Dynamic Systems: Feedback

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Dynamic Analysis: ODE Models

$$\frac{d\,\boldsymbol{x}(t)}{dt} = f\left(\boldsymbol{x}(t), \boldsymbol{u}(t), \boldsymbol{p}, t\right)$$

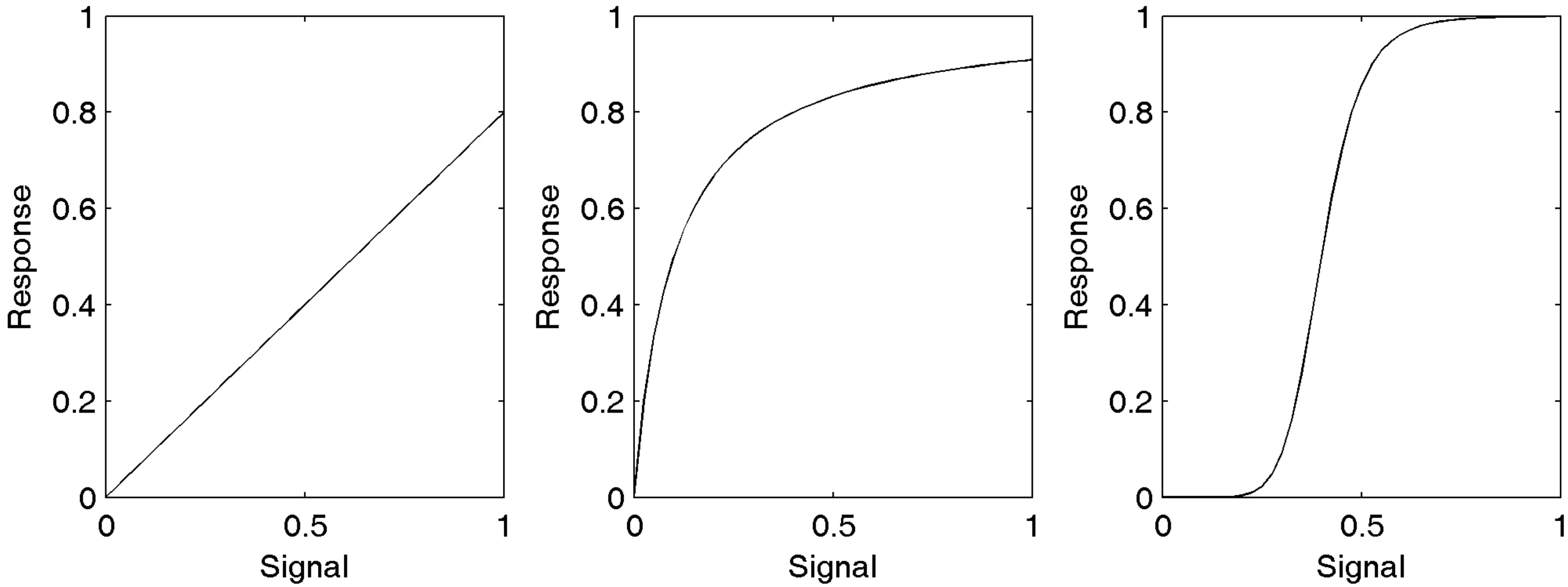
- System of ordinary, first-order, linear or nonlinear differential equations (ODEs) characterized by:
  - Right hand sides $\boldsymbol{f}(\boldsymbol{x}(t),\boldsymbol{u}(t),\boldsymbol{p})$ = function in $\mathbb{R}^{n_x}$.
  - System states $\boldsymbol{x}(t)$ = $n_x\ x\ 1$ state vector.
  - Parameters $\boldsymbol{p}$ = $n_p\ x\ 1$ parameter set.
  - Inputs $\boldsymbol{u}(t)$ = $n_u\ x\ 1$ input vector.

Simple Dynamic Systems: Kinetics

- (Bio)chemical reaction networks → ODE models → Simplifications / assumptions (separation of time- and concentration-scales) → Derivation of rate laws.

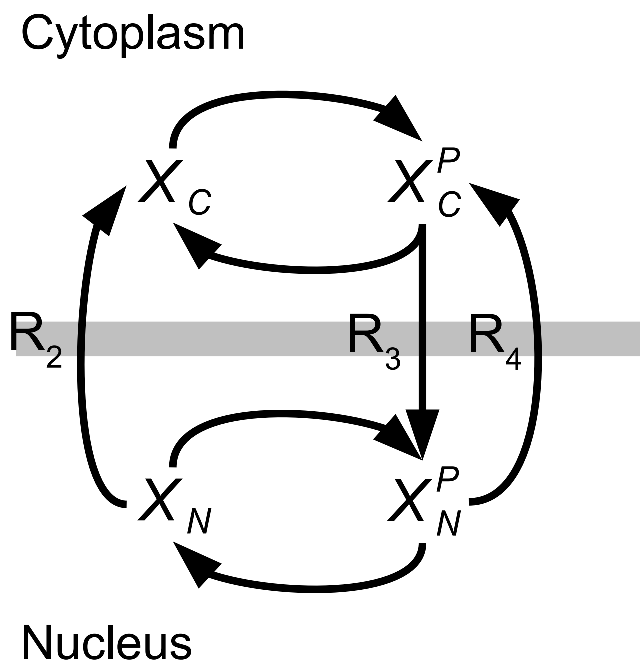
- Example: Gene G bound by transcription factor T:
  - Without repression: $$\left[G\cdot T\right] = \frac{\left[G\right]^T\left[T\right]}{\left[T\right]+K}$$
  - Competitive repressor R: $$\left[G\cdot T\right] = \frac{\left[G\right]^T\left[T\right]}{\left[T\right]+K\left(1+\left[R\right]/K_I\right)}$$
  - Cooperative binding: $$\left[G\cdot T\right] = \frac{\left[G\right]^T\left[T\right]^n}{\left[T\right]^n+K^n}$$

