An automated model reduction tool to guide the design and analysis of synthetic biological circuits

Ayush Pandey[1]; Richard M. Murray[1]

[1]Control and Dynamical Systems, California Institute of Technology

Motivation

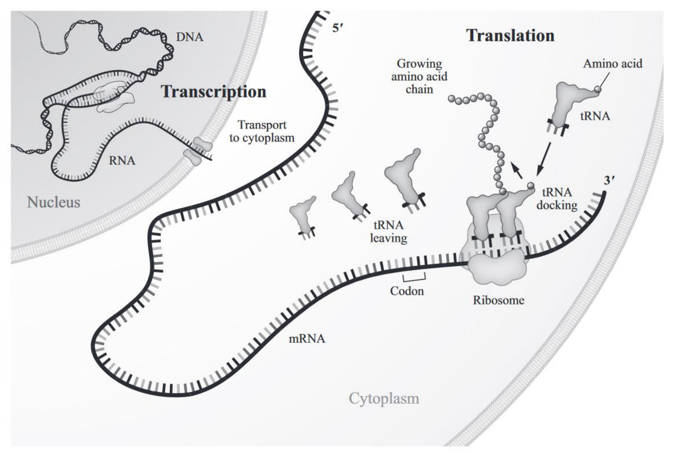
A reduced order model is

- a lower dimensional model that has a simple representation,
- computationally efficient, and
- easier to use for system design

compared to any other higher order, more complex mathematical model.

We aim to use a reduced model to

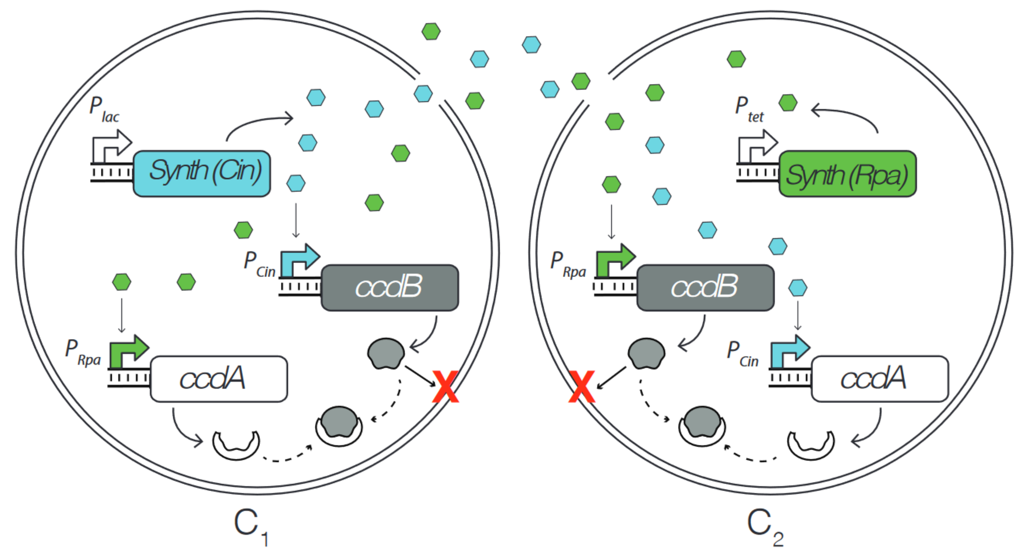
- better understanding of key processes,
- improving parameter identifiability, and
- guide experimental design.



