Layered Synthetic Biomolecular Systems

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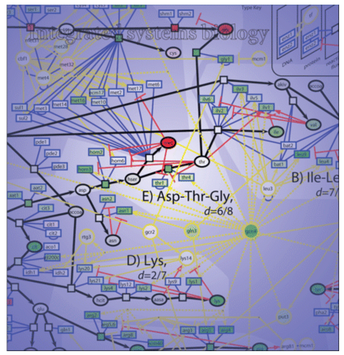
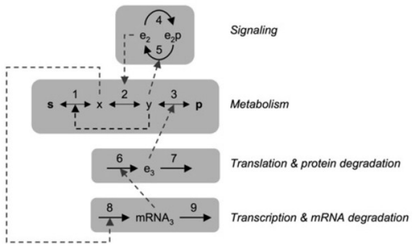
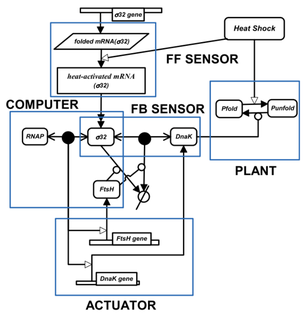
Biomolecular networks are highly nonlinear, extremely large scale, and yet are exceptionally structured







Above: Schematic of complex, integrated, intracellular network [1]

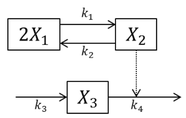
Above right: Biomolecular subnetwork structured through biochemical function [2]

Right: Biomolecular subnetwork structured through system-theoretic function [3]

The concept of LAYERING [4,5] provides a new way to describe a biological system's structure

Biological Network ODE Model:

$$\dot{x} = Sv(x)$$



Concentration vector:

$$x = [x_1, x_2, x_3]^T$$

Flux vector:

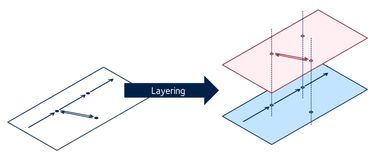
$$v(x) = [k_1(x_1)^2, k_2x_2, k_3, k_4x_2x_3]^T$$

Stoichiometric matrix:

$$S = \begin{bmatrix} -2 & 2 & 0 & 0 \\ 1 & -1 & 0 & 0 \\ 0 & 0 & 1 & -1 \end{bmatrix}$$

Traditional concept of **modular** decomposition concentrates on a simultaneous partition of the reaction-species sets into interconnected sub-networks. Assumes a partition of the state space of the dynamics.

We have instead proposed a new approach, termed **layering**, that considers the contribution of each subsystem to all species. Subsystem dimensions are defined by matrix ranks.



Decompose the stoichiometry

$$S = S^1 + \cdots + S^L$$

System dynamics: $\dot{x}(t) = Sv(x)$, $x(0) = x_0$

Layered dynamics: $\dot{x}^i(t) = S^i v(x^1 + \cdots + x^L)$, $x^i(0) = x^i(0)$

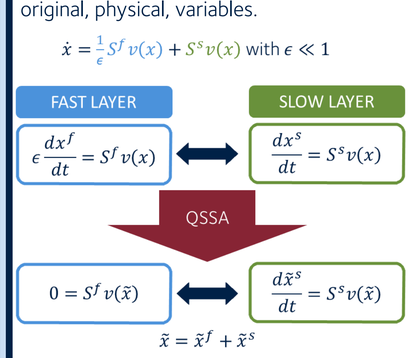
Recompose the layered states

$$x = x^1 + \cdots + x^L$$

We can choose a layered decomposition based on timescale separation [6]

Reaction rates often separate in scale; this in turn implies a natural decomposition of the columns of S. Traditional singular perturbation techniques require transformations to find fast and slow variables. By layering, these are automatically uncovered in terms of the original, physical, variables.

$$\dot{x} = \tfrac{1}{\epsilon} S^f v(x) + S^s v(x) \text{ with } \epsilon \ll 1$$



Original dynamics:

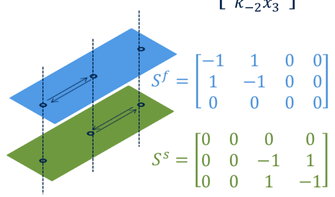
$$\dot{x} = \frac{1}{\epsilon} S^f v(x) + S^s v(x)$$

Approximated dynamics:

$$\dot{\tilde{x}} = \left(I + M^f(\tilde{x})\right) S^s v(\tilde{x})$$

$$X_1 \overset{\sim 1/\epsilon}{\longleftrightarrow} X_2 \overset{\sim 1}{\leftrightarrow} X_3$$

$$\dot{x} = \begin{bmatrix} -1 & 1 & 0 & 0 \\ 1 & -1 & -1 & 1 \\ 0 & 0 & 1 & -1 \end{bmatrix} \begin{bmatrix} k_1x_1/\epsilon \\ k_{-1}x_2/\epsilon \\ k_2x_2 \\ k_{-2}x_3 \end{bmatrix}$$