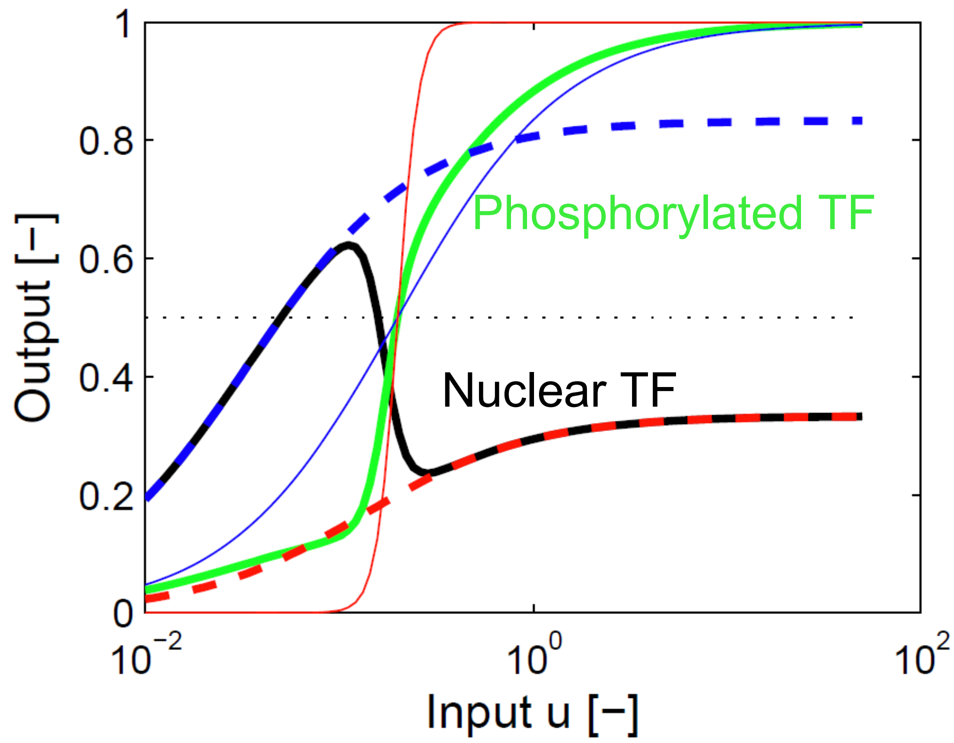
Simple Systems: Signal-Response



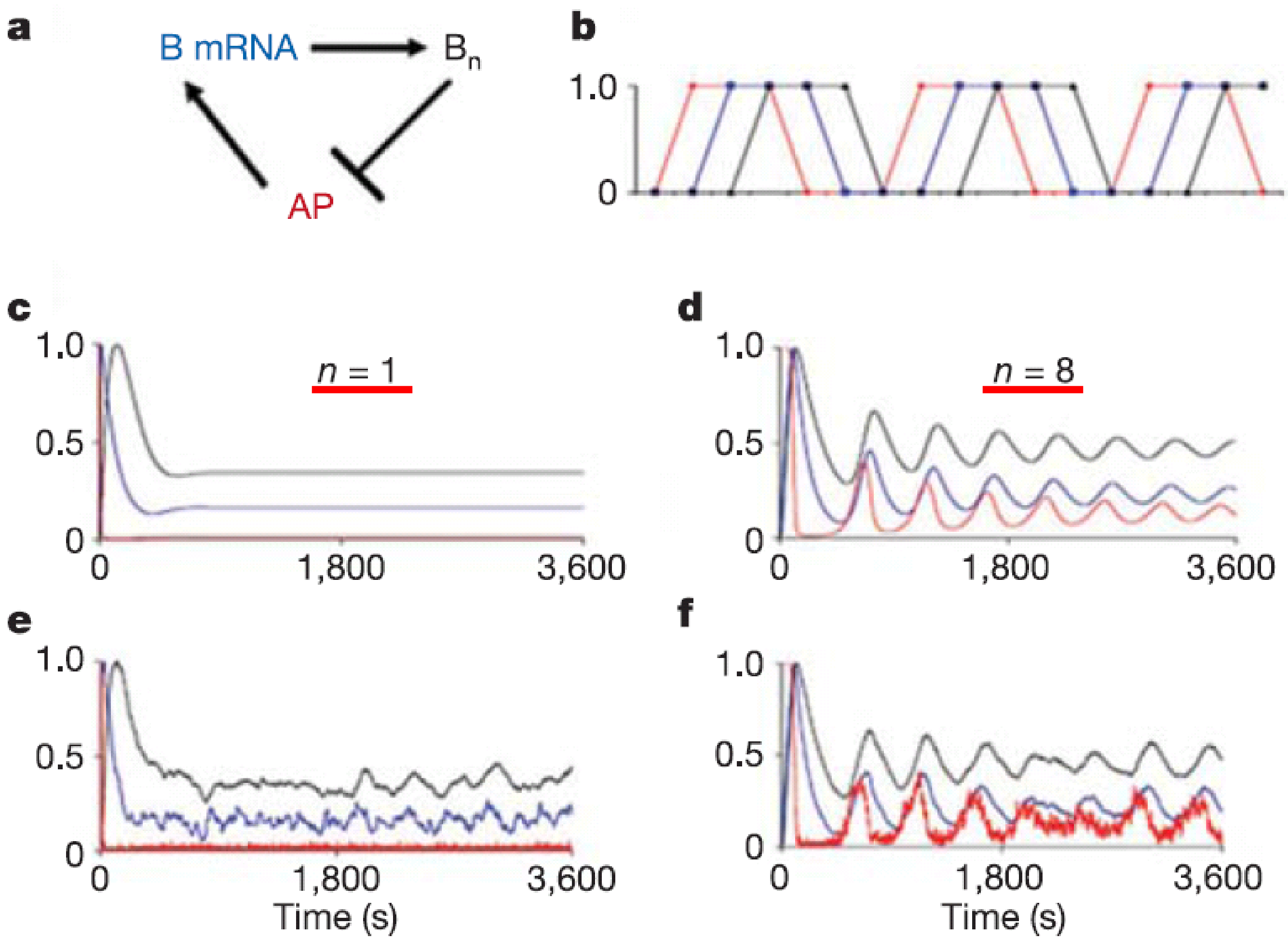
Production / degradation	Simple enzyme	Cooperative enzyme
→ Linear	→ Hyperbolic	→ Sigmoidal

Example: Transcription Factor Control



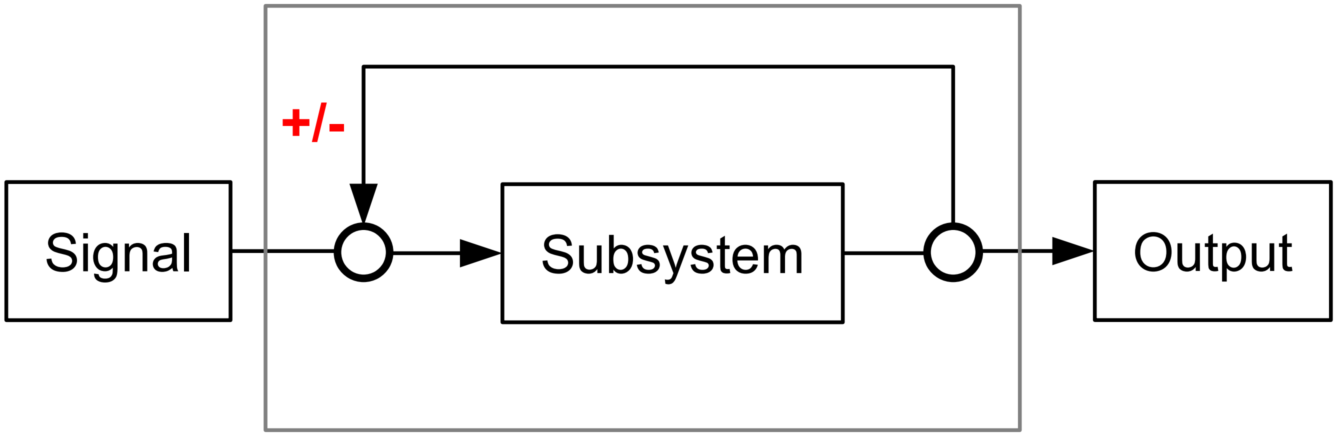


Dynamics of More Complex Systems



From: Di Ventura et al. (2006) Nature 443: 527-533.

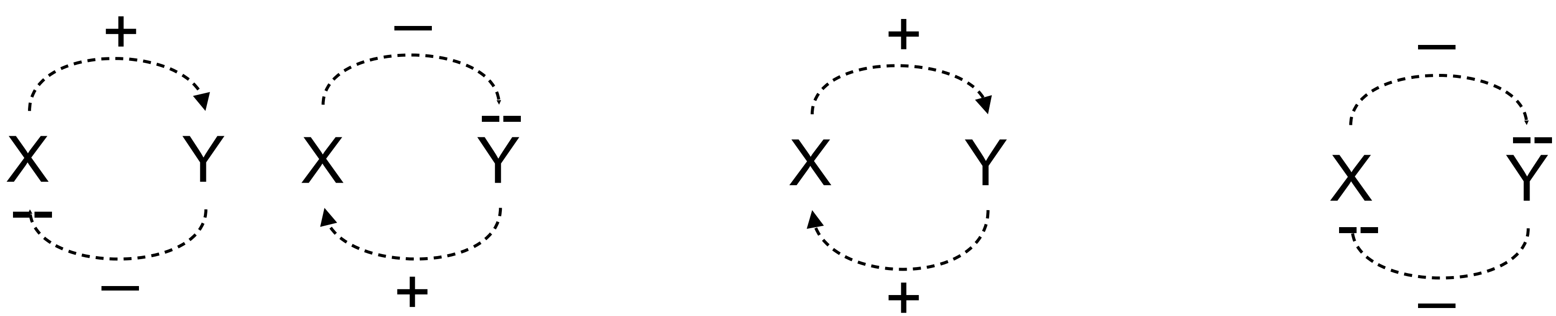
Feedback Systems



- **Circular patterns of interactions can establish feedback loops with positive or negative net effect.**
- Intertwined feedback loops → **Complex dynamics.**

Feedback Systems: Types

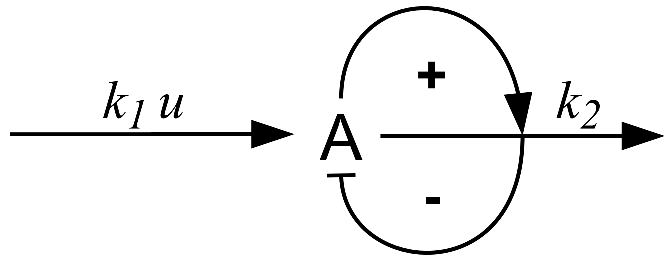
Negative Feedback | Positive Feedback | Mutual Antagonism



- Patterns of interactions between two components

→ **Qualitatively different feedback structures.**

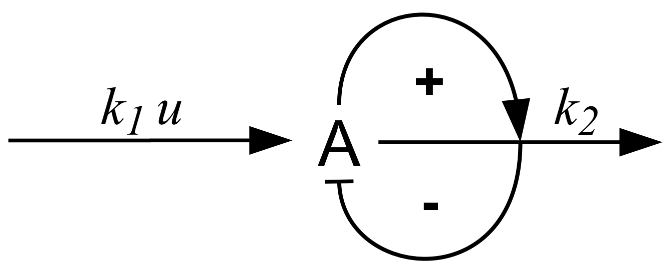
Implicit Feedback: Production-Degradation

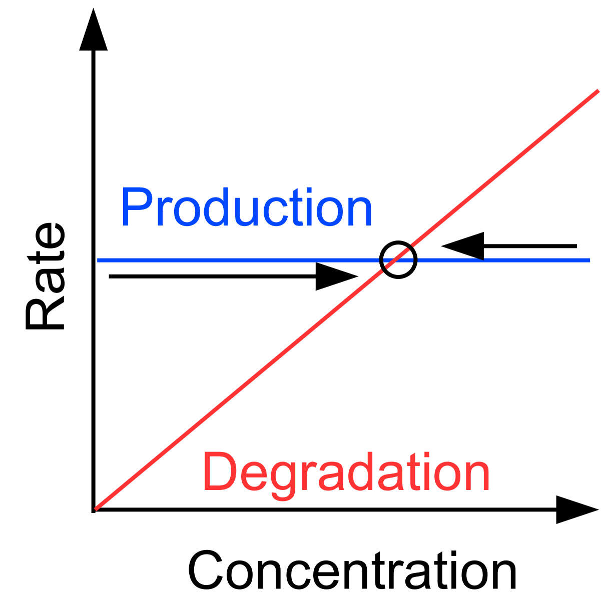


$$\frac{d[A]}{dt} = +k_1 \cdot u - k_2[A] \quad \Rightarrow \quad [A] = \frac{k_1 \cdot u}{k_2}\left(1 - e^{-k_2 \cdot t}\right)$$

- Increased A accelerates degradation, leading to reduced concentration of A → **Negative feedback**.
- From analytic solution: After perturbation, the system will return to (a) steady-state again → **Homeostasis**.

