BioMachine Architecture and Control (BMAC) Lab
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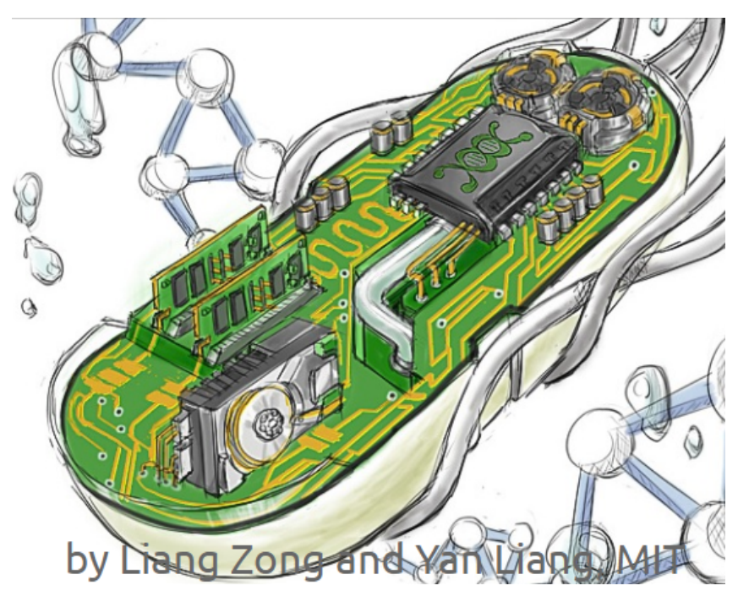
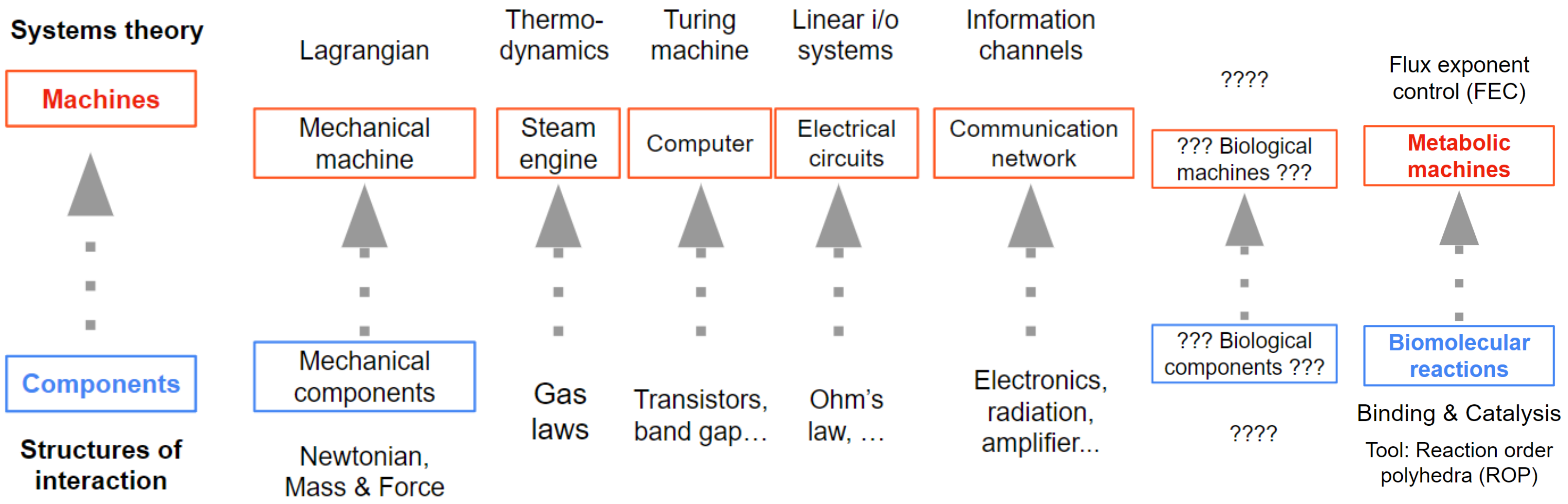
Bioengineers need a systems theory of our own… for a bio-industrial revolution!

Revolutionary engineering advances are driven by understandings of both (1) structures of interaction about how components interact, and (2) systems theory about how components are put together into a functioning machine.


by Liang Zong and Yan Liang, MIT



Our answer for bioregulation

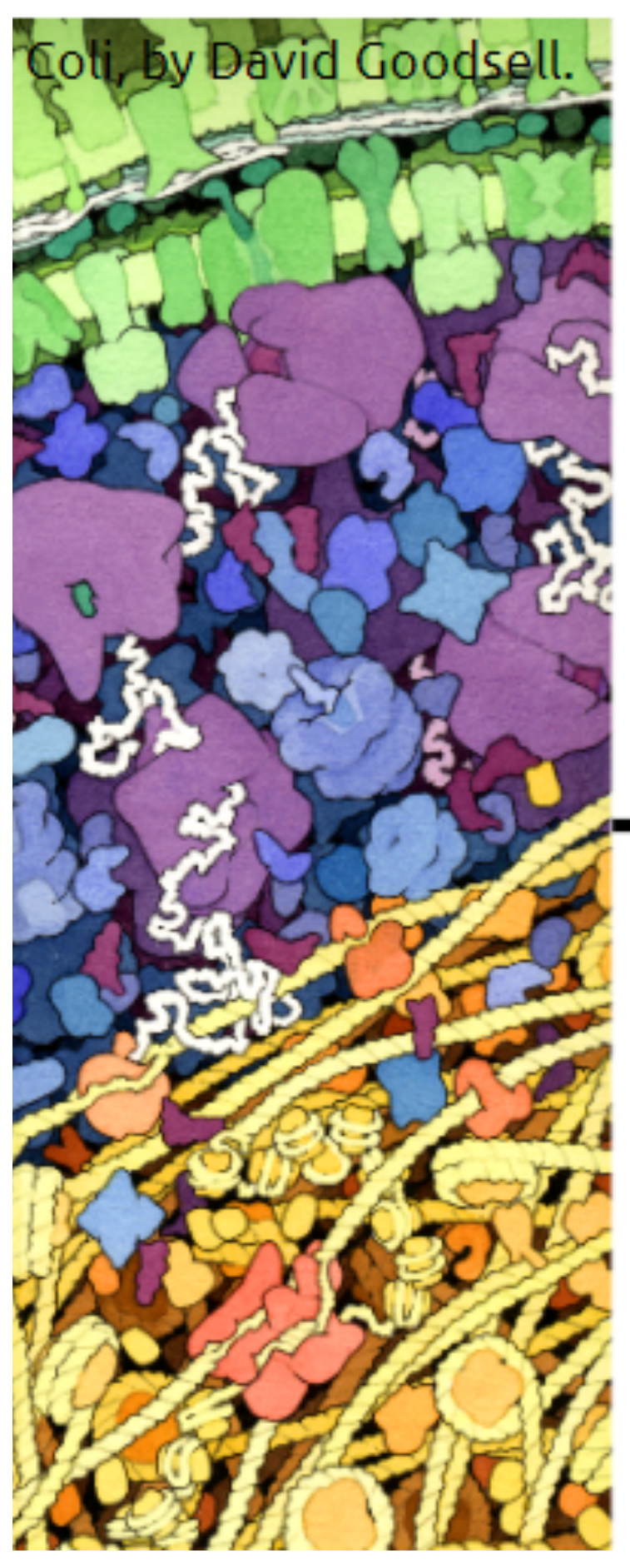
What's next?

Metabolic engineering (comp): large scale computation of metabolism dynamics, combining distributed control and FEC.

Dynamic regulation of microbial survival and growth (comp + exp): speed, accuracy and complexity tradeoff in combinatorial decision making in highly fluctuating environments.

