# Layered Synthetic Biomolecular Systems

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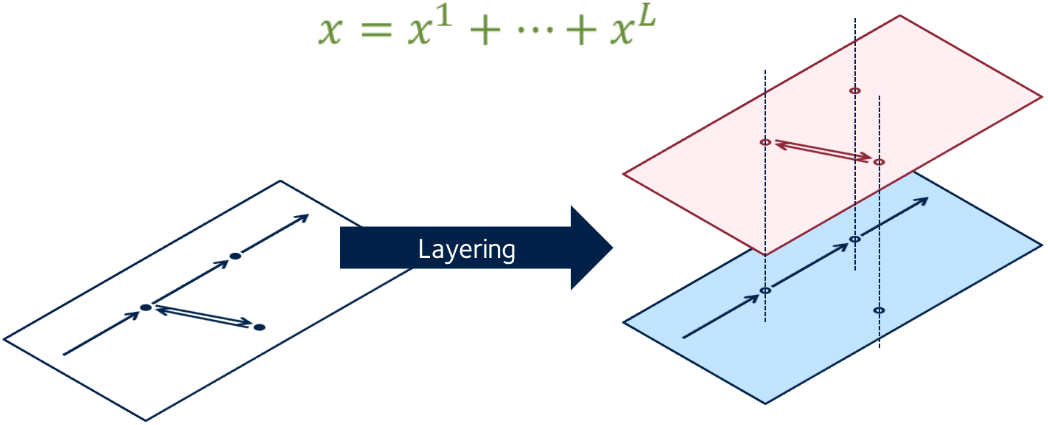
# Decomposition in terms of original variables

Decompose the stoichiometry
$S = S^1 + \dots + S^L$

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

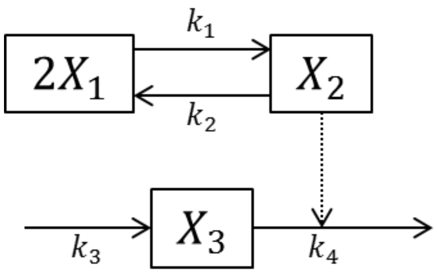
Layered dynamics:
$\dot{x}^i(t) = S^i v(x^1 + \dots + x^L)$
$x^i(0) = x^i(0)$

Recompose the layered states
$x = x^1 + \dots + x^L$




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

Key question – how to decompose? Clearly this depends on the application. In the following example, reactions classed as fast or slow. Normally, singular perturbation requires transformation, but we can keep this system in its original variables by layered decomposition.

# Layered Singular Perturbation

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

**FAST LAYER**

$$\epsilon \frac{dx^f}{dt} = S^f v(x)$$

**SLOW LAYER**

$$\frac{dx^s}{dt} = S^s v(x)$$

QSSA

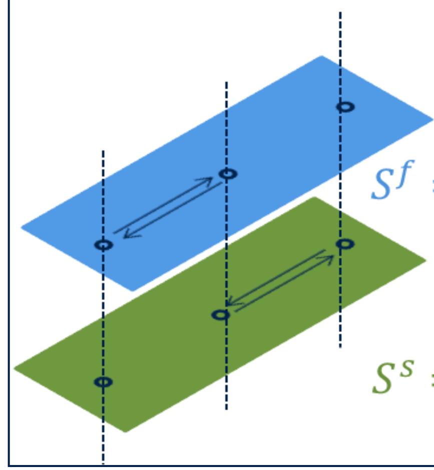
$$0 = S^f v(\tilde{x})$$

$$\frac{d\tilde{x}^s}{dt} = S^s v(\tilde{x})$$

$$\tilde{x} = \tilde{x}^f + \tilde{x}^s$$

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

$$\dot{x} = \begin{bmatrix} -1 & 1 & 0 & 0 \\ 1 & -1 & -1 & 1 \\ 0 & 0 & 1 & -1 \end{bmatrix} \begin{bmatrix} k_1 x_1/\epsilon \\ k_{-1} x_2/\epsilon \\ k_2 x_2 \\ k_{-2} x_3 \end{bmatrix}$$