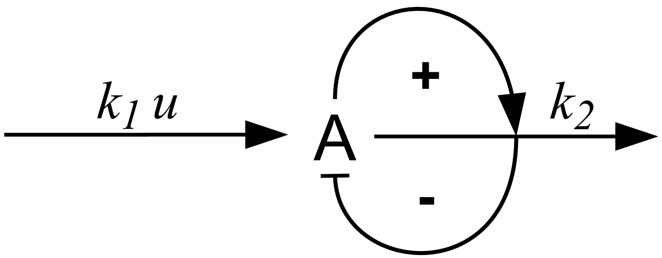
Implicit Feedback: Production-Degradation



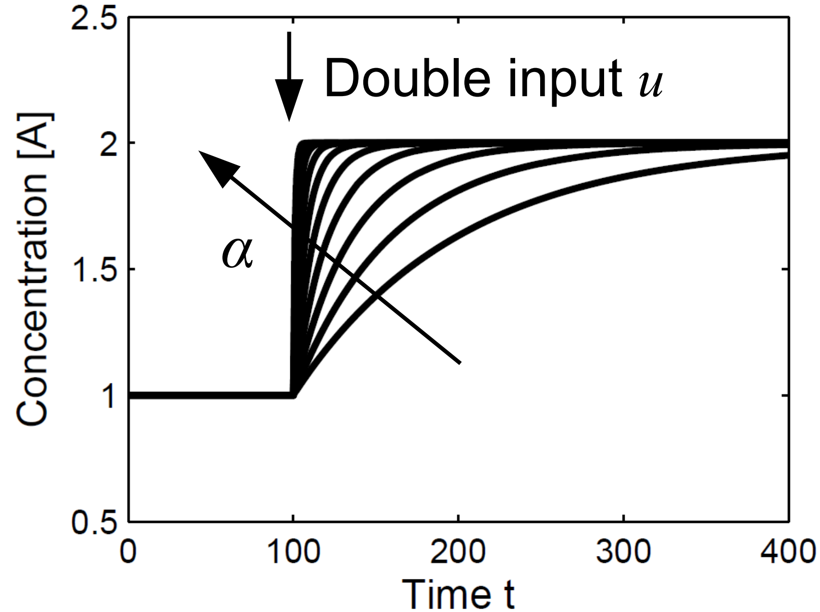


- Increased A accelerates degradation, leading to reduced concentration of A → **Negative feedback**.
- Graphically: After perturbation, the system will return to (a) steady-state again → **Homeostasis**.

Implicit Feedback: Production-Degradation

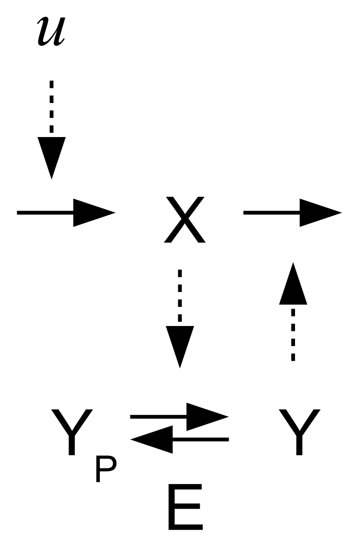


$$\frac{d[A]}{dt} = \alpha\left(k_1 \cdot u - k_2[A]\right)$$



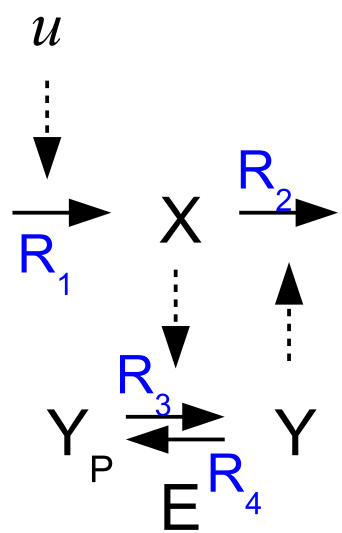
- Assume modified feedback and identical steady-state by scaling of both rates with factor α.
- Increased feedback gain → **Faster responses.**

Negative Feedback: Example System



- Protein X: Phosphatase that dephosphorylates Y_P.
- Protein Y: Dephosphorylated form activates degradation of X → **Negative feedback.**
- Input signal u: Control of production rate for X.

Negative Feedback: Example System

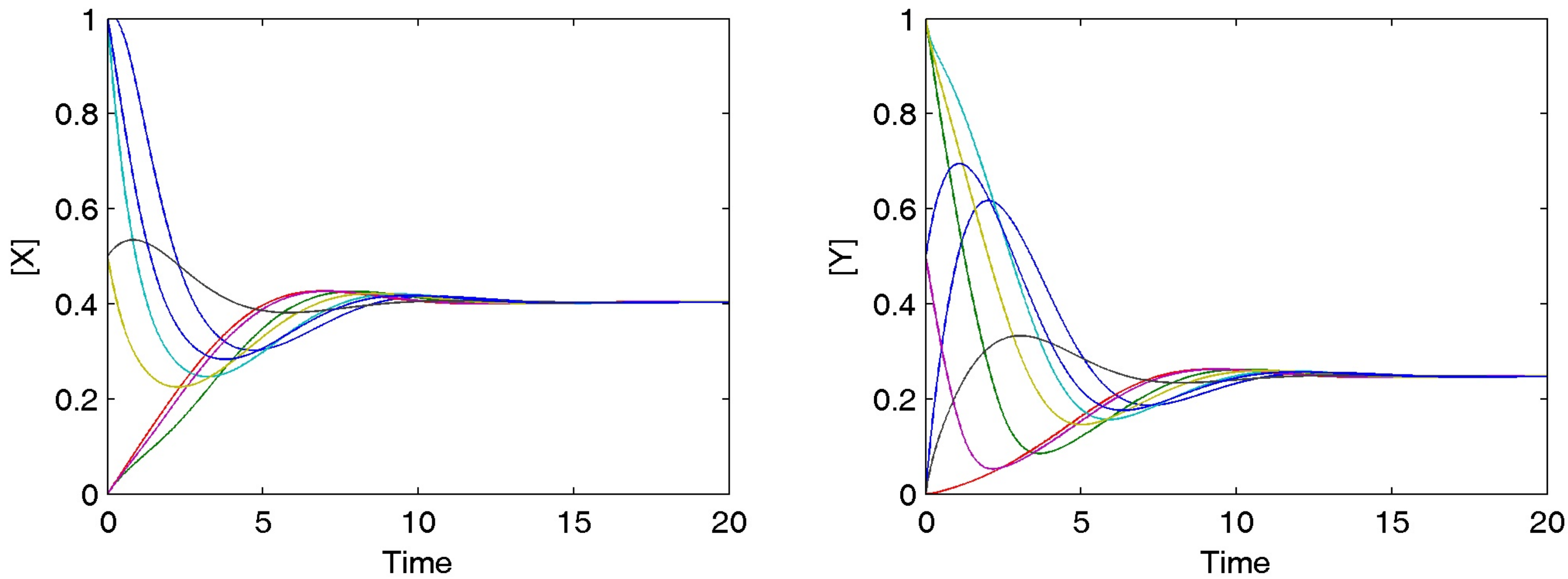


- Two-state (ODE) model: Michaelis-Menten kinetics

$$\frac{d[X]}{dt} = k_1 \cdot u - k_2 \cdot [Y][X]$$

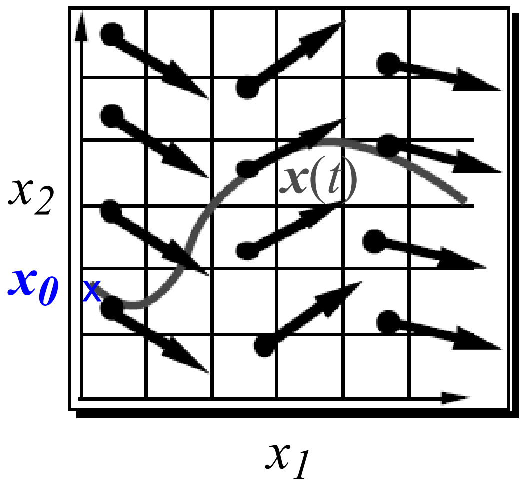
$$\frac{d[Y]}{dt} = \frac{k_3 \cdot [X]\left([Y]^T - [Y]\right)}{K_{M3} + [Y]^T - [Y]} - \frac{k_4 [E][Y]}{K_{M4} + [Y]}$$

Negative Feedback: Numerical Solution



- Complicated dynamics even for two-state system.
- Approaching a steady state on longer time scales.

