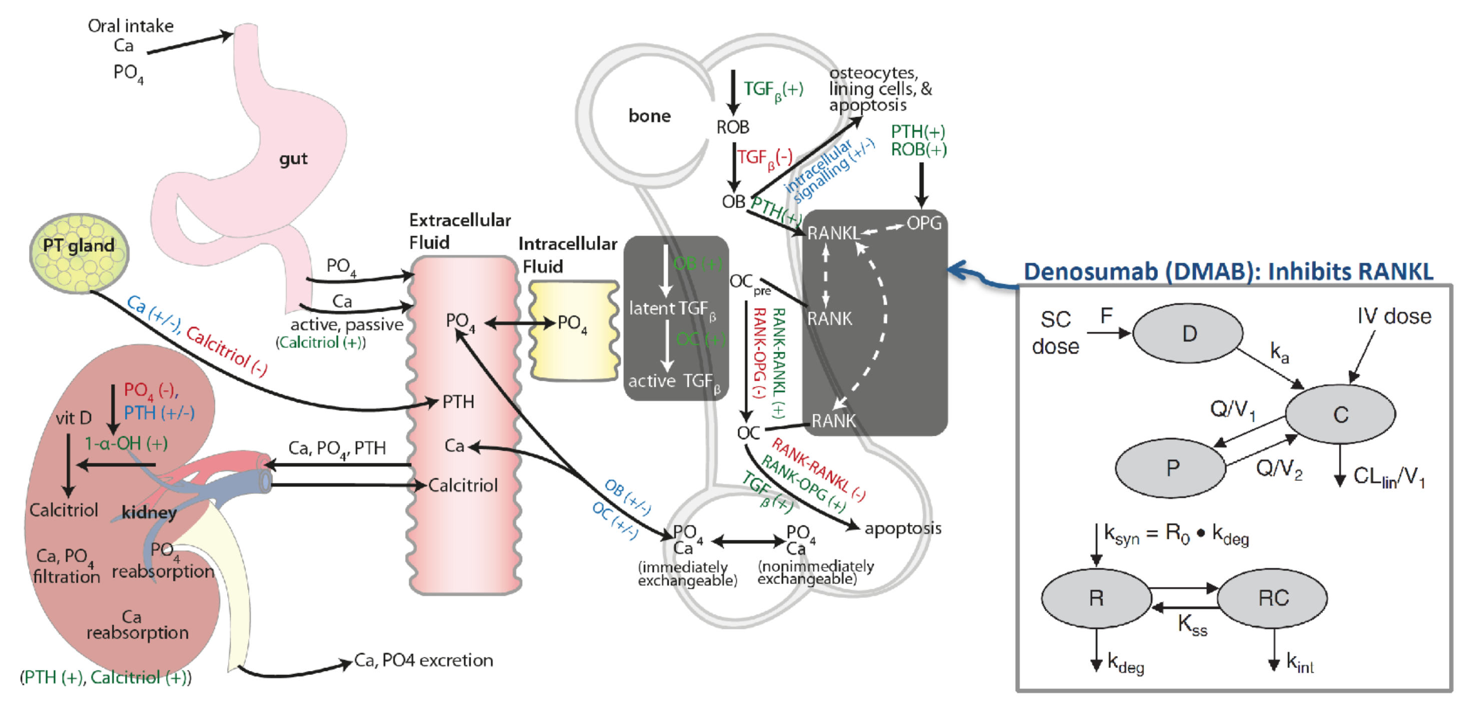
Abstract

Quantitative systems pharmacology (QSP) seeks to bring together the data driven approaches at the core of empirical PKPD modelling with the mechanistic insight found in systems biology. Unfortunately, such systems tend to be complex – containing too many variables to be used in the traditional applications of clinical PKPD. One suggestion is to instead seek to create 'zoomable' models that retain a mechanistic basis, but which can be reduced down to practical applicability.

Such simplification can be achieved via methods of model reduction. In this poster we compare two recently published methodologies of model reduction via application to an example QSP type model of bone biology.

Background

The example used to compare methods is a multiscale model of bone remodelling[1]. This original system contains 36 ODEs. By combining with a description of denosumab PK and RANKL inhibition[2], this can be used as a QSP type model describing the effects of denosumab administration on bone mineral density.