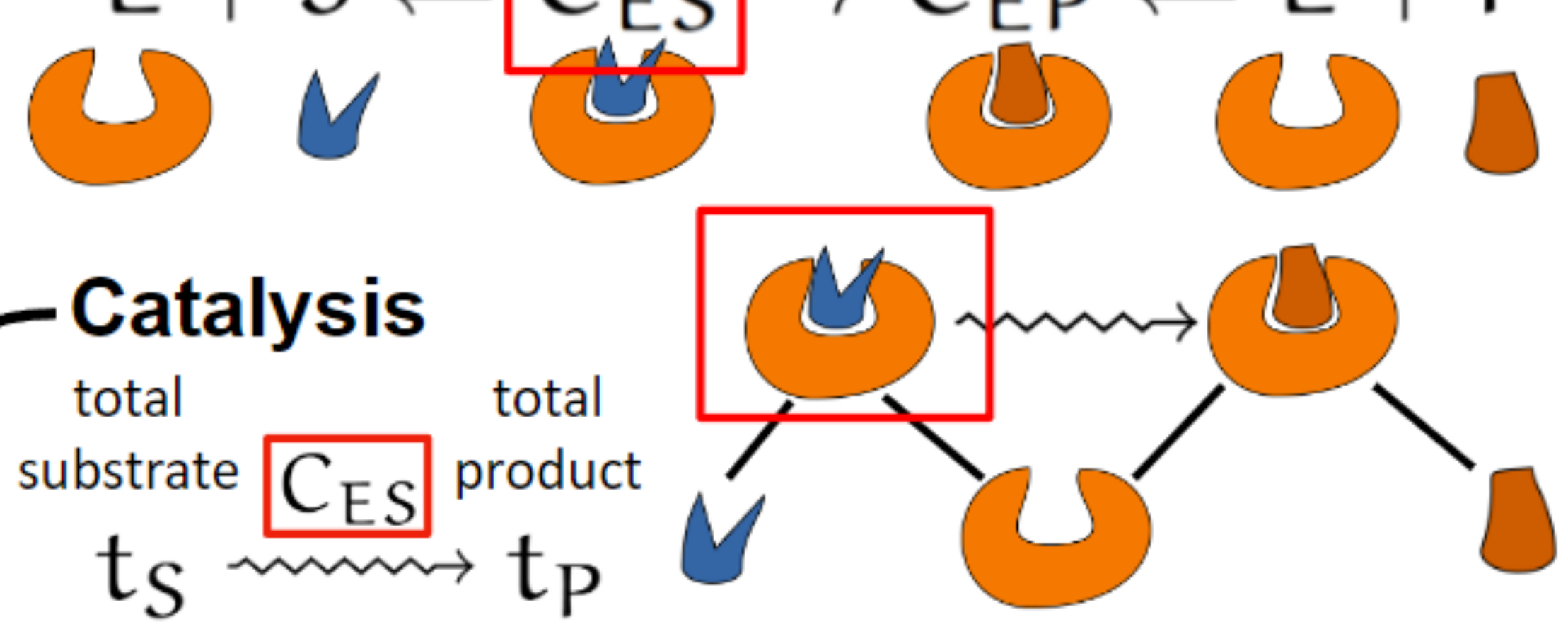
Holistic analysis and foundation of combinatorial regulation in systems biology (math+comp): ROP enables novel analysis of **necessary** conditions (i.e. Laws) of adaptation/hypersensitivity/multistability of biocircuits. ROP also reveals the structure underlying combinatorial complexity in bioreg, laying the cornerstone of a rigorous foundation.

Newton's law for bio: bioregulation is binding regulates catalysis.


Coli, by David Goodsell.

enzyme substrate product

$$\mathrm{E}+\mathrm{S} \rightleftharpoons \boxed{\mathrm{C}_{\mathrm{ES}}} \to \mathrm{C}_{\mathrm{EP}} \rightleftharpoons \mathrm{E}+\mathrm{P}$$



Catalysis

total substrate $\boxed{\mathrm{C}_{\mathrm{ES}}}$ total product

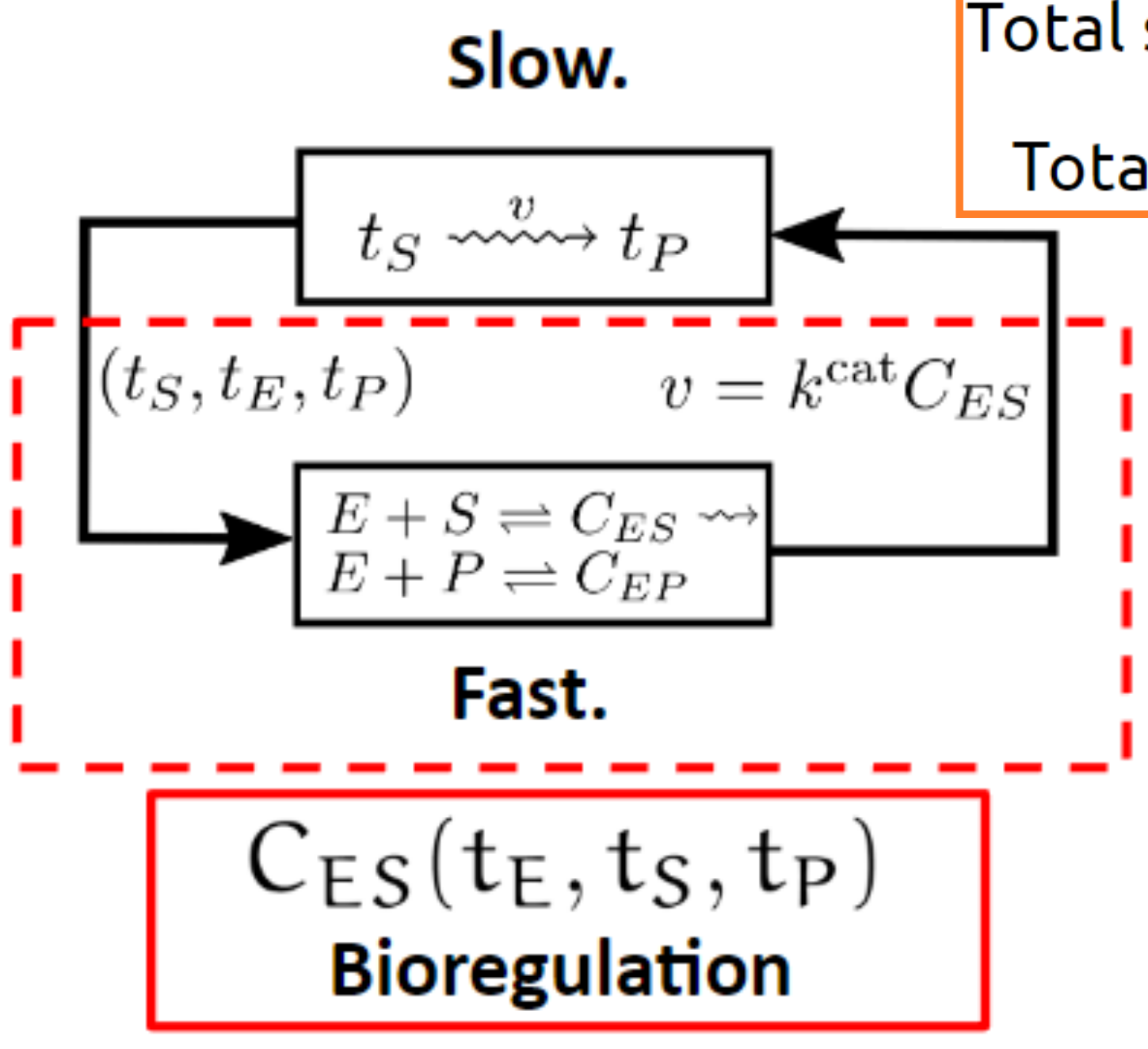
$$\mathrm{t}_{\mathrm{S}} \rightsquigarrow \mathrm{t}_{\mathrm{P}}$$

Determines the **direction** of change.

Binding

Determines the **rate**, regulates catalysis flux.