Negative Feedback: Graphical "Solution"

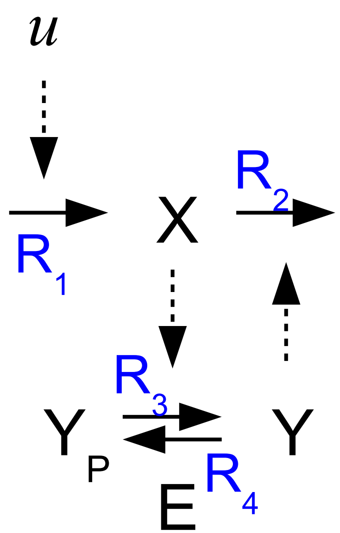


$$\frac{d\,\boldsymbol{x}(t)}{dt} = f(\boldsymbol{x}(t), \boldsymbol{p}, t)$$

$$\boldsymbol{x}(t_0) = \boldsymbol{x_0}$$

- Derivatives $d\boldsymbol{x}(t)/dt$ define vector field in state space.
- Qualitative analysis for two-dimensional systems:
  - **Nullclines**: Zero velocity in a single dimension.
  - **Steady states**: Zero velocity in both dimensions.

Negative Feedback: Nullclines



$$\frac{d[X]}{dt} = k_1 \cdot u - k_2 \cdot [Y][X]$$

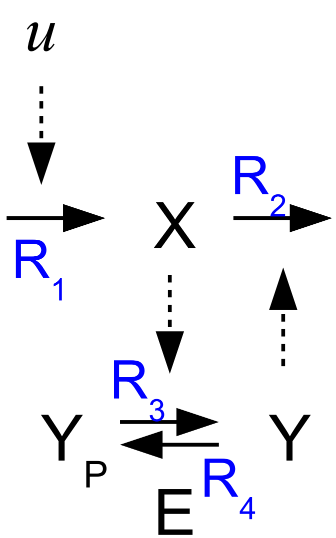
$$\frac{d[Y]}{dt} = \frac{k_3 \cdot [X]\left([Y]^T - [Y]\right)}{K_{M3} + [Y]^T - [Y]} - \frac{k_4 [E][Y]}{K_{M4} + [Y]}$$

- Determination of nullclines → Zero velocity (derivatives):

$$\frac{d[X]}{dt} = 0 \quad \Rightarrow \quad [Y] = \frac{k_1 \cdot u}{k_2 \cdot [X]}$$

$$\frac{d[Y]}{dt} = 0 \quad \Rightarrow \quad \frac{k_3 \cdot [X]\left([Y]^T - [Y]\right)}{K_{M3} + [Y]^T - [Y]} = \frac{k_4 [E][Y]}{K_{M4} + [Y]}$$

Negative Feedback: Y-Nullcline



- Y-nullcline in original variables:

$$\frac{k_3 \cdot [X]\left([Y]^T - [Y]\right)}{K_{M3} + [Y]^T - [Y]} = \frac{k_4 [E][Y]}{K_{M4} + [Y]}$$

- Introduction of new variables:

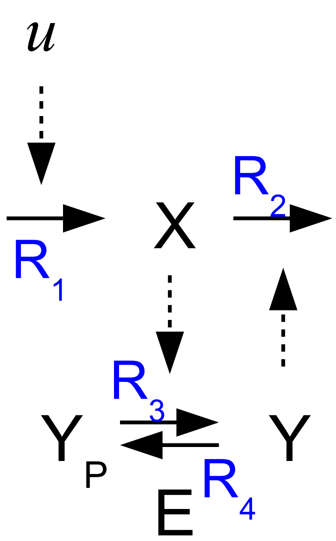
$$y = \frac{[Y]}{[Y]^T}, \quad v_1 = k_3 \cdot [X], \quad v_2 = k_4 \cdot [E]$$

$$J_1 = \frac{K_{M3}}{[Y]^T}, \quad J_2 = \frac{K_{M4}}{[Y]^T}$$

- Rescaled equation for Y-nullcline:

$$v_1 (1 - y)(J_2 + y) = v_2 \cdot y (J_1 + 1 - y)$$

Negative Feedback: Y-Nullcline



- Rescaled equation for Y-nullcline:

$$y = \frac{[Y]}{[Y]^T} \quad , \quad v_1 = k_3 \cdot [X] \quad , \quad v_2 = k_4 \cdot [E]$$

$$J_1 = \frac{K_{M3}}{[Y]^T} \quad , \quad J_2 = \frac{K_{M4}}{[Y]^T}$$

$$v_1 (1-y)(J_2+y) = v_2 \cdot y (J_1+1-y)$$

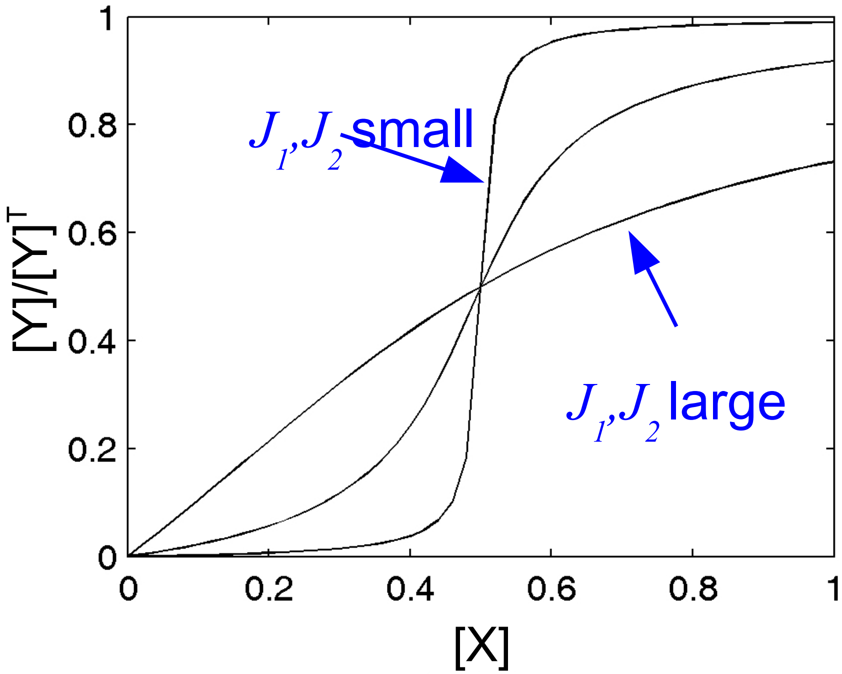
- Solution in new variables →

  Goldbeter-Koshland function:

$$y = G(v_1, v_2, J_1, J_2) = \frac{2 v_1 J_2}{B+\sqrt{B^2-4(v_2-v_1) v_1 J_2}}$$

$$B = v_2 - v_1 + v_2 J_1 + v_1 J_2$$

Negative Feedback: Y-Nullcline

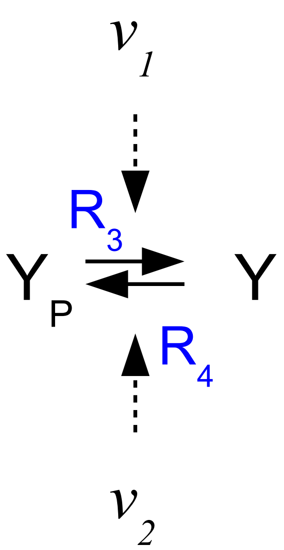


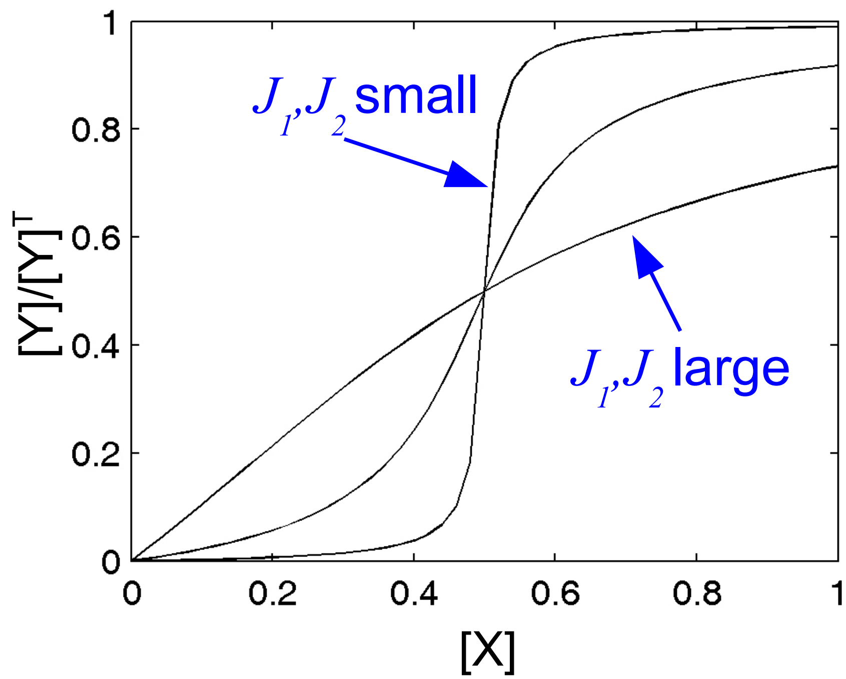
$$y = G(v_1, v_2, J_1, J_2) = \frac{2 v_1 J_2}{B + \sqrt{B^2 - 4(v_2 - v_1) v_1 J_2}} \quad , \quad B = v_2 - v_1 + v_2 J_1 + v_1 J_2$$

$$y = \frac{[Y]}{[Y]^T} \quad , \quad v_1 = k_3 \cdot [X] \quad , \quad v_2 = k_4 \cdot [E] \quad , \quad J_1 = \frac{K_{M3}}{[Y]^T} \quad , \quad J_2 = \frac{K_{M4}}{[Y]^T}$$

- Sigmoidal function of input X → Switch-like for $0 < J_1, J_2 << 1$.

