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Poster Submission

Title:	Preservation of bistability in the reduction of an apoptosis model
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Text (250 words only):	Many biological processes depend on complex dynamic behaviour like bistability or limit cycles. When reducing a model of such a process, it is important that the applied method preserves this behaviour in the reduced model. We study a bistable model for receptor-induced apoptosis introduced by Eissing et al. (2004). The model has two stable steady states, one where the cell is alife, the other where it undergoes apoptosis. There is a third, unstable steady state, which determines the regions of attraction for the stable steady states. We analyse the relevance of the system's components to bistability using an approach introduced by Schmidt and Jacobsen (2004). It is based on a reformulation of the system as a closed feedback loop. By introducing disturbances in the feedback, the relevance of each component can be estimated. Based on the results of this method, we reduce the model to half its original dimension by using only the relevant components as dynamic states. The remaining components are only included with their steady state map. Due to our approach, the steady states as well as their local stability behaviour are reproduced, leading to the preservation of bistability in the reduced model. This preservation is shown in simulations of both models: The qualitative behaviour is well reproduced by the reduced model. When setting the initial condition close to one of the steady states, the reduced model is also a good quantitative approximation of the full model. Current research is focussed on analysing the effect of parameter variations on the relevance of each component. Thus we expect to establish a link between our approach and established measures of robustness.

Preservation of Bistability in the Reduction of an Apoptosis Model

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Introduction

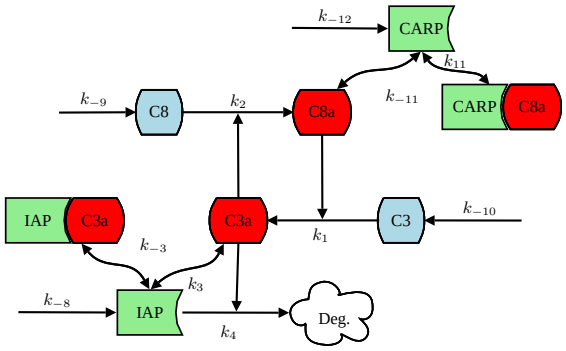
Apoptosis:

- Process of programmed cell death, involved in major diseases.
- Executed by activation of several caspases.

$\Rightarrow$ Necessary to understand dynamic features.

Bistability is a key factor in modelling apoptosis. There are **two stable steady states**, one can be identified with the state where the cell is alive, the other one with the state where the cell undergoes apoptosis. Convergence to either the living state or the apoptotic state depends on whether the input exceeds a certain **threshold** or not. We study a caspase activation model proposed by [1]. Key features are

- 8 species based on the caspases 8 and 3 and the inhibitors IAP and CARP.
- **Positive feedback loop** of caspase activation.
- Bistable within a reasonable parameter range.
- Initial concentration of active caspase 8 [C8a] as **input**.
- Apoptosis induced if [C8a] above a certain threshold.



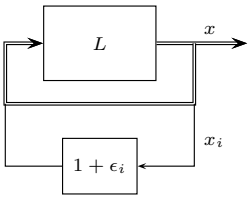
Note: All species undergo degradation, but only the C3a-mediated degradation of IAP is shown in the figure.

Determination of Component Relevance

The **relevance** of each component to bistability is computed with a method introduced by [3]:

- Consider the third, **unstable steady state** (part of the threshold manifold).
- Linearise the system around this state.
- Consider all interactions between different components as **feedback paths**.
- The relevance of each component is given by the **perturbation in its feedback path** which is necessary to stabilise the unstable steady state. (Small perturbations indicate a high relevance.)

Block diagram for perturbation in feedback path:



The relevance of component i is computed as

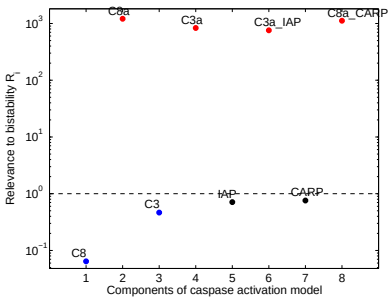
$$R_i = \frac{1}{|\epsilon_i|}.$$

Applied to the apoptosis model, we get the relevance for each of the 8 components as displayed in the following diagram.

