Rule-based Systems Theory for Regulation in Networks of Biomolecules, Microbial Cells and Populations

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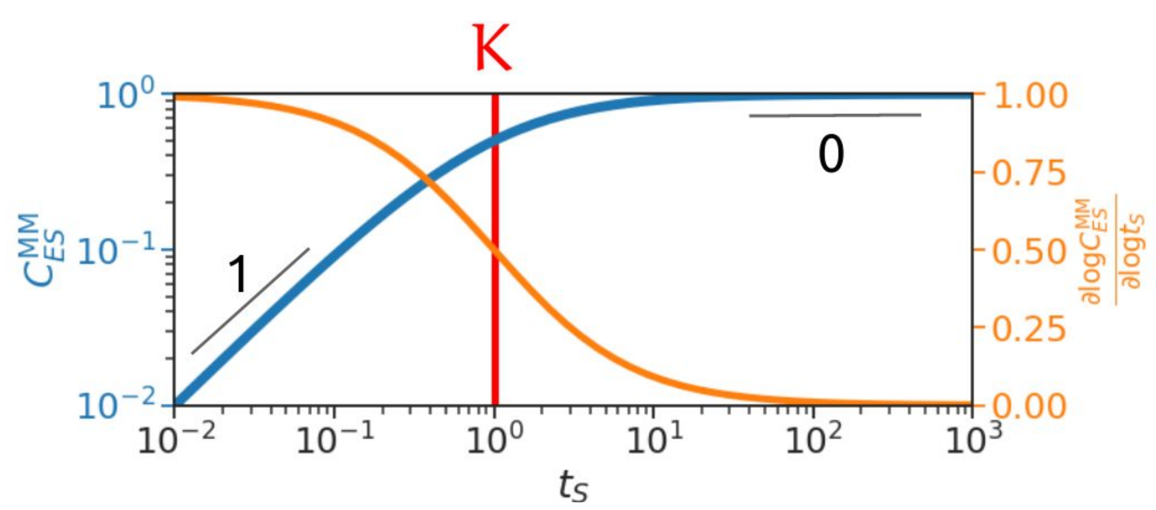
Theory Foundation: Full Profile of Bioregulation

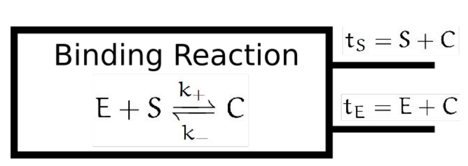
$$\mathrm{E}+\mathrm{S} \rightleftharpoons \mathrm{C}_{\mathrm{ES}} \rightarrow \mathrm{E}+\mathrm{P}$$

Catalysis: direction of change.

$$(t_S, t_P) \xrightarrow{C_{ES}(t_S)} (t_S - 1, t_P + 1)$$

Binding: regulates catalysis rate.