Negative Feedback: Y-Nullcline



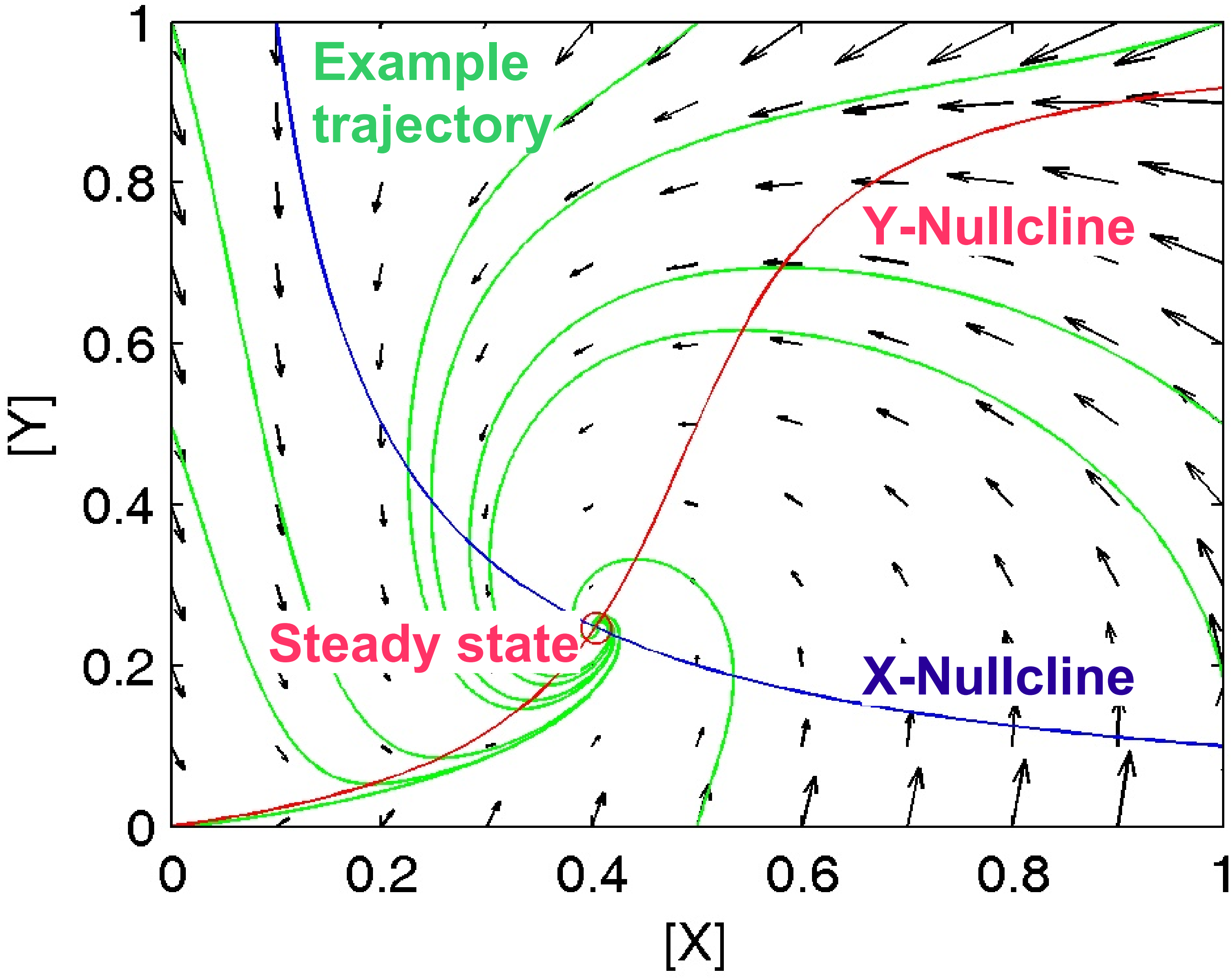


$$y = \frac{[Y]}{[Y]^T} \;,\quad v_1 = k_3 \cdot [X] \;,\quad v_2 = k_4 \cdot [E] \;,\quad J_1 = \frac{K_{M3}}{[Y]^T} \;,\quad J_2 = \frac{K_{M4}}{[Y]^T}$$

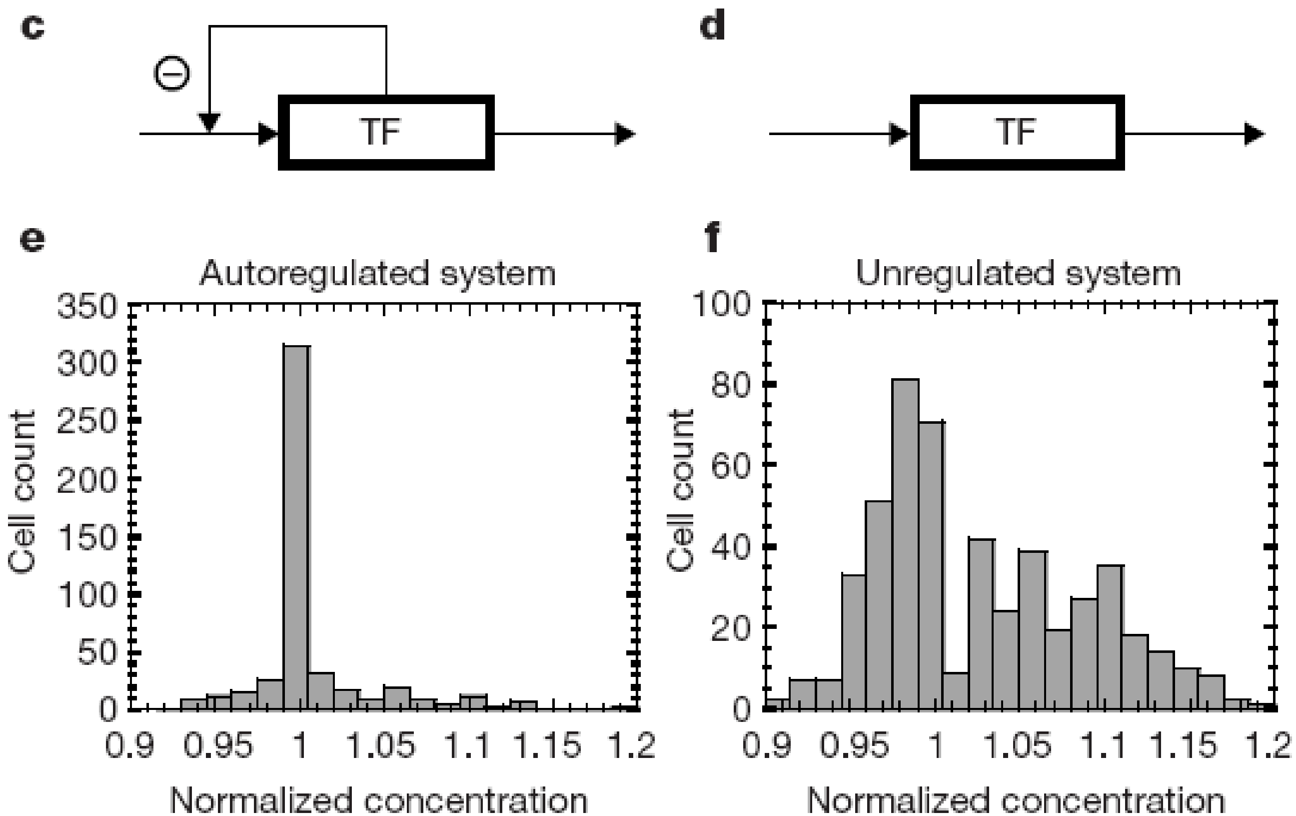
- **General: Switch-like functions with reversible reactions.**

- Necessary: High enzyme affinities and / or total substrate.