Methods

Model reduction refers to any method designed to construct a lower order representation of a model with which some set of the original dynamical behaviour can be satisfactorily reproduced[3]. To apply a model reduction we seek some projection $T: \mathbb{R}^n \to \mathbb{R}^r$ of the species, such that $\tilde{x} = T(x)$ gives a reduced set of pseudo-species with $\tilde{x} \in \mathbb{R}^r$ with $r < n$.

Lumping[4] is a method of model reduction which creates a reduced set of states as a linear projection of the originals (an example schematic is depicted in fig.1).

Empirical balanced truncation[5] is a method of model reduction which transforms states in such a way as to account for as much of the input-output relationship in as few state-variables as possible.

The first approach compared here is developed by Hasegawa and Duffull uses iterative linearization[6] and subsequent criterion lead proper lumping to achieve a reduction[7]. The second approach is developed by the authors of this poster and applies a combined approach of lumping and empirical balanced truncation to the nonlinear system directly under the Petrov-Galerkin projection[8].

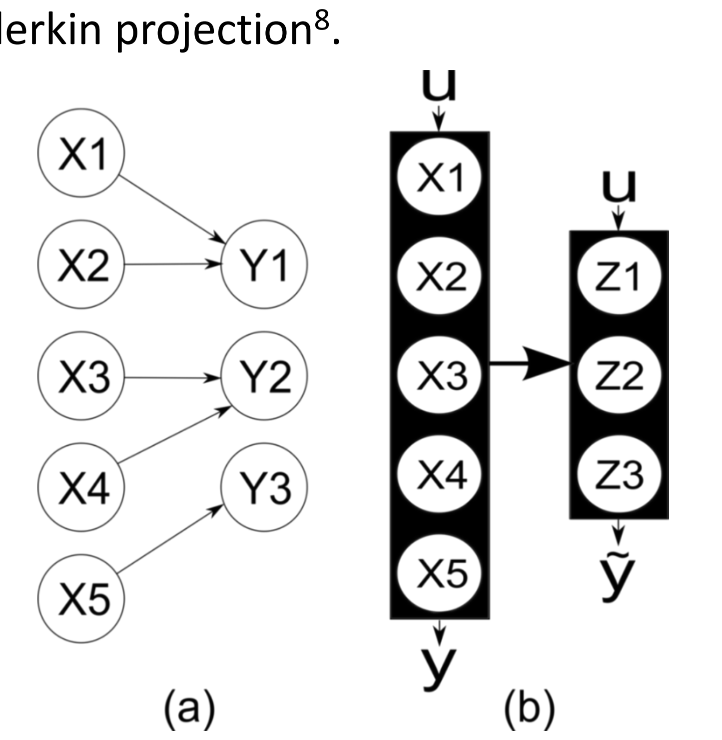


Fig.1

(a) A schematic representation of proper lumping[1].