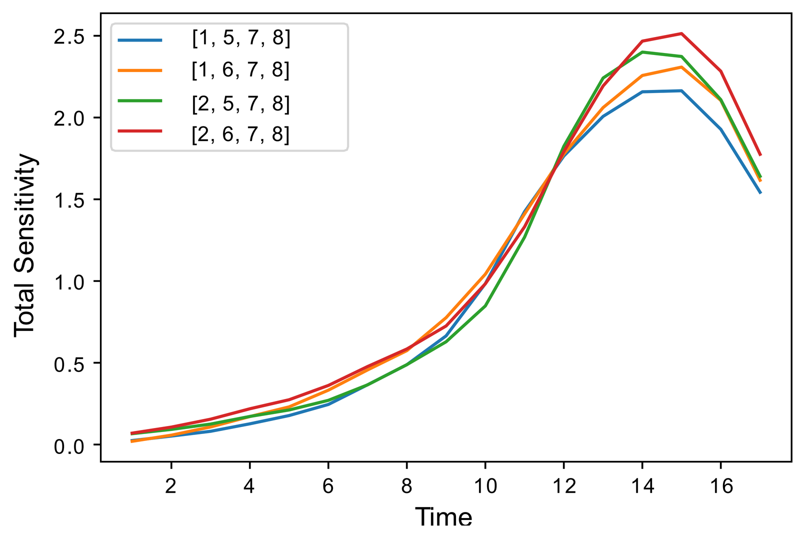
$$\frac{dm_P}{dt} = \alpha - \delta m_P$$

$$\frac{dP}{dt} = \kappa m_P - \gamma P.$$

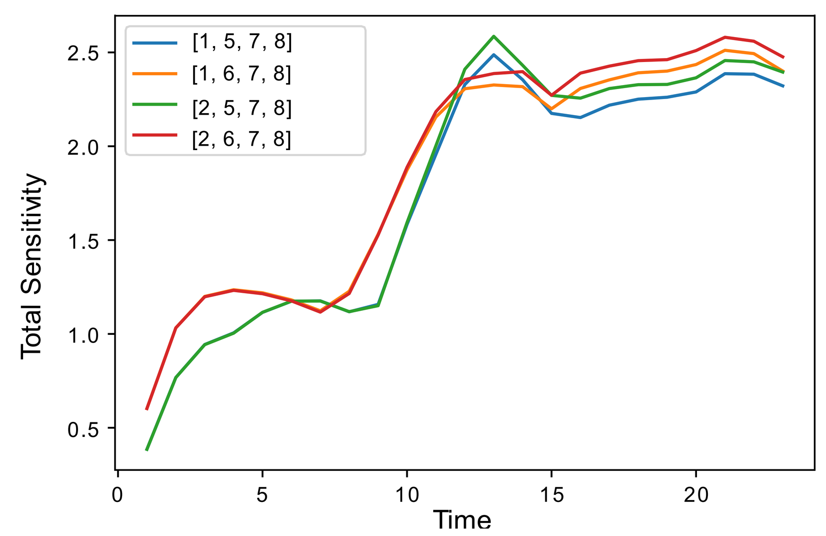
Population and Composition Control Circuit



Schematic of the composition and population density control synthetic biological circuit of a two-member bacterial community. It is a symmetric circuit motif in its two cells to create cis-acting negative feedback loops on each member and trans acting rescues from negative feedback from each member to the other. Negative feedback and sequestration rescue are effected by ccdB toxin (T_i in the model) and its ccdA antitoxin (A_i), respectively. Signals S_1 and S_2 are chemical inducers that activate transcription of AHL synthase genes. The observations are fluorescent outputs corresponding to the population of each cell strain C_1 and C_2. Note here that the Strain A corresponds to C_1 and Strain B to C_2.



The total sensitivity of output y_1 that corresponds to the population of C_1, with time for all four reduced models. The legend indicates the state indices that form the reduced model state vector.



The total sensitivity of output y_2, that corresponds to the total population of C_2, with time for all four reduced models. The legend indicates the state indices that form the reduced model state vector.

Observe that for both outputs we see that the reduced model with the states [1, 5, 7, 8] has the lowest total sensitivity.

Results

Problem Formulation

Full model
Nonlinear dynamics
n states (x)
p outputs (y)