Negative Feedback: Phase Plane Analysis



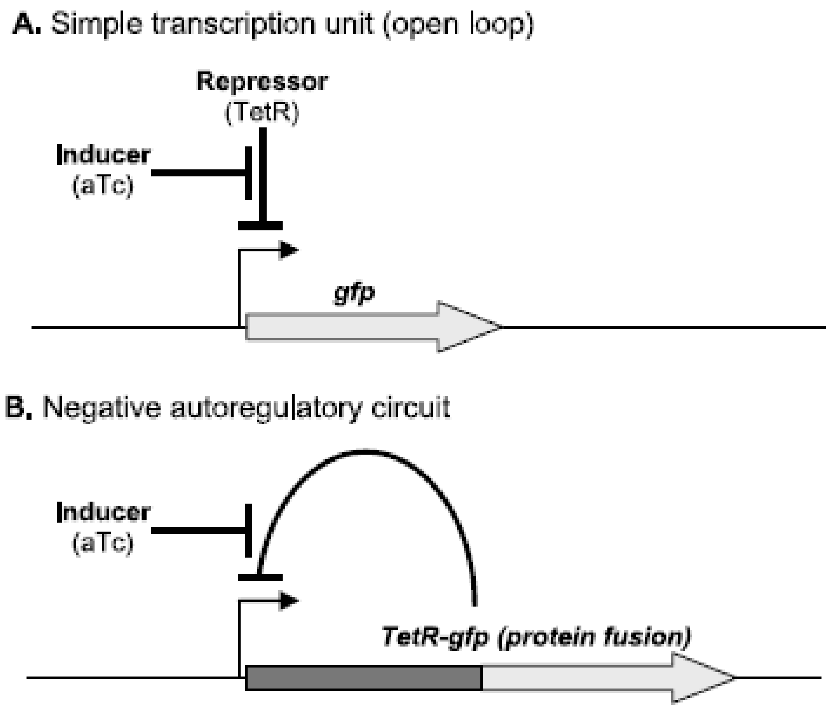
Negative Feedback: Application #1

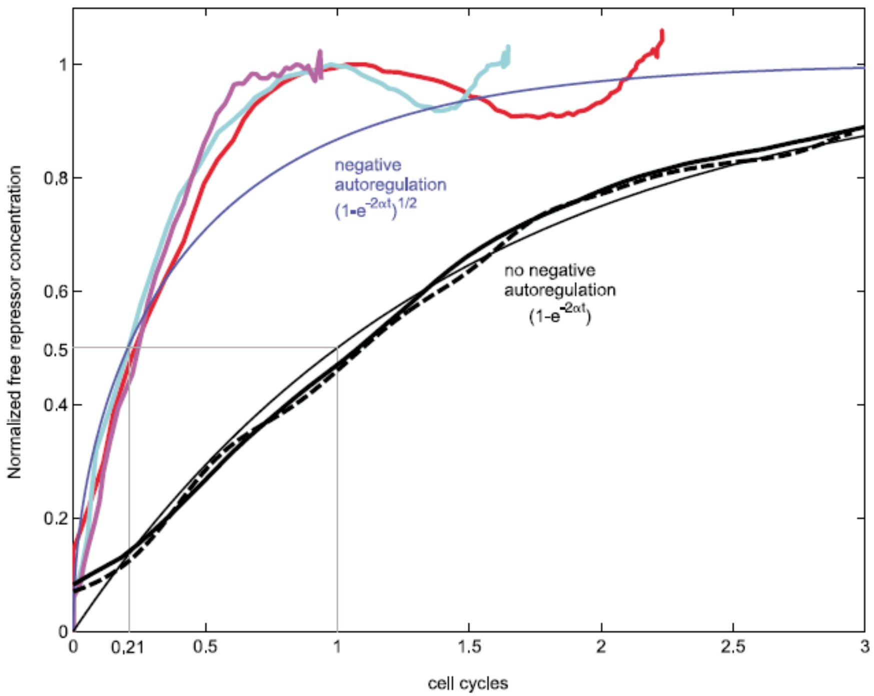


From: Becskei & Serrano (2000) Nature 405: 591-593.

Negative Feedback: Application #2

Negative Autoregulation Speeds the Response Times of Transcription Networks





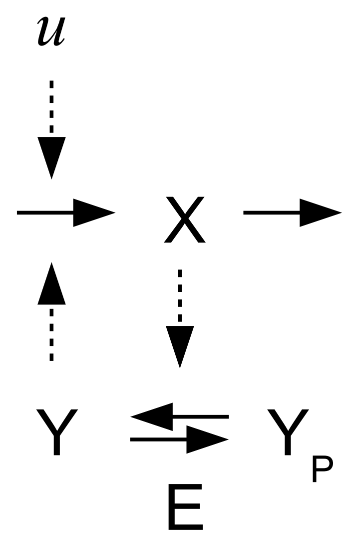
From:Rosenfeld et al. (2002) J. Mol. Biol. 323: 785-793.

Negative Feedback: Functions

- **Simple negative feedback systems:**
  - Approaching steady state (transient dynamics).
  - Existence of a unique steady state.

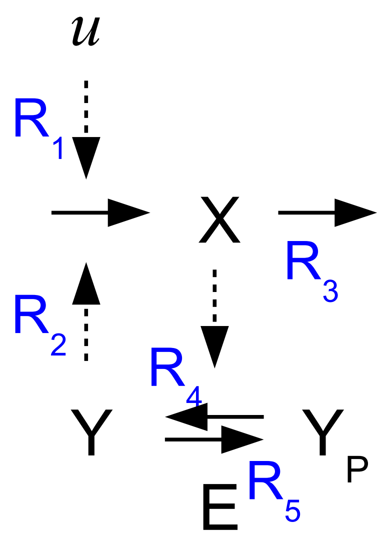
- **Functions in biological networks:**
  - Set point regulation → Homeostasis.
  - Rejection of external or internal perturbations.

Positive Feedback: Example System



- Protein X: Phosphatase that dephosphorylates Y_P.
- Protein Y: Dephosphorylated form activates production of X → **Positive feedback.**
- Input signal u: Control of production rate for X.

Positive Feedback: Example System

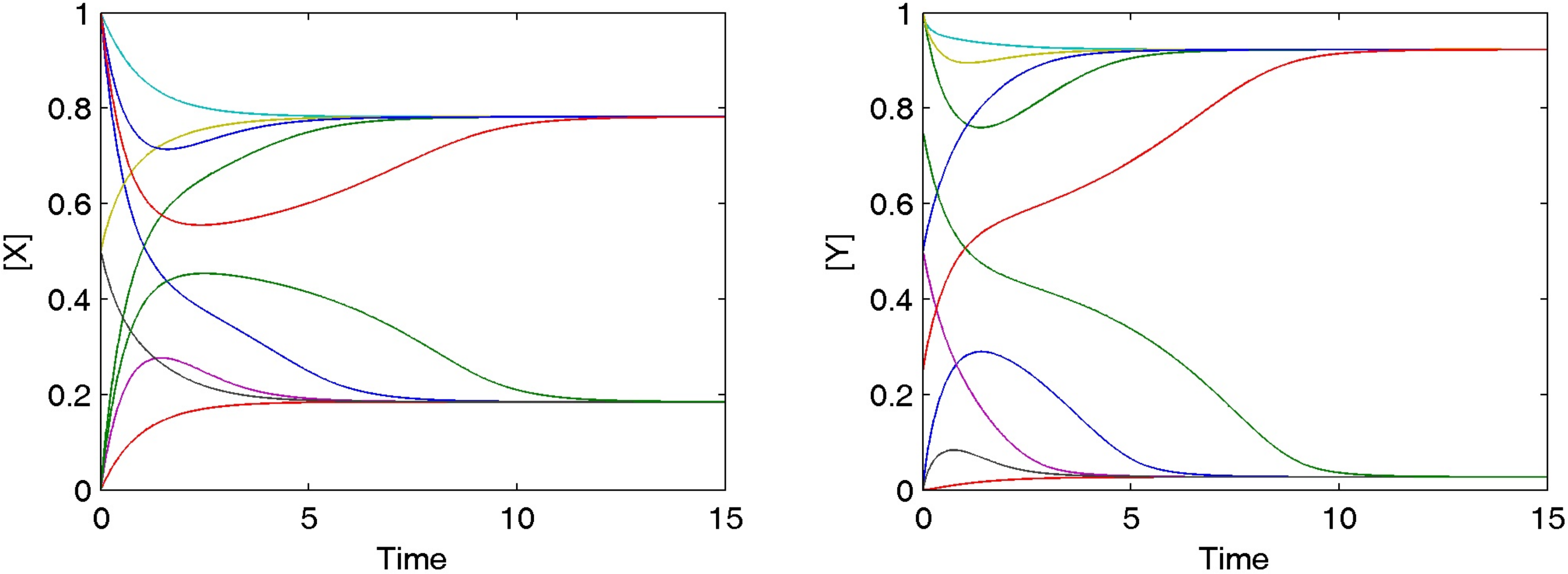


- Two-state (ODE) model: Michaelis-Menten kinetics

$$\frac{d[X]}{dt} = k_1 \cdot u + k_2 \cdot [Y] - k_3 \cdot [X]$$

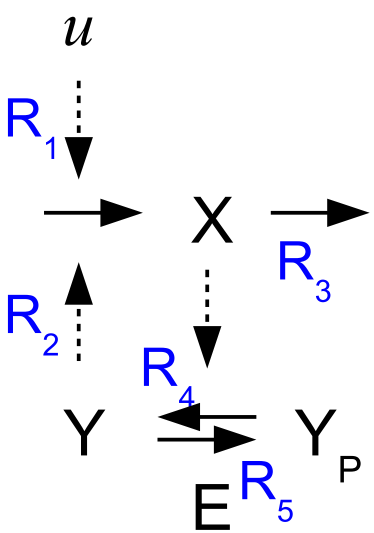
$$\frac{d[Y]}{dt} = \frac{k_4 \cdot [X]\left([Y]^T - [Y]\right)}{K_{M4} + [Y]^T - [Y]} - \frac{k_5 [E][Y]}{K_{M5} + [Y]}$$

Positive Feedback: Numerical Solution



- System moves to either one of two steady states.
- Path dependency on initial conditions not obvious.