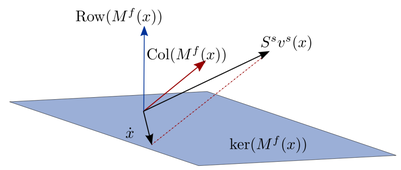
The key result of [6] is given to the left. The system dynamics are a projection of the slow dynamics, defined by the formula:

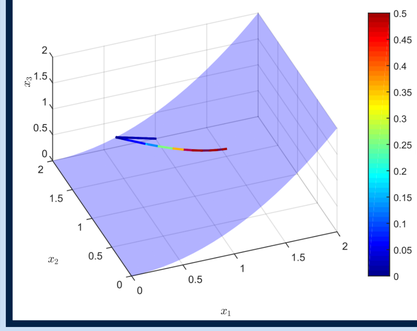
$$M^f(x) = -U^f \left(C^f v'(x) U^f\right)^{-1} C^f v'(x)$$

for the full rank matrices defining $S^f = U^f C^f$

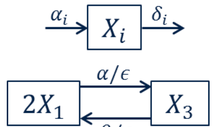
Timescale Separation implies that the biochemical network dynamics proceed according to additional nonlinear conservation constraints [7]

The projection of the slow dynamics given above implies that the approximated dynamics are always orthogonal to the row space of $M^f(x)$, which varies with the state.





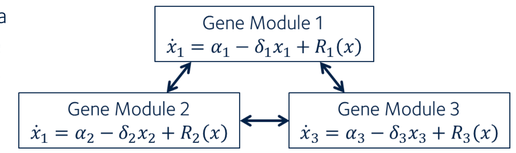
The nonlinear conservation $x_3 = k{x_1}^2$ is not implied by the empty left null space of the full system's stoichiometric matrix:



$$S = \begin{bmatrix} 1 & 0 & 0 & -2 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 1 \end{bmatrix}$$

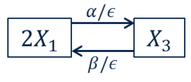
This has implications for designing Synthetic Biomolecular networks across multiple timescales

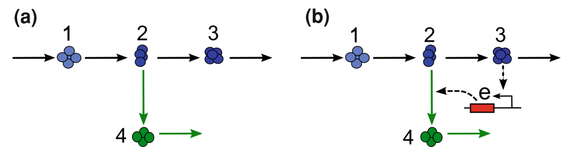
Consider the layered design of a gene regulatory network whose transcription factors participate in a fast protein interaction network.



- What constraints can the PIN implement?
- How to design the genetic interactions (dynamics) together with the PIN (constraints) for the network to achieve the desired behaviour with the required performance?

The genetic layer is designed by $R_i(x)$ while the fast PIN (i.e. nonlinear constraint) is tuned separately.





Similarly, we can consider the design of genetic dynamics for the production of enzymes to control a fast metabolic network [8].

- Nonlinear constraints defined by enzyme-dependent (quasi-) steady states of the metabolic network
- Slower, genetic dynamics can be externally driven by modulating metabolic influxes
- Where should the metabolic network be tuned through redesign of metabolic parameters (constraint design)? Where should the genetic network be constructed and tuned (design of dynamics)?

Conclusions and Future Work

- Through layered decomposition we have formulated the QSS approximation of a timescale separated system as a state-dependent projection of the slow dynamics, written in terms of the fast layer's stoichiometric structure and kinetic form.
- We can thus approximate complex dynamics in high dimension into lower-dimensional dynamics, yet remain embedded in the original state space.
- The design of fast dynamics can thus implement tuneable, nonlinear static constraints into a synthetic biomolecular network.
- Conversely, when investigating natural networks, the dynamics on one, fast, timescale define nonlinear static constraints on other, slower timescales, on which dynamics have evolved to perform biological functionalities.
- Consider also layered decomposition without timescale separation, or in other dynamical systems. How can the decomposition of dynamics be interpreted as a decomposition into multiple functionalities and constraints on the entire set of original system variables?

[1] Image from Gregory Stephanopoulos (PNAS Cover, 21 April 2009)
[2] Bruggeman *et al.* (2008) *Control, responses and modularity of cellular regulatory networks: a control analysis perspective.* IET Syst Biol 2(6):397
[3] Kurata *et al.* (2006) *Module-based analysis of robustness tradeoffs in the heat shock response system.* PLoS Comp. Biol. 2(7):e59
[4] TPP & AP (2013) *Layering in networks: The case of biochemical systems.* Proc. American Control Conference
[5] TPP & AP (2014) *Signal propagation across layered biochemical networks.* Proc. American Control Conference
[6] TPP & AP (2014) *Layered decomposition for the model order reduction of timescale separated biochemical reaction networks.* J. Theor. Biol. 356:113
[7] TPP & AP (under review) *Designed conservation relations in layered synthetic biomolecular networks.*
[8] Kuntz *et al.* (2014) *Model reduction of genetic-metabolic networks...* In Kulkarni *et al.*, A Systems Theoretic Approach to Systems and Synthetic Biology (Ch.7)

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