$$\dot{x} = f(x, \Theta)$$
$$y = Cx$$

Structured model reduction

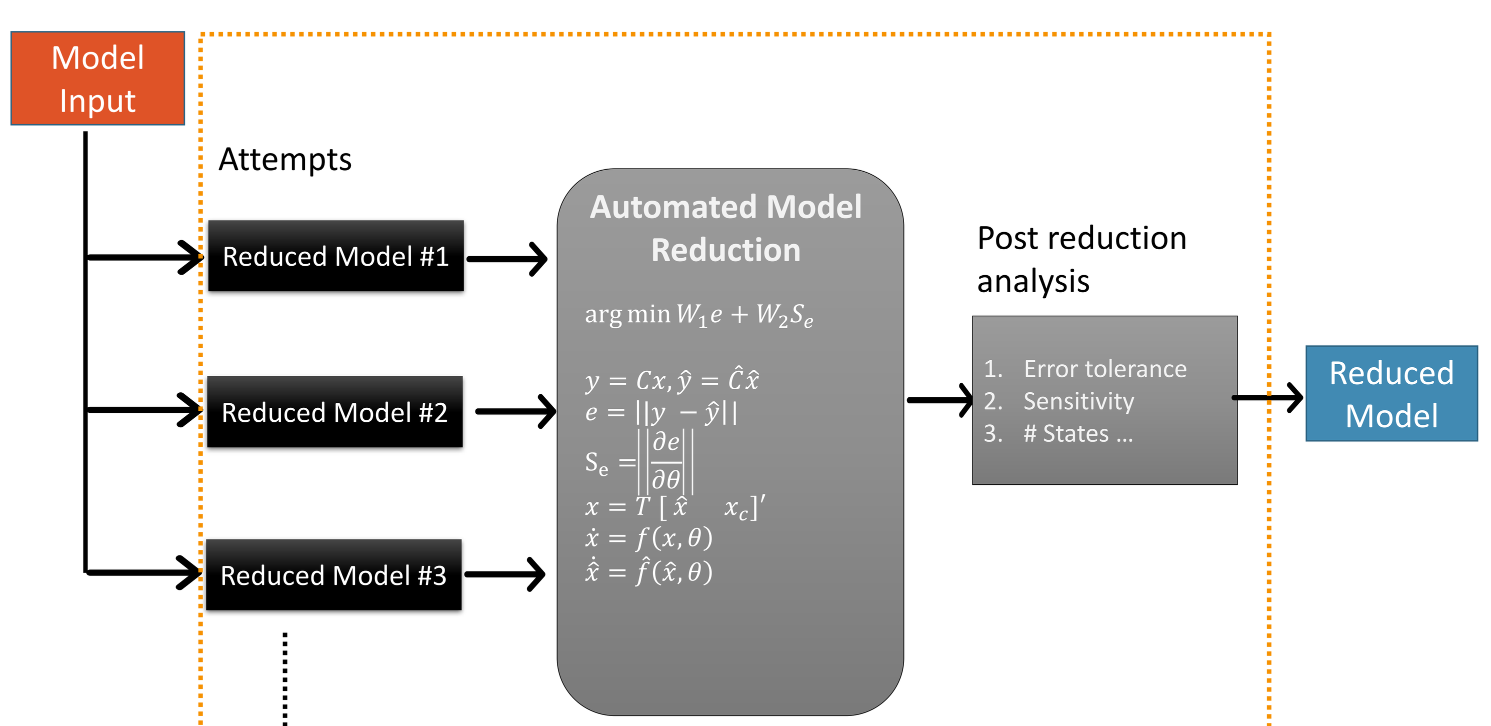
- Collapse a subset of states.
- Outputs are always retained.
- $\hat{x}$: Reduced state vector
- x_c: Collapsed state vector
- T : Permutation matrix

$$x = T\begin{bmatrix}\hat{x}\\ x_c\end{bmatrix} = \begin{bmatrix}T_1 & T_2\end{bmatrix}\begin{bmatrix}\hat{x}\\ x_c\end{bmatrix} \longrightarrow$$

Reduced model
Nonlinear dynamics
$\hat{n}$ states
p outputs

$$\dot{\hat{x}} = \hat{f}(\hat{x}, \Theta)$$
$$\hat{y} = \hat{C}\hat{x}$$

Algorithm



Theoretical results

From [1], we have,

$$\max_{\|\bar{x}_0\|_2^2 = 1} \|e\|_2^2 = \max(\lambda_Q)$$

(for linear dynamics)
Brute force or approximation methods for nonlinear dynamics

$$Q = \begin{bmatrix} T_1^T P_{11} T_1 + T_1^T P_{12} + P_{21} T_1 + P_{22} & T_1 P_{11} T_2 + P_{21} T_2 \\ T_2^T P_{11} T_1 + T_2^T P_{12} & T_2^T P_{11} T_2 \end{bmatrix}$$