Positive Feedback: Nullclines



$$\frac{d[X]}{dt} = k_1 \cdot u + k_2 \cdot [Y] - k_3 \cdot [X]$$

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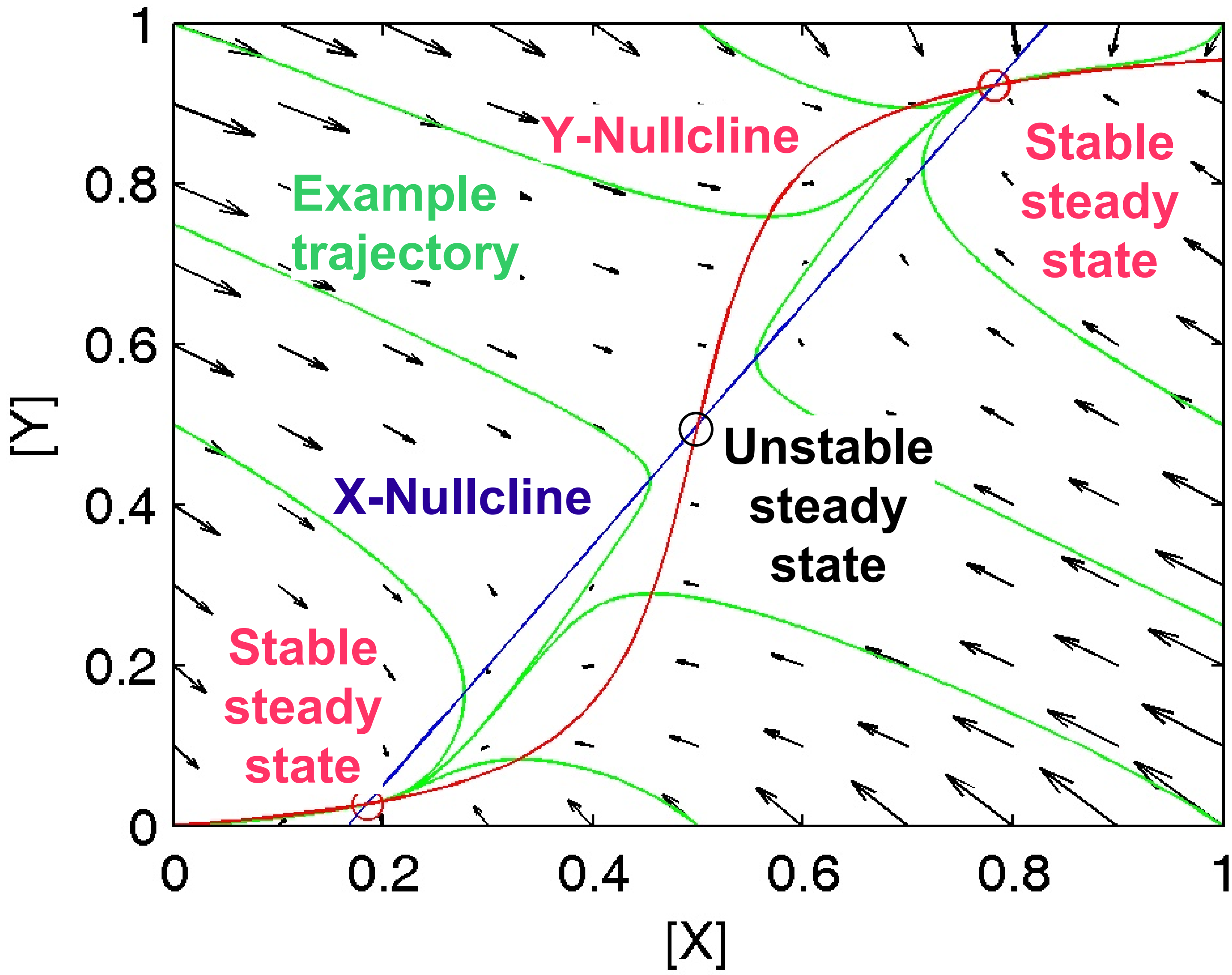
- Determination of nullclines → Zero velocity (derivatives):

$$\frac{d[X]}{dt} = 0 \quad \Rightarrow \quad [Y] = \frac{k_3 \cdot [X] - k_1 \cdot u}{k_2}$$

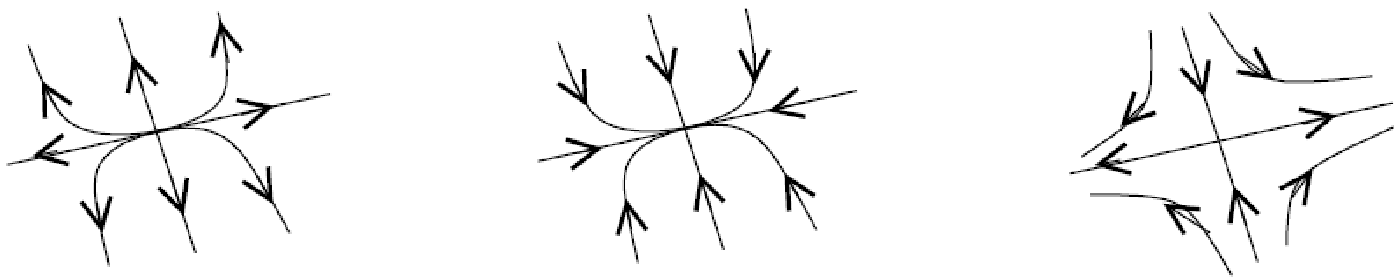
$$\frac{d[Y]}{dt} = 0 \quad \Rightarrow \quad [Y] = [Y]^T \cdot G\left(k_4 [X], k_5 E, K_{M4} / [Y]^T, K_{M5} / [Y]^T\right)$$

Positive Feedback: Phase Plane Analysis



Positive Feedback: Stability

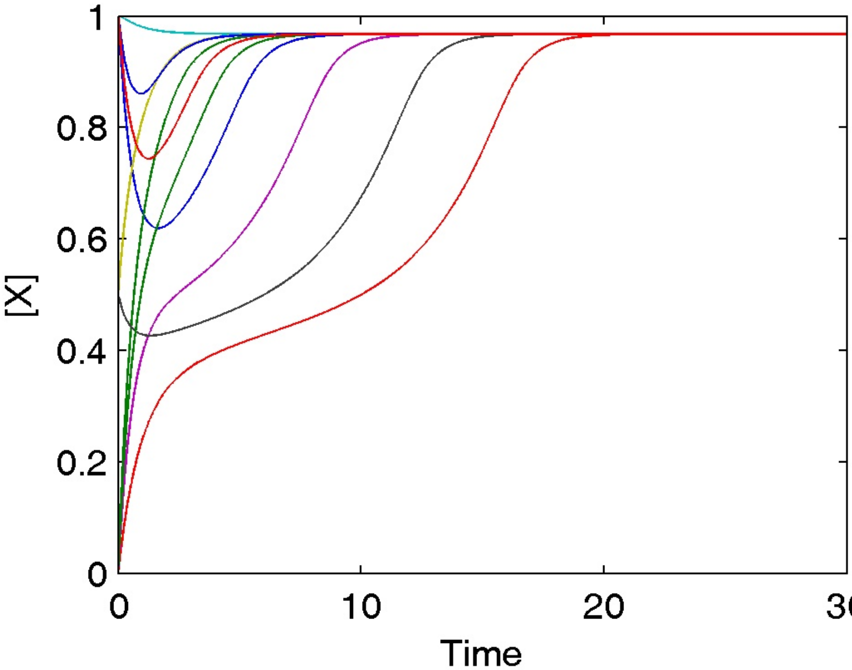
- Classification of steady states (nodes) according to directions of the vector field:

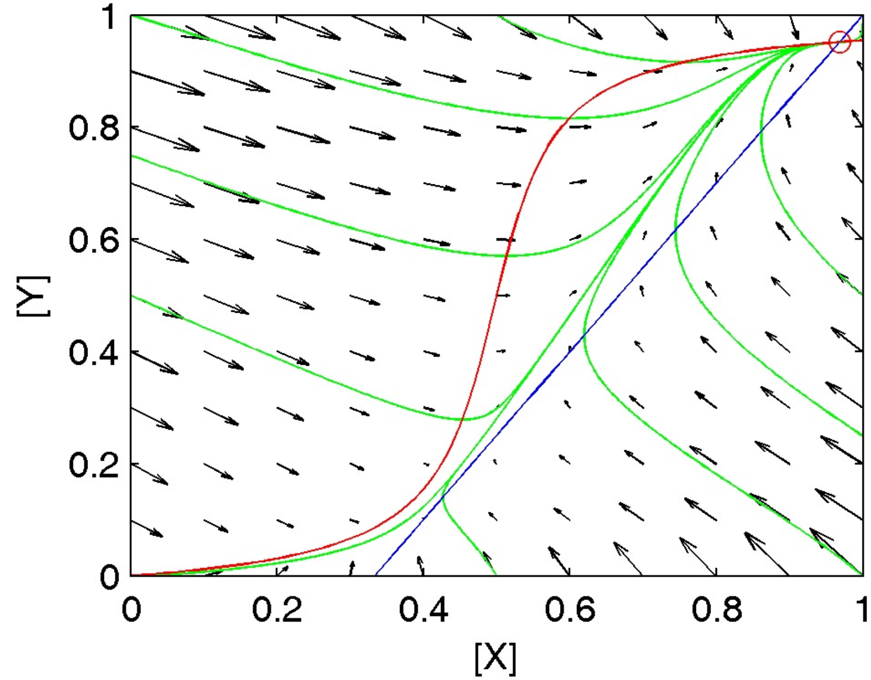


unstable node | stable node | saddle point (unstable)