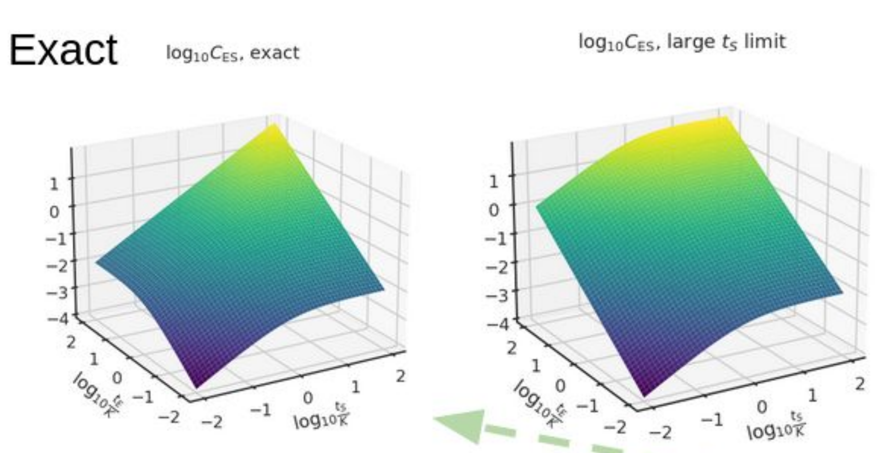


$$C_{ES} = \frac{ES}{K}$$

$$t_S = C_{ES} + S$$

$$t_E = C_{ES} + E$$

Exact

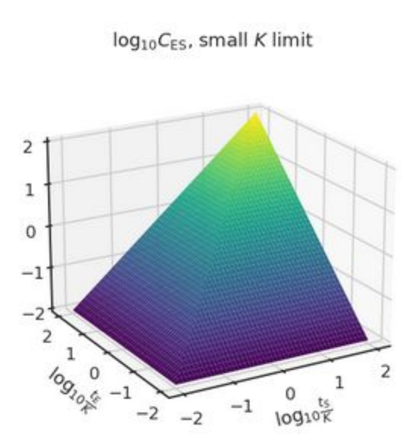


Large tS limit

$t_S \gg t_E$

$C_{ES} \approx C_{ES}^{MM} = t_E \frac{t_S}{t_S + K}$

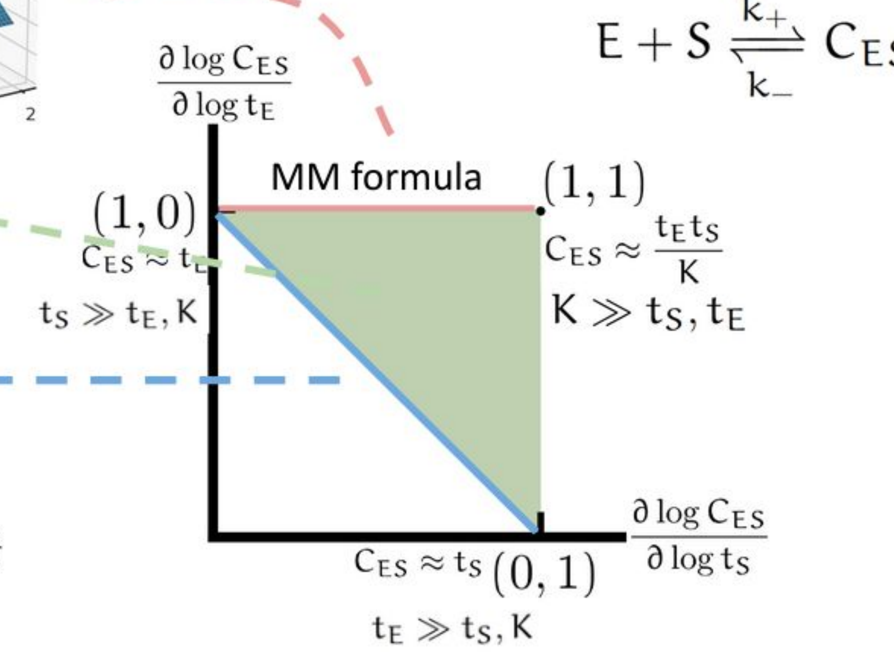
$E + S \underset{k_-}{\overset{k_+}{\rightleftharpoons}} C_{ES}$