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



$\mathrm{C}_{\mathrm{ES}}(\mathrm{t}_{\mathrm{E}}, \mathrm{t}_{\mathrm{S}}, \mathrm{t}_{\mathrm{P}})$

Bioregulation

Holistic solution of bioreg via reaction order polyhedra (ROP)

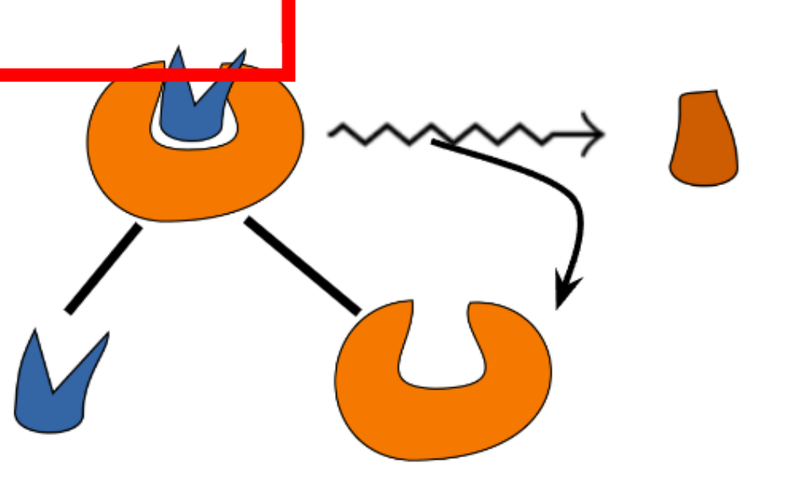
Full bioreg profile is HARD to describe.

Steady state equation: $\mathrm{C}_{\mathrm{ES}} = \frac{\mathrm{ES}}{\mathrm{K}}$ $\boxed{\mathrm{E}+\mathrm{S} \underset{\mathrm{k}_-}{\overset{\mathrm{k}_+}{\rightleftharpoons}} \mathrm{C}_{\mathrm{ES}}} \to \mathrm{E}+\mathrm{P}$

Conserved quantities:

Total substrate: $\mathrm{t}_{\mathrm{S}} = \mathrm{C}_{\mathrm{ES}} + \mathrm{S}$

Total enzyme: $\mathrm{t}_{\mathrm{E}} = \mathrm{C}_{\mathrm{ES}} + \mathrm{E}$

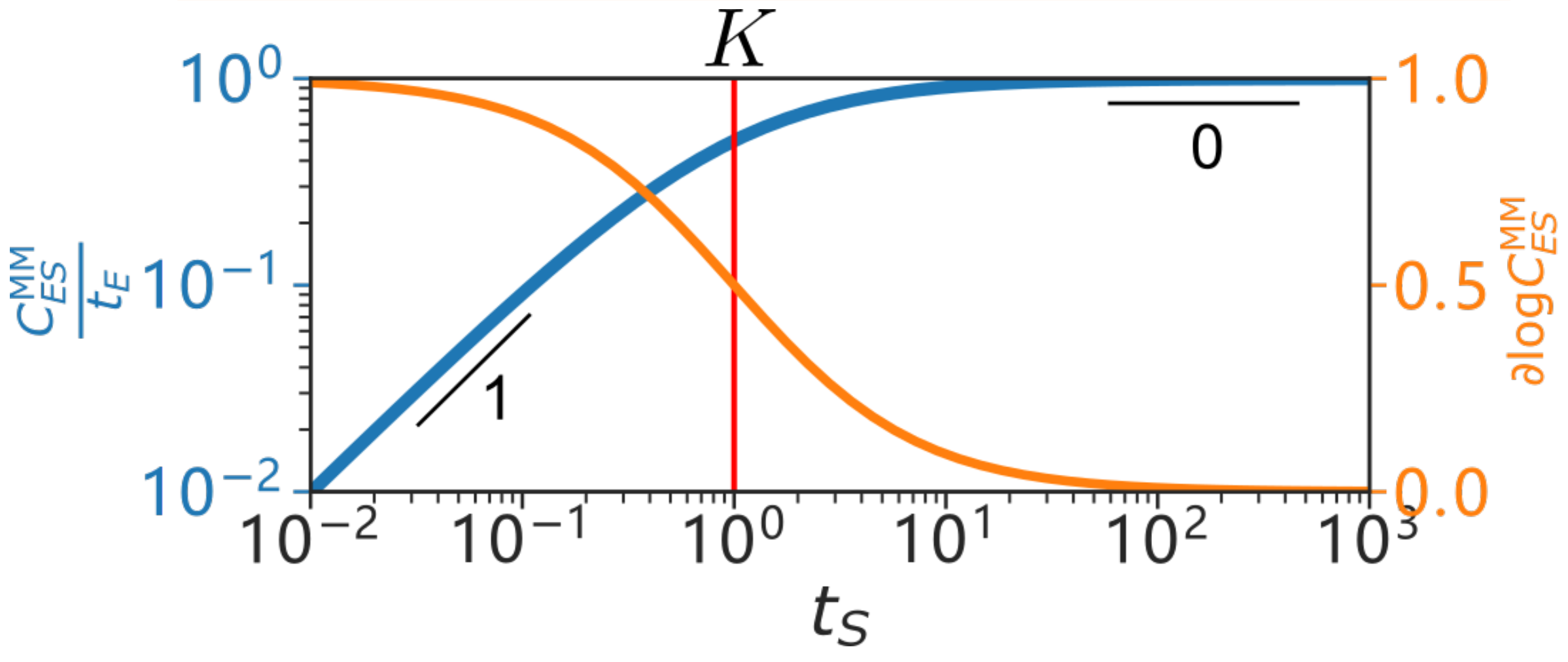


Traditional methods are restrictive.

Assuming $\mathrm{t}_{\mathrm{S}} \gg \mathrm{t}_{\mathrm{E}}$ (Michaelis-Menten), ← Such assumptions are made in all existing methods, making them invalid in combinatorial regulations and highly dynamic scenarios.

$$\boxed{\mathrm{C}_{\mathrm{ES}} \approx \mathrm{C}_{\mathrm{ES}}^{\mathrm{MM}} = \mathrm{t}_{\mathrm{E}}\frac{\mathrm{t}_{\mathrm{S}}}{\mathrm{t}_{\mathrm{S}}+\mathrm{K}}}$$

Reaction order can also capture bioreg.



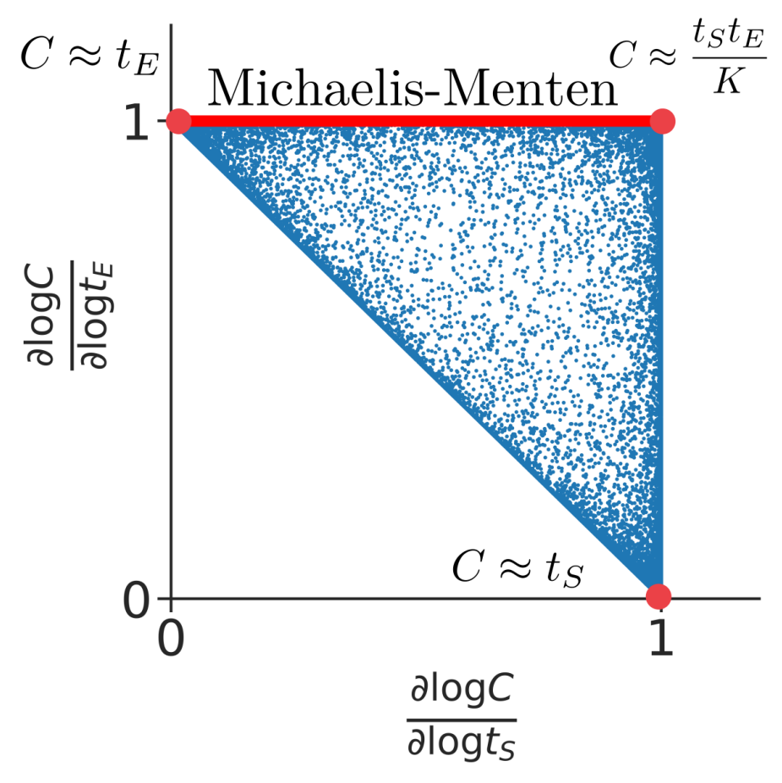
The holistic approach via differential geometry

$\mathrm{F}: \mathbb{R}^6_{>0} \to \mathbb{R}^3$ defines a 3d manifold in $\mathbb{R}^6_{>0}$.

$$0 = \mathrm{F}(\mathrm{E},\mathrm{S},\mathrm{C}_{\mathrm{ES}},\mathrm{t}_{\mathrm{S}},\mathrm{t}_{\mathrm{E}},\mathrm{K}) = \begin{bmatrix} \mathrm{ES}-\mathrm{KC}_{\mathrm{ES}} \\ \mathrm{t}_{\mathrm{E}}-\mathrm{E}-\mathrm{C}_{\mathrm{ES}} \\ \mathrm{t}_{\mathrm{S}}-\mathrm{S}-\mathrm{C}_{\mathrm{ES}} \end{bmatrix}$$

Directly use implicit function theorem.

$$\boxed{\frac{\partial \log \mathrm{C}_{\mathrm{ES}}}{\partial \log \mathrm{t}_{\mathrm{S}}, \mathrm{t}_{\mathrm{E}}} = \frac{1}{1+e+s}\begin{bmatrix} 1+e & 1+s \end{bmatrix}} \quad s = \frac{\mathrm{S}}{\mathrm{K}}, e = \frac{\mathrm{E}}{\mathrm{K}}$$



Reaction order polyhedra (ROP) can be computed at scale.