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

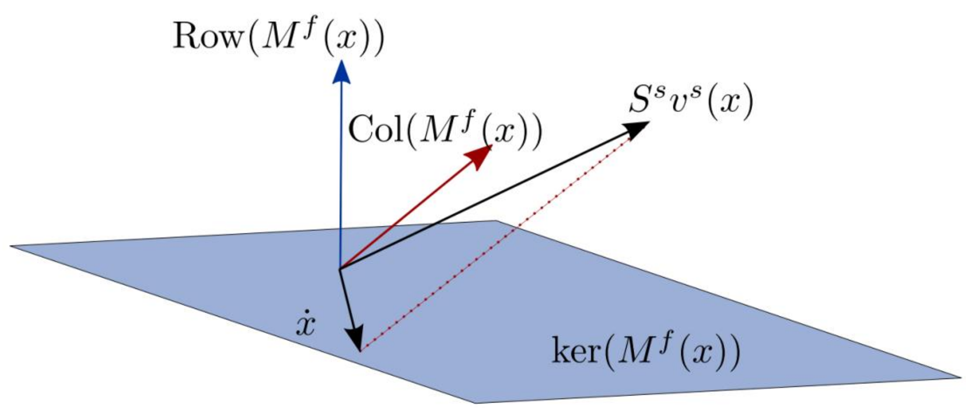
$$S^s = \begin{bmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & -1 & 1 \\ 0 & 0 & 1 & -1 \end{bmatrix}$$

Original dynamics:

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

Approximated dynamics:

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



# Dynamics under Nonlinear, Tuneable Constraints

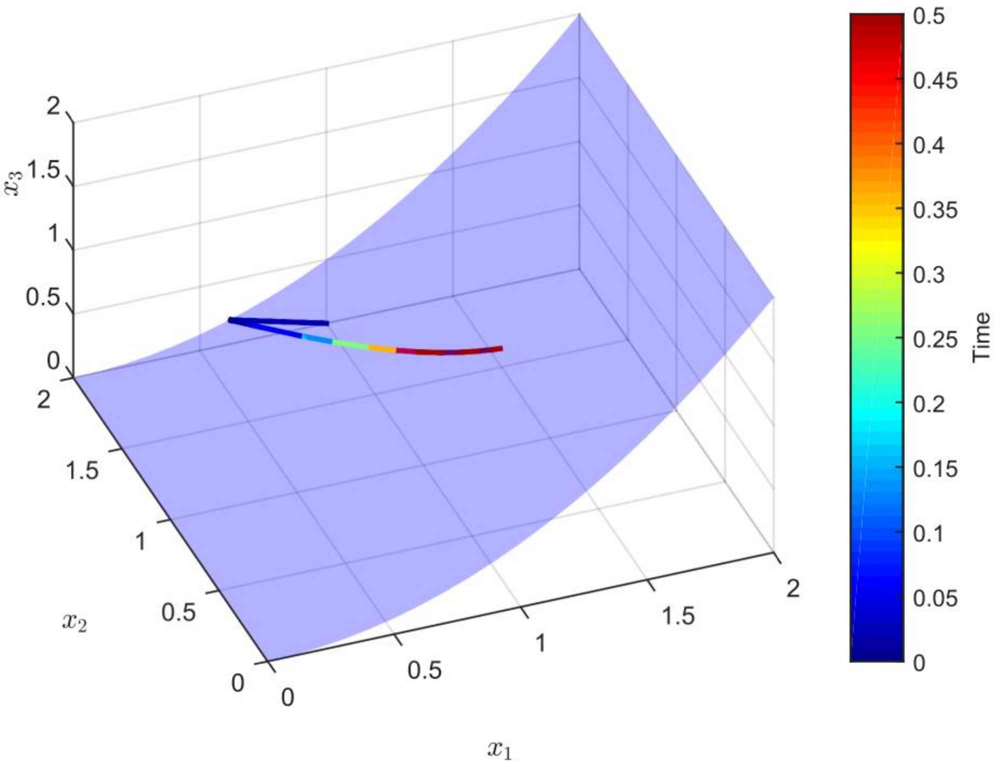
Gene Module 1
$$\dot{x}_1 = \alpha_1 - \delta_1 x_1 + R_1(x)$$

Gene Module 2
$$\dot{x}_1 = \alpha_2 - \delta_2 x_2 + R_2(x)$$

Gene Module 3
$$\dot{x}_3 = \alpha_3 - \delta_3 x_3 + R_3(x)$$

$$2X_1 \underset{\beta/\epsilon}{\overset{\alpha/\epsilon}{\rightleftharpoons}} X_3$$

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




$$\xrightarrow{\alpha_i} X_i \xrightarrow{\delta_i}$$

$$2X_1 \underset{\beta/\epsilon}{\overset{\alpha/\epsilon}{\rightleftharpoons}} X_3$$

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