Our work extends this to include bounds on sensitivity of error for both linear and nonlinear dynamics. The full bioRxiv paper for our work is available at [2].

$$\|S_e\|_2^2 \le \lambda_{\max}(P) + 2N \max_t \left\| \begin{bmatrix} \frac{\partial f}{\partial \theta} \\ \frac{\partial \hat{f}}{\partial \theta} \end{bmatrix} Q_s \begin{bmatrix} \frac{\partial \hat{x}}{\partial \theta} \\ \frac{\partial x_c}{\partial \theta} \end{bmatrix} \right\|_2$$

$$Q_s = \begin{bmatrix} P_{11} T_1 + P_{12} & P_{11} T_2 \\ P_{21} T_1 + P_{22} & P_{21} T_2 \end{bmatrix}$$

Full Model

Mathematical model

States : $T_1, A_1, T_2, A_2, S_1, S_2, C_1, C_2$

Possible retained states :

T_1, T_2, C_1, C_2

A_1, A_2, C_1, C_2

T_1, A_2, C_1, C_2

A_1, T_2, C_1, C_2

$$\frac{dT_1}{dt} = \beta_{S_1}\left(l_{S_1} + \frac{S_1^2}{K_{S_1} + S_1^2}\right) - k_b A_1 T_1 - d_T T_1$$

$$\frac{dA_1}{dt} = K_r \beta_{S_2}\left(l_{S_2} + \frac{S_2^2}{K_{S_2} + S_2^2}\right) - k_b A_1 T_1 - d_T A_1$$

$$\frac{dS_1}{dt} = \beta_{tac}\left(l_{tac} + \frac{I^2}{K_{tac} + I^2}\right) C_1 - d_S S_1$$

$$\frac{dS_2}{dt} = \beta_{sal}\left(l_{sal} + \frac{L^2}{K_{sal} + L^2}\right) C_2 - d_S S_2$$

$$\frac{dT_2}{dt} = \beta_{S_2}\left(l_{S_2} + \frac{S_2^2}{K_{S_2} + S_2^2}\right) - k_b A_2 T_2 - d_T T_2$$

$$\frac{dA_2}{dt} = K_r \beta_{S_1}\left(l_{S_1} + \frac{S_1^2}{K_{S_1} + S_1^2}\right) - k_b A_2 T_2 - d_T A_2$$

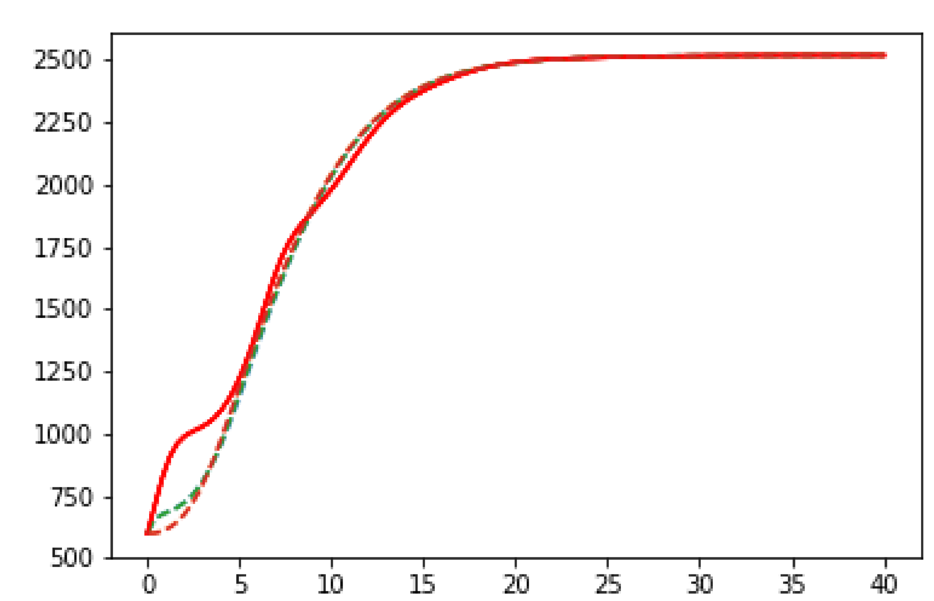
Possible reduced states

$$\frac{dC_1}{dt} = k_C\left(1 - \frac{C_1 + C_2}{C_{max}}\right) C_1 - d_c C_1 \frac{T_1}{K_{tox} + T_1} - dC_1$$

$$\frac{dC_2}{dt} = k_C\left(1 - \frac{C_1 + C_2}{C_{max}}\right) C_2 - d_c C_2 \frac{T_2}{K_{tox} + T_2} - dC_2$$