① Specify a binding network

$$R+S \rightleftharpoons C_{RS}$$
$$G+C_{RS} \rightleftharpoons C_{GRS}$$

② Write down stoichiometry matrix

$$\mathbf{N} = \begin{array}{c} \begin{matrix} G & R & S & C_{RS} & C_{GRS} \end{matrix} \\ \begin{bmatrix} 0 & -1 & -1 & 1 & 0 \\ -1 & 0 & 0 & -1 & 1 \end{bmatrix} \end{array}$$

atomic species

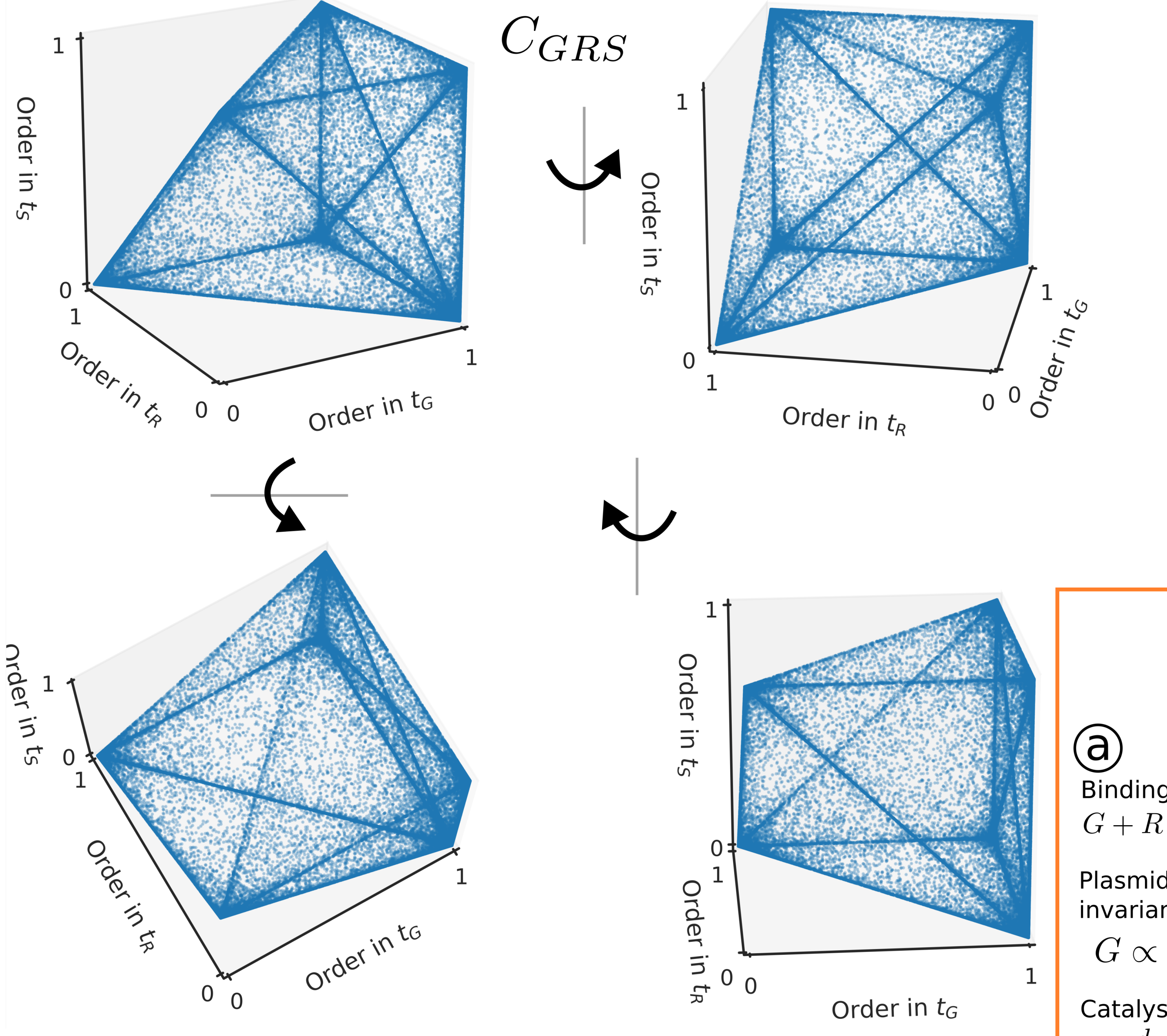
$$\mathbf{L} = \begin{array}{c} \begin{matrix} G & R & S & C_{RS} & C_{GRS} \end{matrix} \\ \begin{bmatrix} 1 & 0 & 0 & 0 & 1 \\ 0 & 1 & 0 & 1 & 1 \\ 0 & 0 & 1 & 1 & 1 \end{bmatrix} \end{array} \begin{matrix} t_G \\ t_R \\ t_S \end{matrix}$$

③ Compute conservation law matrix

④ Compute reaction orders by formula

$$\mathbf{x} = (G, R, S, C_{RS}, C_{GRS})$$
$$\mathbf{t} = (t_G, t_R, t_S) = \mathbf{Lx}$$
$$\frac{\partial \log \mathbf{x}}{\partial \log(\mathbf{t}, \mathbf{k})} = \begin{bmatrix} \Lambda_{\mathbf{t}}^{-1}\mathbf{L}\Lambda_{\mathbf{x}} \\ \mathbf{N} \end{bmatrix}^{-1}$$

⑤ Sample points in reaction order polyhedron of target species



ROP can discover hidden regimes in biocircuits, e.g. plasmid number invariance.