Relevant components:

- C8a
- C3a
- C3a_IAP
- C8a_CARP

$\Rightarrow$ Only **activated caspases** are relevant for bistability.



Model Reduction Method

In model reduction, it is important that **qualitative system properties** like bistability are **preserved**.

Our reduction method is based on relevance and consists of three steps:

- Compute the **steady–state maps** of the irrelevant components, depending only on relevant components.

  Using x_1 = [C8], x_2 = [C8a], $x3$ = [C3], x_4 = [C3a], x_5 = [IAP], x_6 = [C3a_IAP], x_7 = [CARP], x_8 = [C8a_CARP], we get

$$x_1^* = \frac{k_{-9}}{k_9 + k_2 x_4} \qquad x_5^* = \frac{k_{-8} + k_{-3} x_6}{(k_3 + k_4) x_4 + k_8}$$
$$x_3^* = \frac{k_{-10}}{k_{10} + k_1 x_2} \qquad x_7^* = \frac{k_{-12} + k_{-11} x_8}{k_{12} + k_{11} x_2}$$

- Drop the differential equations for the irrelevant components from the model.
- Replace the irrelevant components in the remaining equations with their steady–state maps:

$$\dot{x}_2 = k_2 x_4 x_1^* - k_5 x_2 - k_{11} x_2 x_7^* + k_{-11} x_8$$
$$\dot{x}_4 = k_1 x_2 x_3^* - k_3 x_4 x_5^* + k_{-3} x_6 - k_6 x_4$$
$$\dot{x}_6 = k_3 x_4 x_5^* - k_{-3} x_6 - k_7 x_6$$
$$\dot{x}_8 = k_{11} x_2 x_7^* - k_{-11} x_8 - k_{13} x_8$$

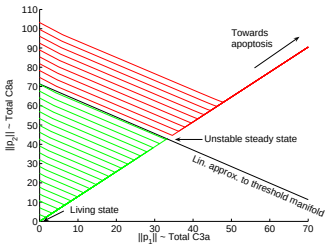
$\Rightarrow$ This gives a reduced model with **half the original size**.

Preservation of Bistability & Simulation Results

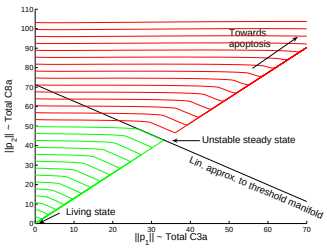
Comparing the reduced and the full model, we find:

- Both models have the same steady states.
- Steady states have the same **local stability behaviour** in both models.
- The linear approximation to the **threshold manifold** is equivalent.

These points as well as some differences between the models are illustrated in the following plots.



Original model



Reduced model

Projection of the trajectories for both models. The x- and y-axis correspond approximatively to the total amount (bound and free) of active caspase 3 and 8, respectively.

Relevance as a Robustness Measure

- Relevance $\approx$ Sensitivity, the inverse of robustness.
- Measures robustness vs. disturbances in the influence of **one component** on the rest of the system.
- Relation to a robustness measure vs. **parameter changes**, introduced by [2], has been shown via a local sensitivity analysis:

$$\frac{1}{R_i} \sim \sum_{j=1}^{p} |S_{ij}| Rob_j$$

Conclusion

- The presented reduction method is well suited to preserve bistability as a qualitative property.
- In our case, a model reduced to half the original size still yields the same qualitative behaviour.

References

[1] T. Eißing, H. Conzelmann, E. D. Gilles, F. Allgöwer, E. Bullinger, and P. Scheurich. Bistability analyses of a caspace activation model for receptor-induced apoptosis. *J. Biol. Chem.*, 279(35):36892–36897, August 2004.

[2] L. Ma and P. A. Iglesias. Quantifying robustness of biochemical network models. *BMC Bioinformatics*, 3:38, 2002.

[3] H. Schmidt and E. W. Jacobsen. Linear systems approach to analysis of complex dynamic behaviours in biochemical networks. *IEE Systems Biology*, 1:149–158, 2004.