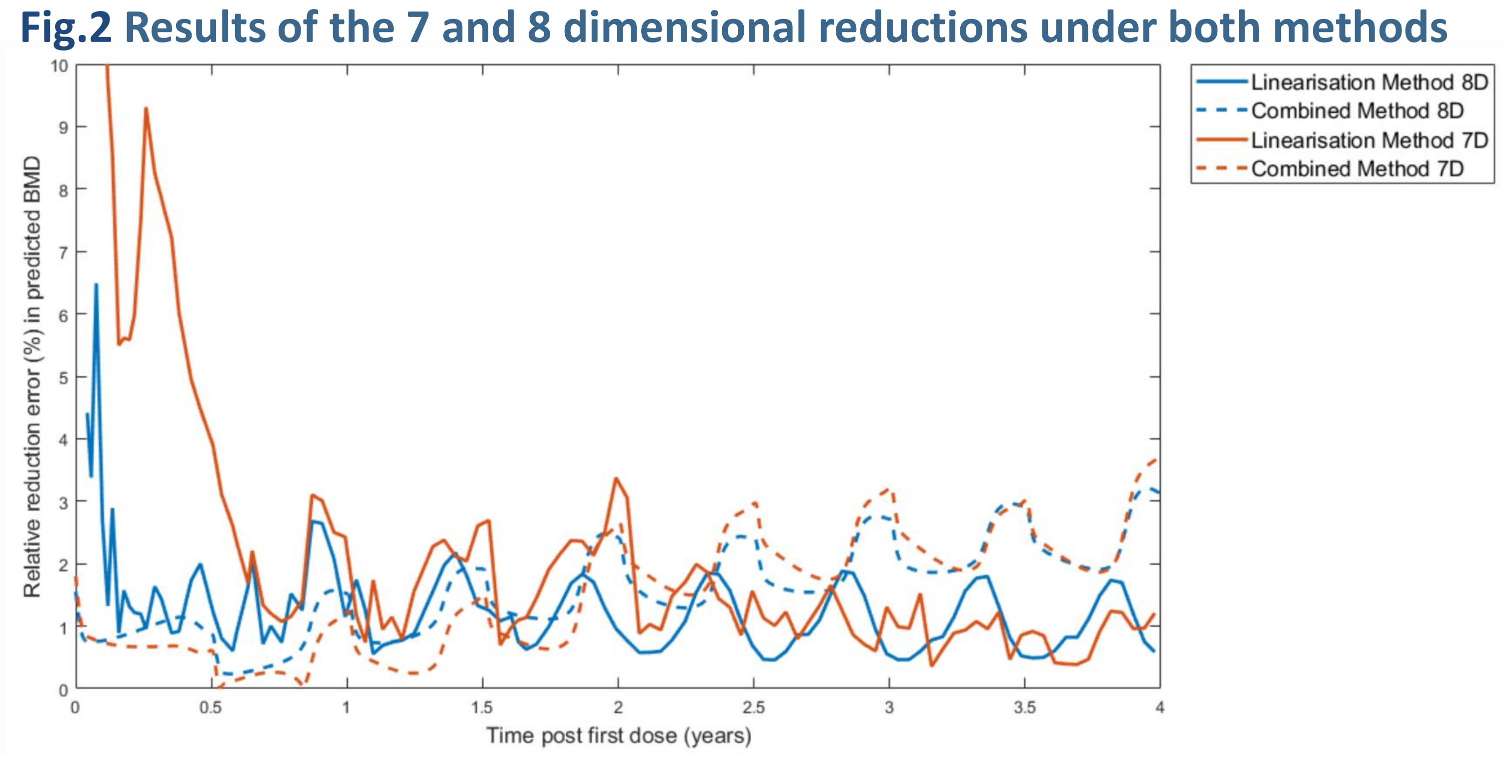
(b) A schematic representation of empirical balanced truncation[2].

Results

A perfect comparison of the two methods was not possible. Hasegawa et al. have not yet published their full methodology nor the precise version of the original model they used. Their system begins with 28 state-variables and results are given for the 8 and 7 dimensional reductions. Our methodology, however, is applied to the 36 dimensional system.

Given this caveat, our results do demonstrate preferable results for the combined approach as opposed to the linearization and lumping approach. Overall, a 3.1% improvement in reduction error for the 8 dimensional case, and a 19.7% improvement in the 7 dimensional reduction case (due to initial transient error) were observed. Furthermore, through subsequent application of empirical balanced truncation we were able to reduce the model to 5 dimensions and incur only a 6.7% maximal relative error.

Fig.2 Results of the 7 and 8 dimensional reductions under both methods



Conclusions

- Linearising a system can allow for a number of further analyses of a model, particularly enabling the use of matrix exponentiation to obtain model solutions as opposed to traditional simulation approaches.
- However, we do not believe it is a necessary or often appropriate first step in model reduction via lumping. In such cases it seems preferable to retain the nonlinearity of the system under the Petrov-Galerkin projection. Such an approach is straightforward, retains the structure of the model and automatically yields a closed form, time-invariant reduced system. The linearization approach, on the other hand, does introduce a time-varying set of coefficients into the system which can obscure some of the mechanistic meaning of the system.
- Additionally, as has been demonstrated here (at least given the caveats previously stated), the reduction error can often be significantly reduced by taking the nonlinear approach.
- One possibility, combining both approaches, would be to apply linearization to enable the application of linear balanced truncation. The authors expect that for input-output type systems this may perform favourably to either approach compared.

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