ⓐ

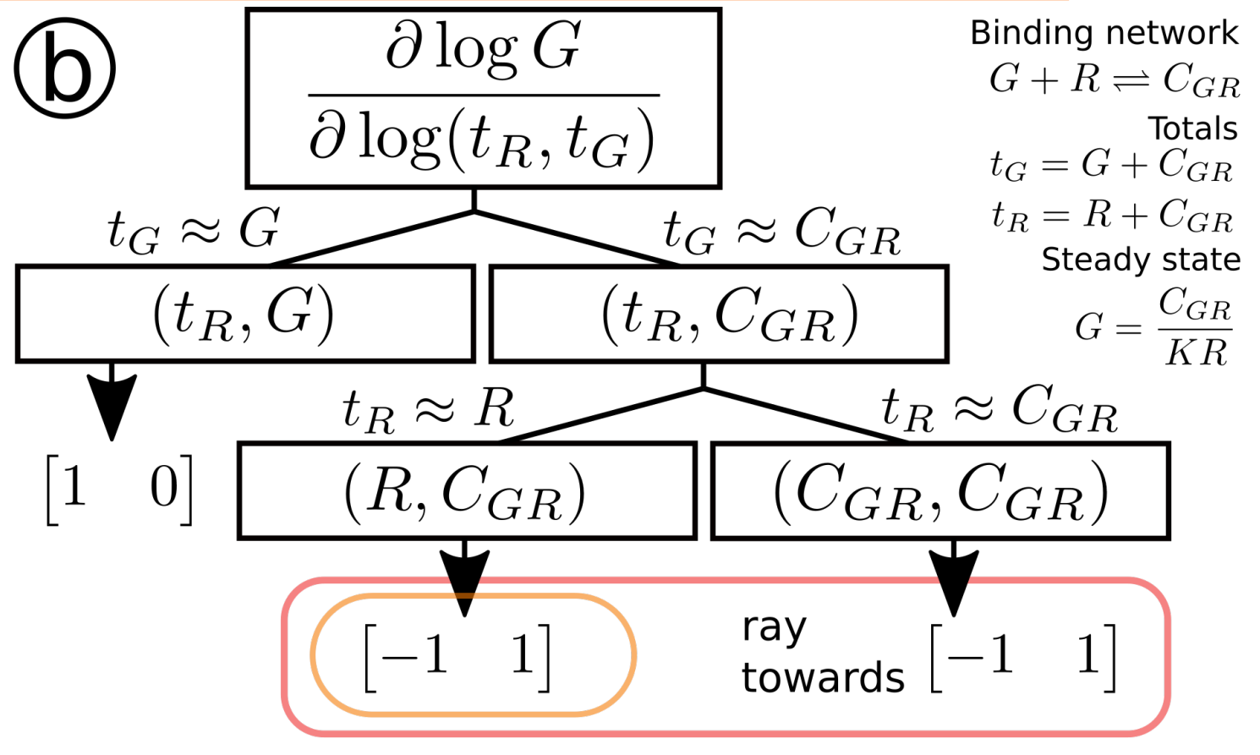
Binding network $G+R \rightleftharpoons C_{GR}$ $\implies$ $G \propto t_G^{a_G} t_R^{a_R}$, $(a_R, a_G) \in \mathcal{P}_{\mathrm{bind}}$

Plasmid number invariance $G \propto t_G^0$ $\Big\}$ $\boxed{a_G + a_R = 0, \ (a_R, a_G) \in \mathcal{P}_{\mathrm{bind}}}$

Catalysis dynamics

$$\frac{d}{dt}t_R = kt_G - \gamma t_R \implies t_R = \frac{k}{\gamma}t_G \text{ at steady state}$$

ⓑ



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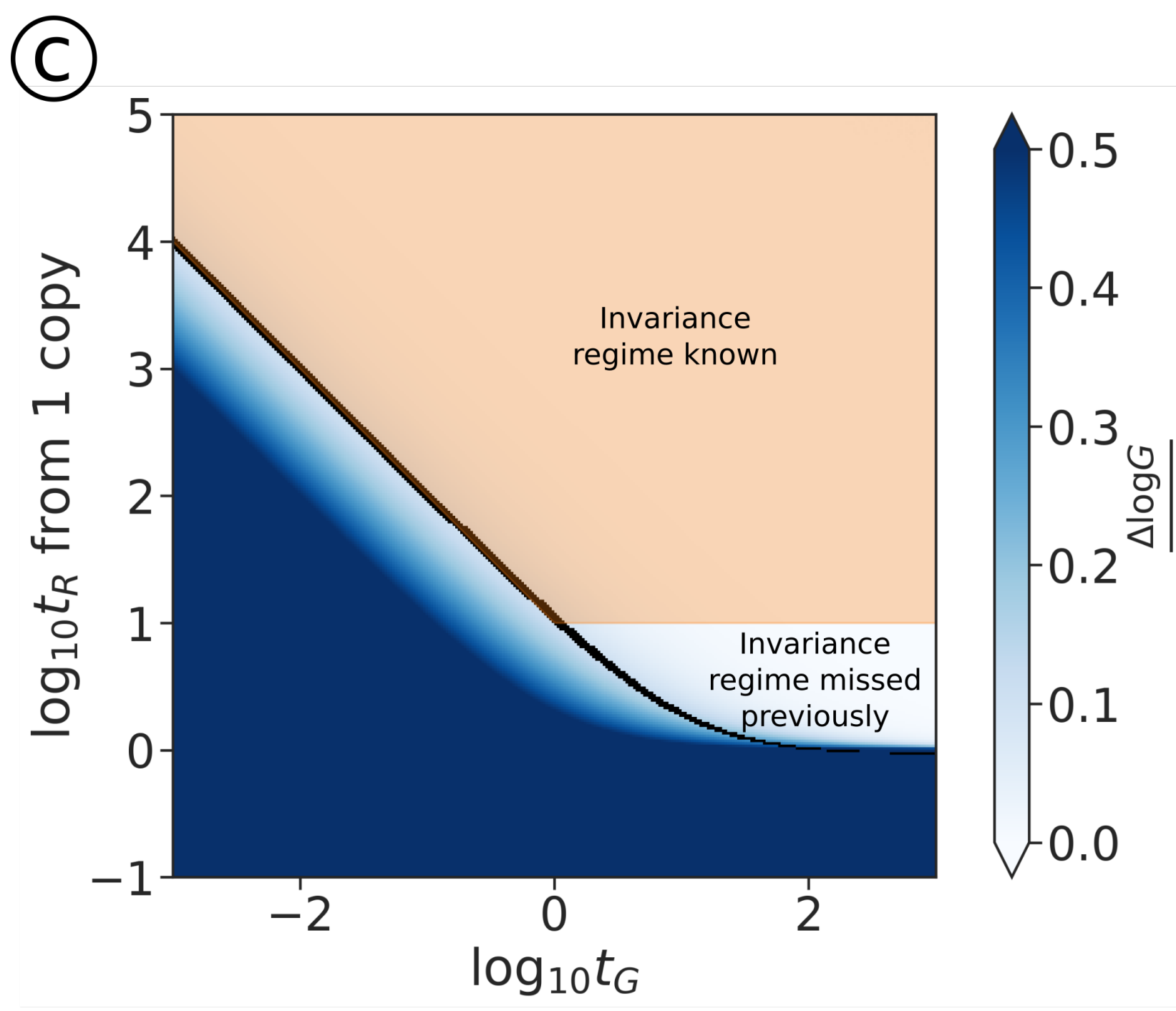