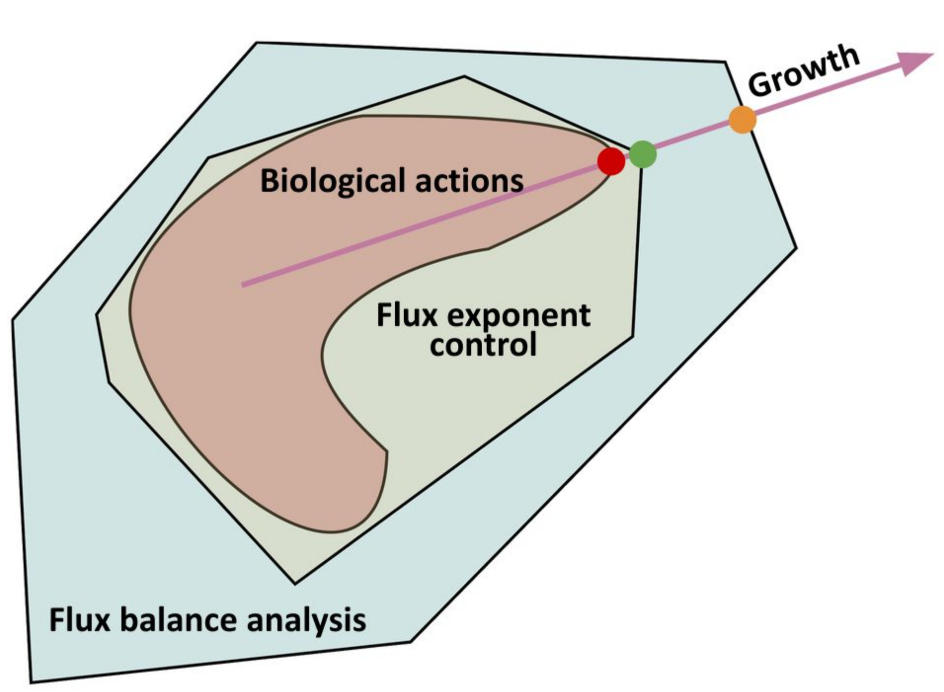
Small K limit

$K \ll t_E, t_S$

$C_{ES} \approx \min\{t_E, t_S\}$



Flux Exponent Control for Dynamic Metabolism



Metabolism: known stoichiometry, unknown flux.

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

Constraint based methods: flux is optimal for some goal.

$$\dot{x} = Su, \quad u(t) \in \mathcal{U}$$

$$v(x) = \arg\max_{u} G(u, x)$$

Flux Balance Analysis: steady state

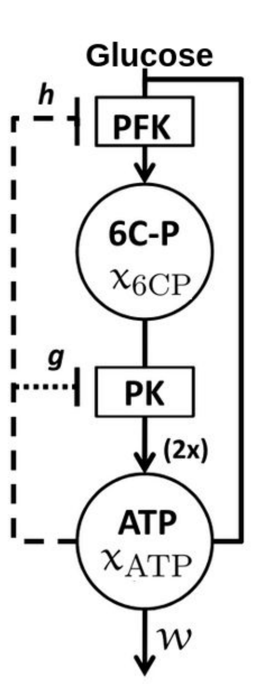
$$v(x) = \arg\max_{u} c^T u$$

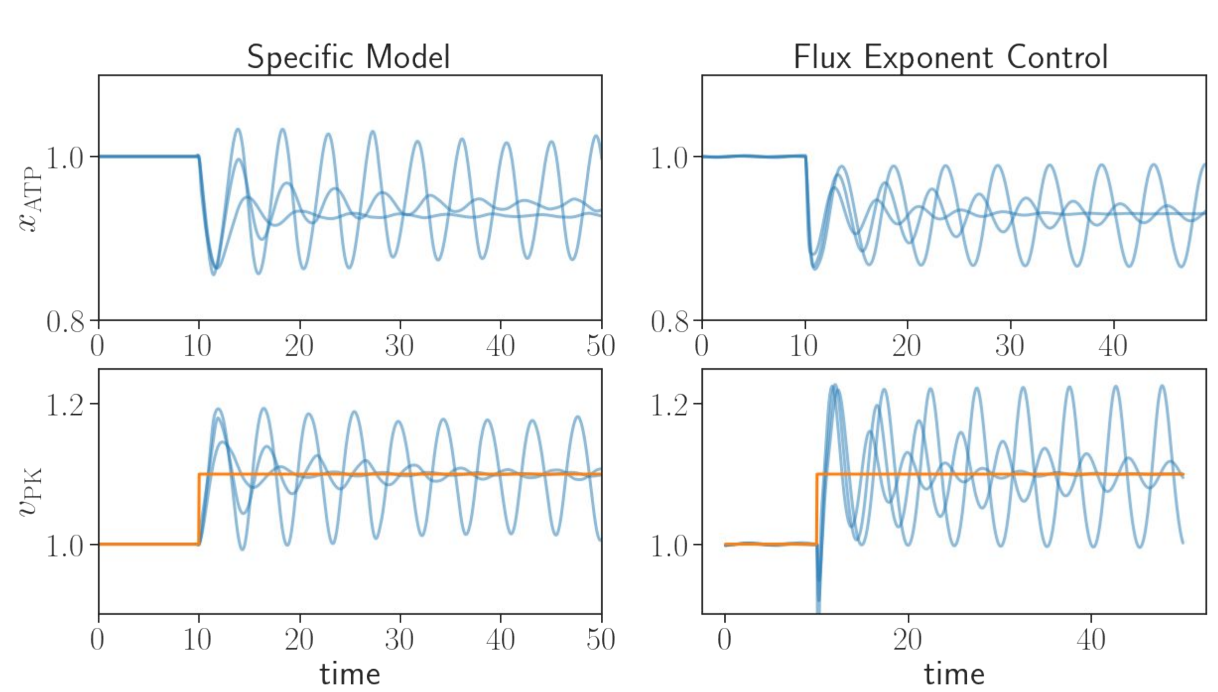
$$\dot{x} = 0 = Su, \quad u \in \mathcal{U}_{\text{static}}$$