Retained states (outputs)

Total population dynamics for the full and the reduced models



Control of total population density of the consortium to a desired level compared for the full model and the different reduced models obtained when only considering the normed error metric. It is clear that all of the four models have similar performance and so it is not clear from this metric what the final reduced model choice should be. Note that the total population response of two of the reduced models are stacked on top of others in this figure.

Reduced model

Retained states : T_1, T_2, C_1, C_2

$$\hat{f}_1 = \left(l_{S1} + \frac{\beta_{S1} x_7^2}{x_7^2 + K_{I0}}\right) - d_T x_1 - \frac{\beta_{S2} k_b x_1 \left(K_{a0} l_{S2} + x_8^2\right)}{k_b x_1 x_8^2 + K_{a0} k_b x_1 + d_T x_8^2 + K_{a0} d_T},$$

$$\hat{f}_2 = \left(l_{S2} + \frac{\beta_{S2} x_8^2}{x_7^2 + K_{a0}}\right) - d_T x_5 - \frac{\beta_{S1} k_b x_5 \left(K_{I0} l_{S1} + x_7^2\right)}{k_b x_5 x_7^2 + K_{I0} k_b x_5 + d_T x_7^2 + K_{I0} d_T},$$

$$\hat{f}_3 = k_c\left(1 - \frac{x_7 + x_8}{C_{max}}\right) x_7 - \frac{d_c x_1 x_7}{x_1 + K_{tox}} - d x_7,$$

$$\hat{f}_4 = k_c\left(1 - \frac{x_7 + x_8}{C_{max}}\right) x_8 - \frac{d_c x_5 x_8}{x_5 + K_{tox}} - d x_8.$$

Lumped parameters

$$K_{ta} \triangleq \left(K_{tet} l_{tet} + atc^2 l_{tet} + atc^2\right)^2$$

$$K_{lI} \triangleq \left(I^2 l_{lac} + I^2 + K_{lac} l_{lac}\right)^2$$

$$K_a \triangleq \left(K_{tet} + atc^2\right)^2$$

$$K_I \triangleq \left(K_{lac} + I^2\right)^2$$

$$K_{a0} \triangleq \frac{K_{S2}}{K_{\beta a}}; \quad K_{\beta a} \triangleq \frac{\beta_{tet}^2 K_{ta}}{d_s^2 K_a}$$

$$K_{\beta I} \triangleq \frac{\beta_{lac}^2 K_{lI}}{d_s^2 K_I} \quad K_{I0} \triangleq \frac{K_{S1}}{K_{\beta I}}$$

Conclusion

Summary :

- Automated algorithm based on QSSA but with error convergence bounds.
- Bounds on sensitivity of error guarantees robust performance.
- Python based implementation to reduce SBML models. Available on Github.

Open questions :

- How generalizable to bigger/more complicated models?
- Using model reduction methods to go from mass-action CRN based models to minimal Hill function models.

Contact

Ayush Pandey
California Institute of Technology
Email : apandey@caltech.edu

Acknowledgements

We would like to thank Chelsea Hu for the population control circuit figure used. The project or effort depicted was or is sponsored by the Defense Advanced Research Projects Agency (Agreement HR0011-17-2-0008). The content of the information does not necessarily reflect the position or the policy of the Government, and no official endorsement should be inferred.

References

1. Antonis Papachristodoulou et al. "Structured model reduction for dynamical networked systems." *49th IEEE Conference on Decision and Control (CDC)*. IEEE, 2010, pp. 2670–2675.
2. Ayush Pandey and Richard M. Murray. "An automated model reduction tool to guide the design and analysis of synthetic biological circuits." *bioRxiv* (2019): 640276.