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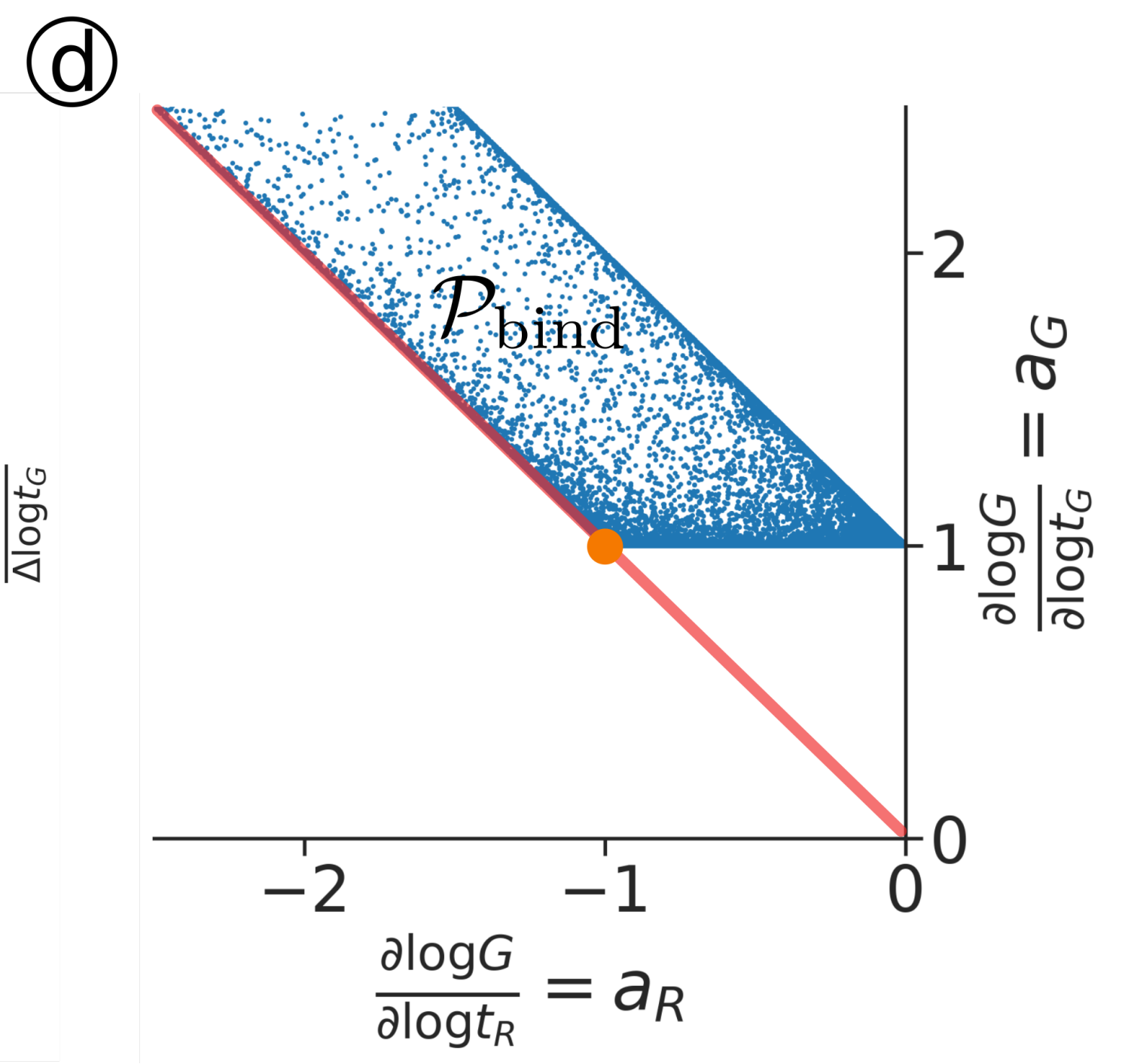
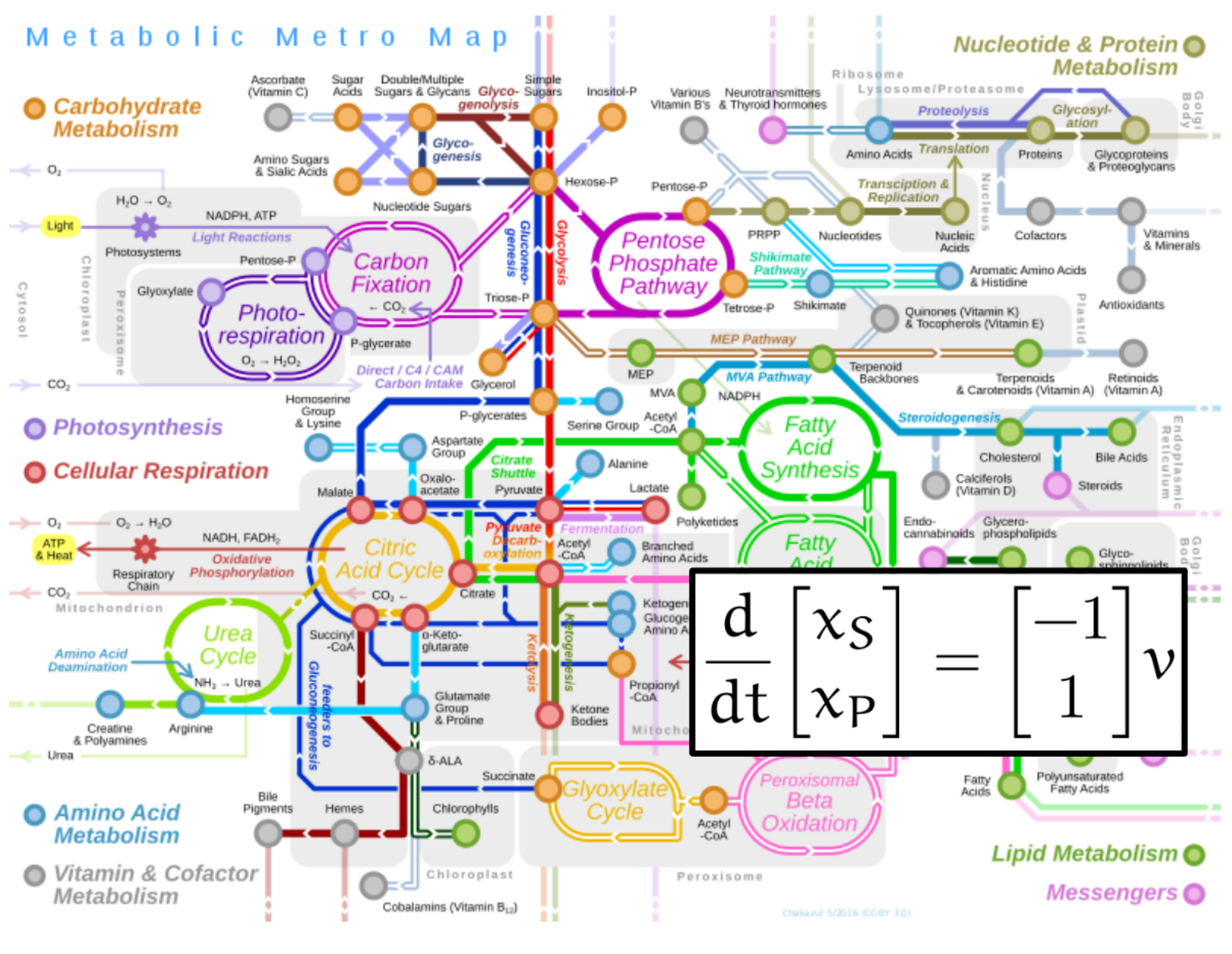


ROP implies a rule of life: flux exponent control (FEC), predicting metabolism dynamics from network structure



$$\frac{\mathrm{d}}{\mathrm{dt}}\begin{bmatrix} \mathrm{x}_{\mathrm{S}} \\ \mathrm{x}_{\mathrm{P}} \end{bmatrix} = \begin{bmatrix} -1 \\ 1 \end{bmatrix} v$$

Lack knowledge about enzyme regulation.