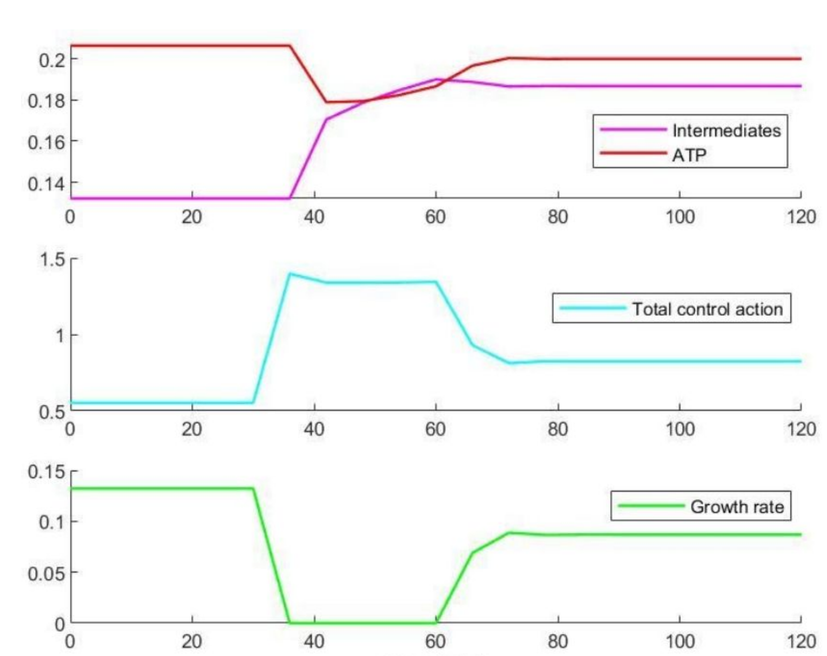
Flux Exponent Control: dynamic

$$v(x) = e^{A \log x + Bu^*}, \quad u^* = \arg\max_{u} G(x, u)$$

$$\dot{x} = Se^{A \log x + Bu}, \quad u \in \mathcal{U}_{\text{dynamic}}$$







System Level Synthesis for Dynamic Metabolic Modeling

Scalable, distributed computation

$$\min_{\Phi_x, \Phi_u} \ \text{cost}(\Phi_x, \Phi_u)$$

$$\text{s.t.} \ \begin{bmatrix} zI - A & -B \end{bmatrix} \begin{bmatrix} \Phi_x \\ \Phi_u \end{bmatrix} = I$$

$$\text{constraint}(\Phi_x, \Phi_u)$$

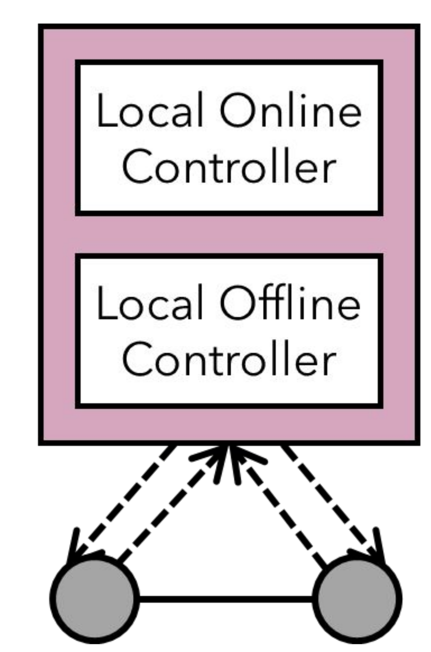
"Rules of biology": What cost(s) do metabolic networks try to optimize?

Can capture any optimal behavior

"Rules of biology": What constraint(s) do metabolic networks obey? Local information, minimum concentrations, etc.

Applicable to online control, offline control, adaptive control, etc.

Fluxes are influenced by information on local metabolite concentrations. Use local controllers to generate optimal fluxes for a given cost and constraint



Online control: Model predictive control. Plan optimal time-trajectories of fluxes and metabolites in response to large changes

Offline control: react to small perturbations

Use optimal control to determine optimal time-trajectories of fluxes and metabolites. Metabolites are in grey, controllers (which control flux) are in green. Not all controllers are shown.