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

You see this: $\boxed{\mathrm{C}_{\mathrm{ES}}}$

$$\mathrm{t}_{\mathrm{S}} \rightsquigarrow \mathrm{t}_{\mathrm{P}}$$

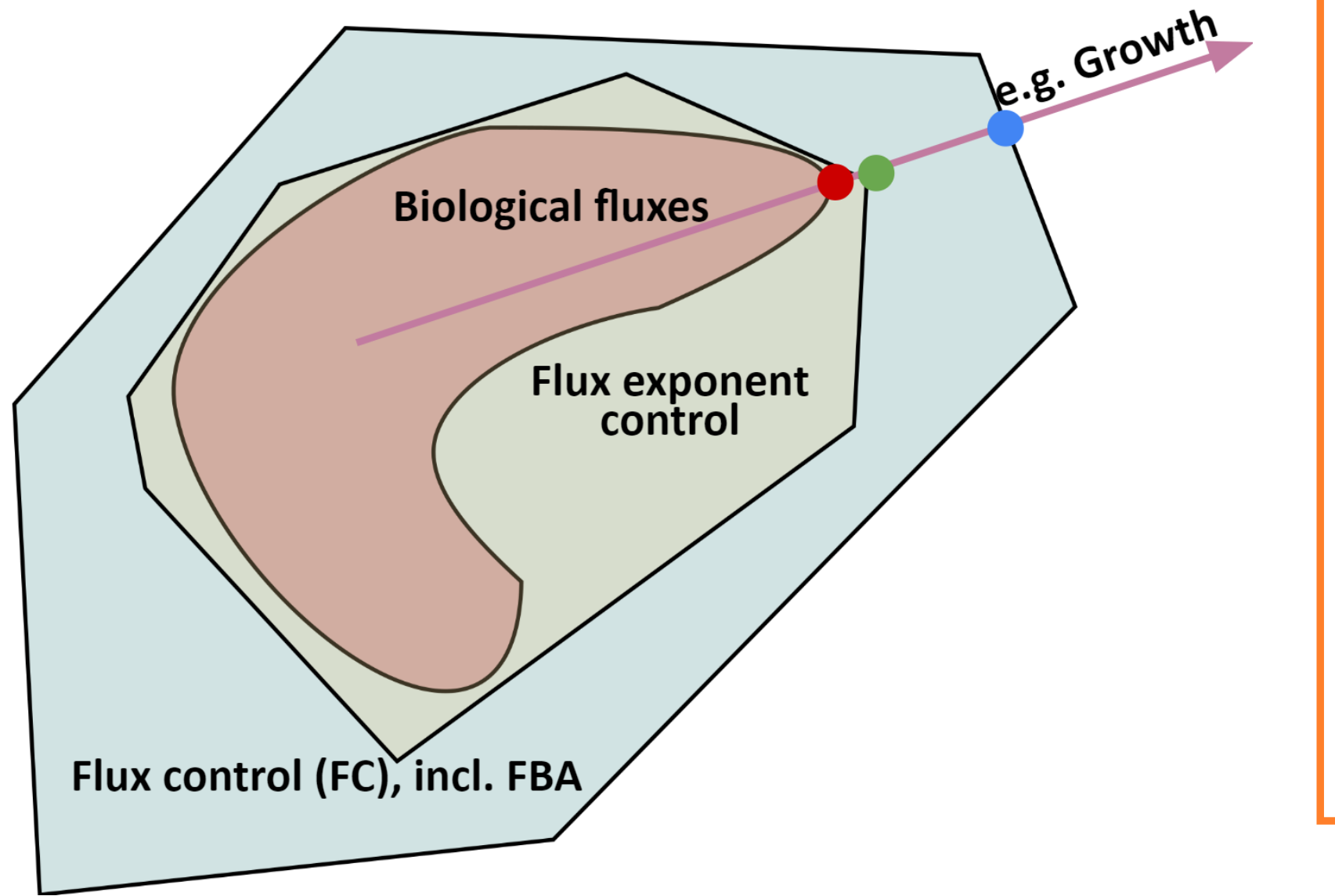
substrate (total) product (total)

More generally:

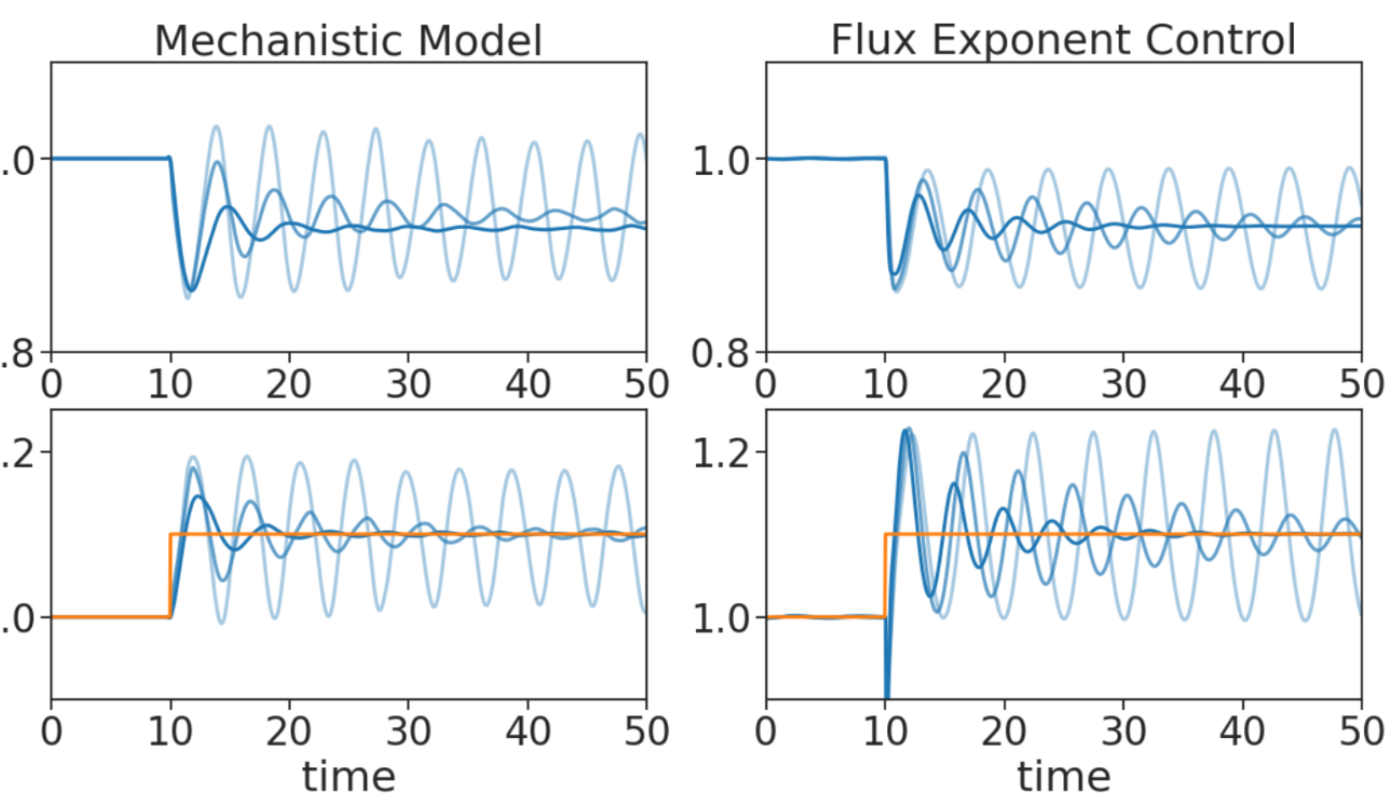
$$\frac{\mathrm{d}}{\mathrm{dt}}x = Sv$$

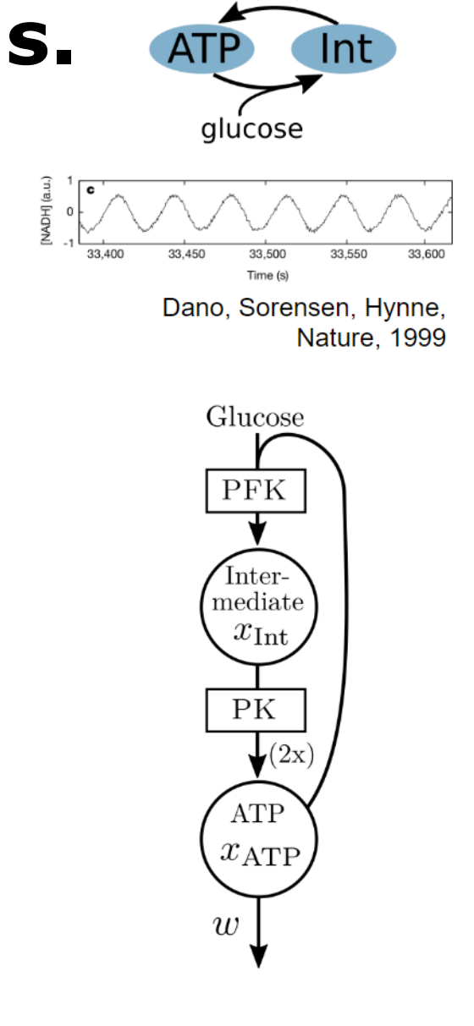
x, metabolite conc., variable
S, stoichiometry, known.
v, flux, unknown.

FEC fully upgrades flux balance analysis (FBA) to capture dynamics.



Example: oscillations in glycolysis.



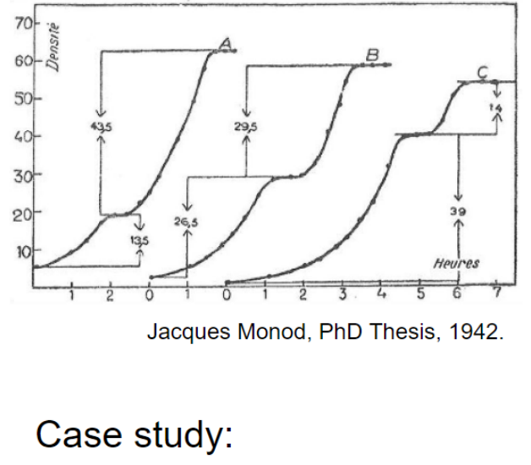


Dano, Sorensen, Hynne, Nature, 1999

Example: growth arrest under stress.

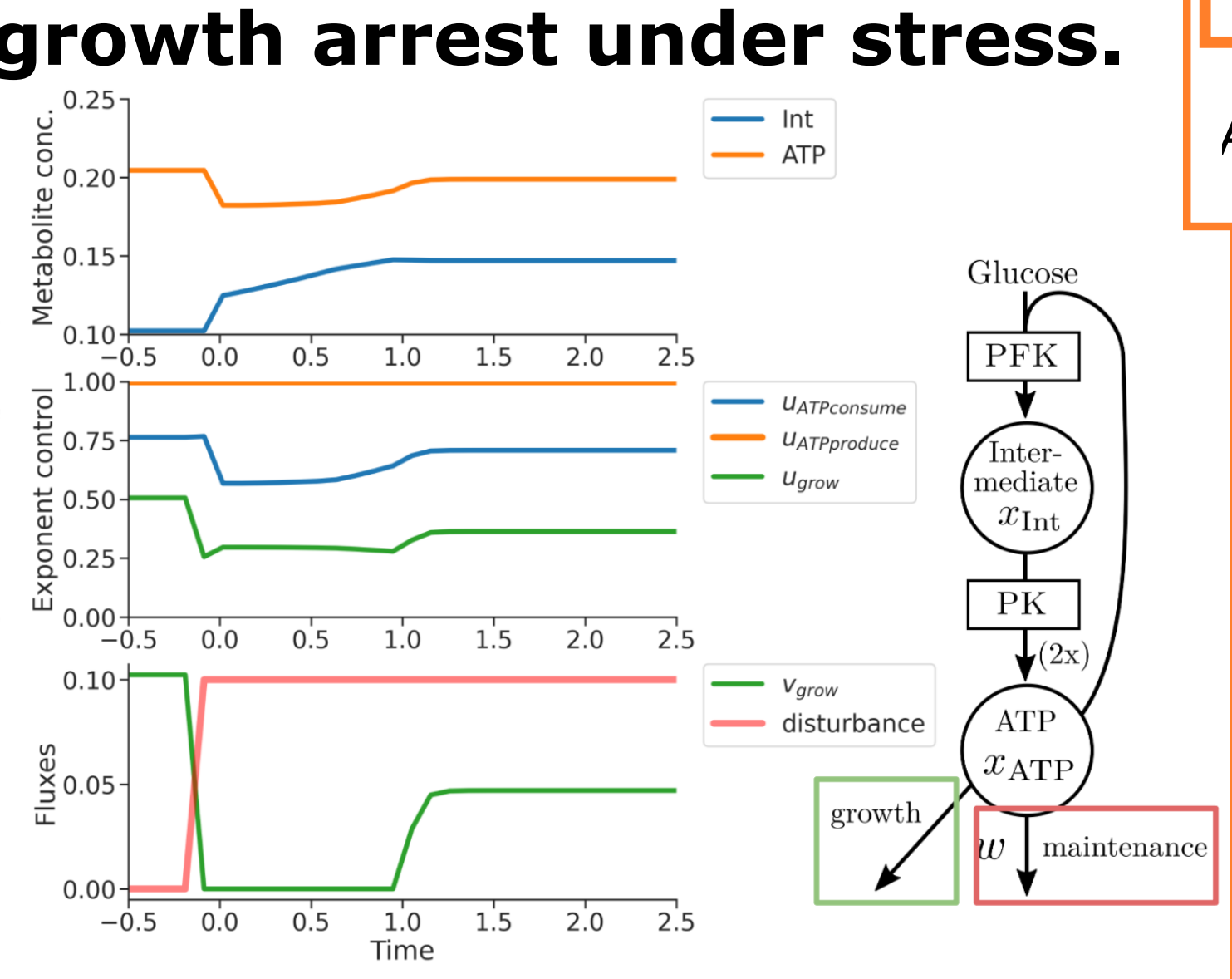
Cell growth arrest under stress is another hallmark of biological adaptation.

e.g. diauxic growth.



Jacques Monod, PhD Thesis, 1942.

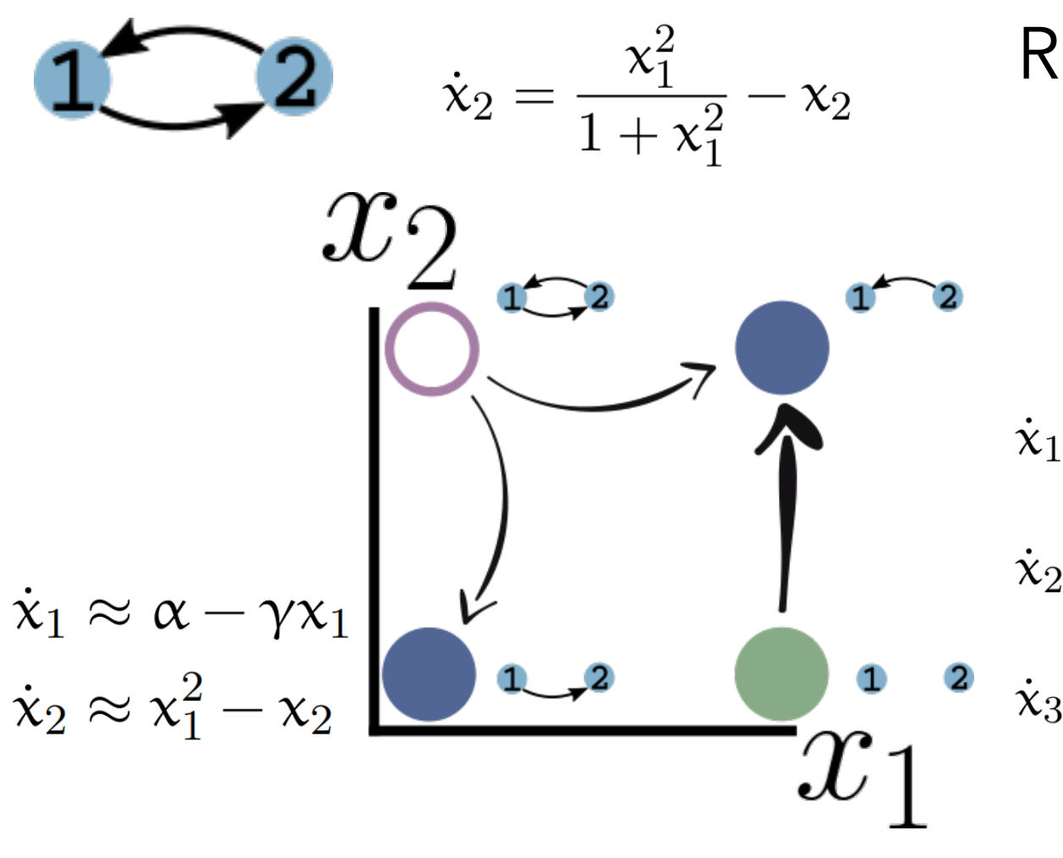
Case study:
Cell grown on glycolysis with sudden increase in maintenance cost.



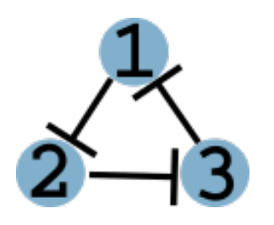
ROP describe dynamics elegantly via structural regimes.

Autoactivator

$$\dot{x}_1 = \alpha + \beta x_2 - \gamma x_1$$
$$\dot{x}_2 = \frac{x_1^2}{1+x_1^2} - x_2$$



Repressilator



$$\dot{x}_1 = \frac{\alpha}{1+x_3^n} - x_1$$
$$\dot{x}_2 = \frac{\alpha}{1+x_1^n} - x_2$$
$$\dot{x}_3 = \frac{\alpha}{1+x_2^n} - x_3$$

$$\dot{x}_1 \approx \alpha - x_1$$
$$\dot{x}_2 \approx \alpha x_1^{-n} - x_2$$
$$\dot{x}_3 \approx \alpha x_2^{-n} - x_3$$