- **Stability: Global vs. local (with respect to 'small' perturbations of the system's state).**

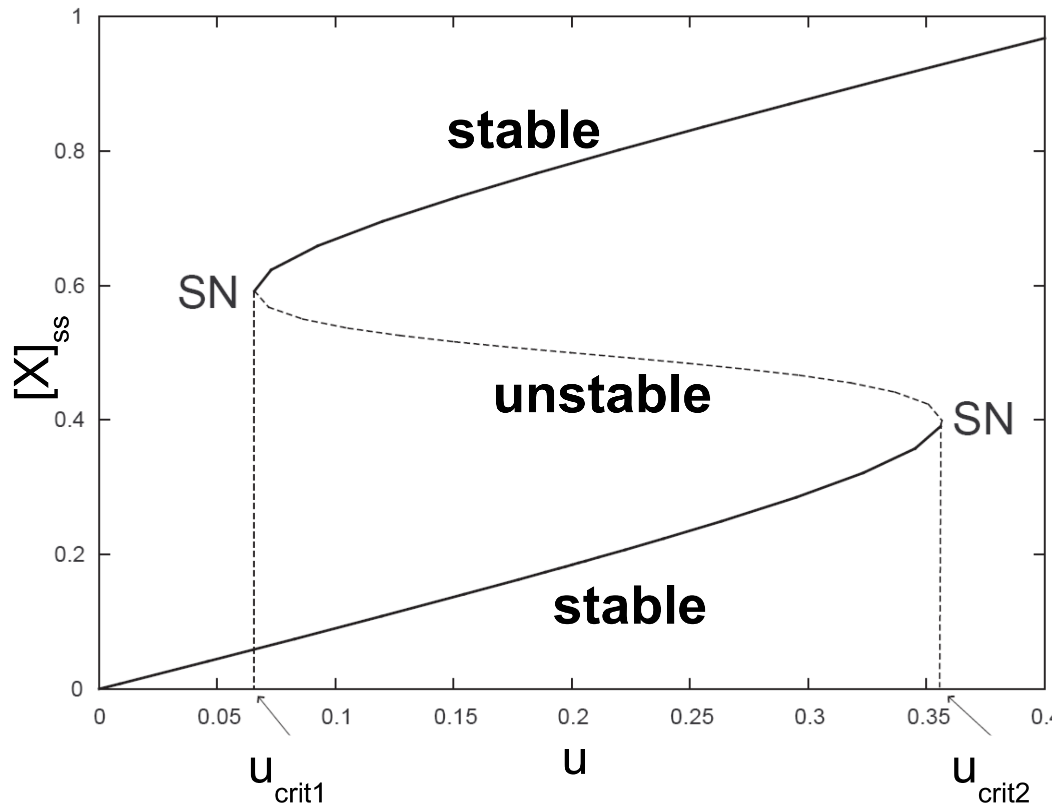
Positive Feedback: Bifurcation





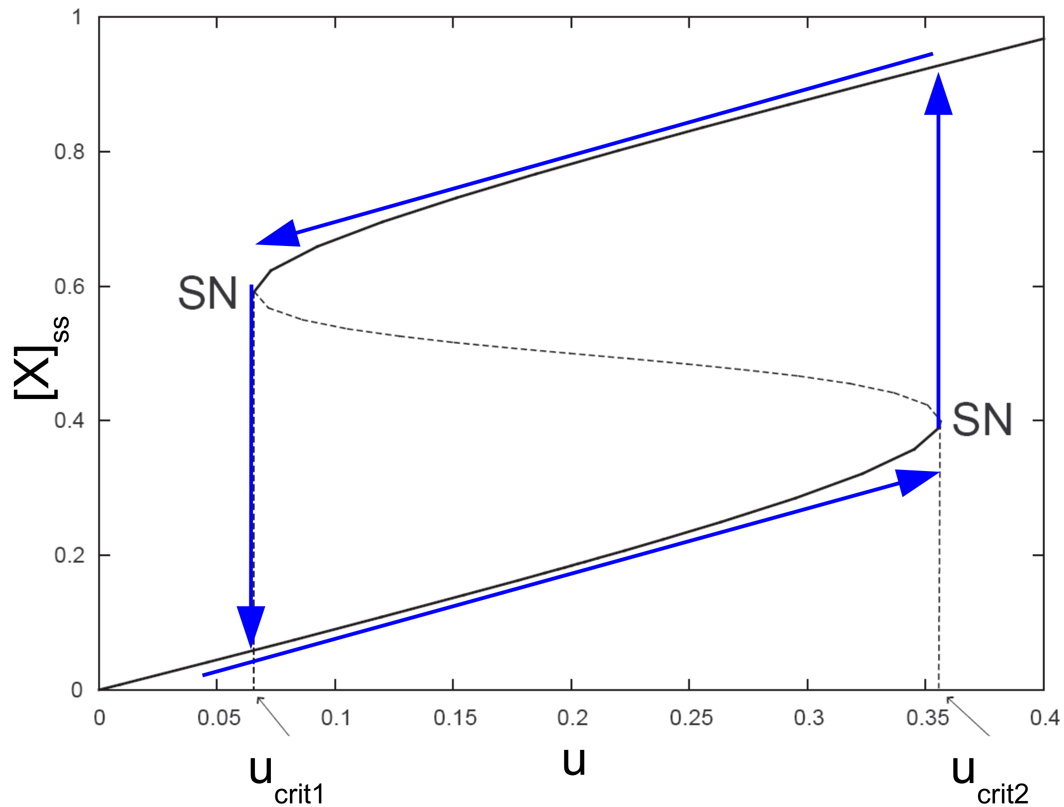
- Doubling of input $u \rightarrow$ Qualitatively different dynamics.
- X-nullcline depending on u: $\left[Y\right]_{X-NC} = \dfrac{k_3 \cdot \left[X\right] - k_1 \cdot u}{k_2}$

Positive Feedback: Bifurcation Diagram



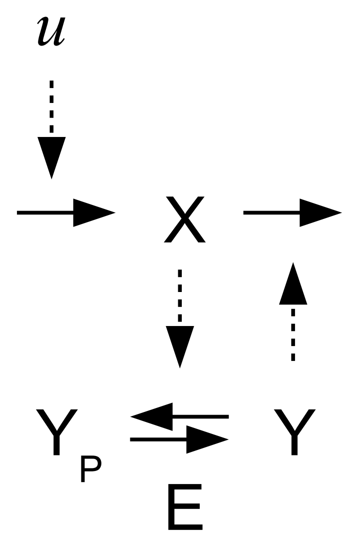
- **Bifurcation:** Change of the number of attractors in a (nonlinear) dynamic system upon parameter changes.
  - For $u < u_{crit1}$ and $u > u_{crit2}$: Globally monostable system.
  - For $u_{crit1} \leq u \leq u_{crit2}$: Bistable system → Switch possible.

Positive Feedback: Bifurcation Diagram



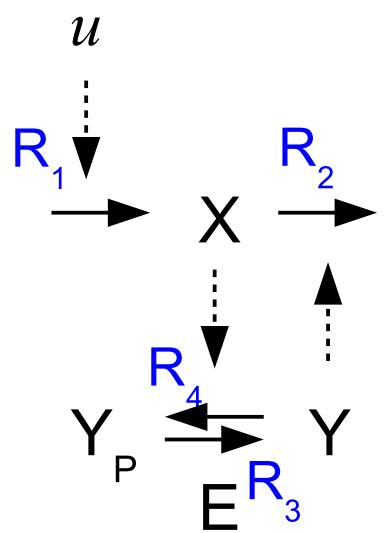
- History dependence of the system's state (here with respect to changes in the input): **Hysteresis.**
- Used, for example, to establish (computer) memory.

Mutual Antagonism: Example System



- Protein X: Kinase that inactivates Y → Y_P.
- Protein Y: Dephosphorylated form activates degradation of X → **Mutual antagonism**.
- Input signal u: Control of production rate for X.

Mutual Antagonism: Example System

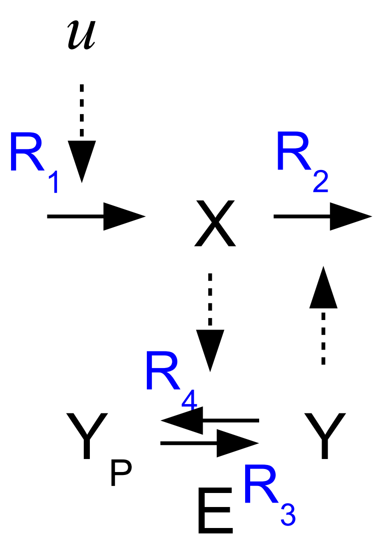


- Two-state (ODE) model: Michaelis-Menten kinetics

$$\frac{d[X]}{dt} = k_1 \cdot u - \left(k_2' + k_2 \cdot [Y]\right)[X]$$

$$\frac{d[Y]}{dt} = \frac{k_3 \cdot [E]\left([Y]^T - [Y]\right)}{K_{M3} + [Y]^T - [Y]} - \frac{k_4 [X][Y]}{K_{M4} + [Y]}$$

Mutual Antagonism: Nullclines



$$\frac{d[X]}{dt} = k_1 \cdot u - \left(k_2' + k_2 \cdot [Y]\right)[X]$$

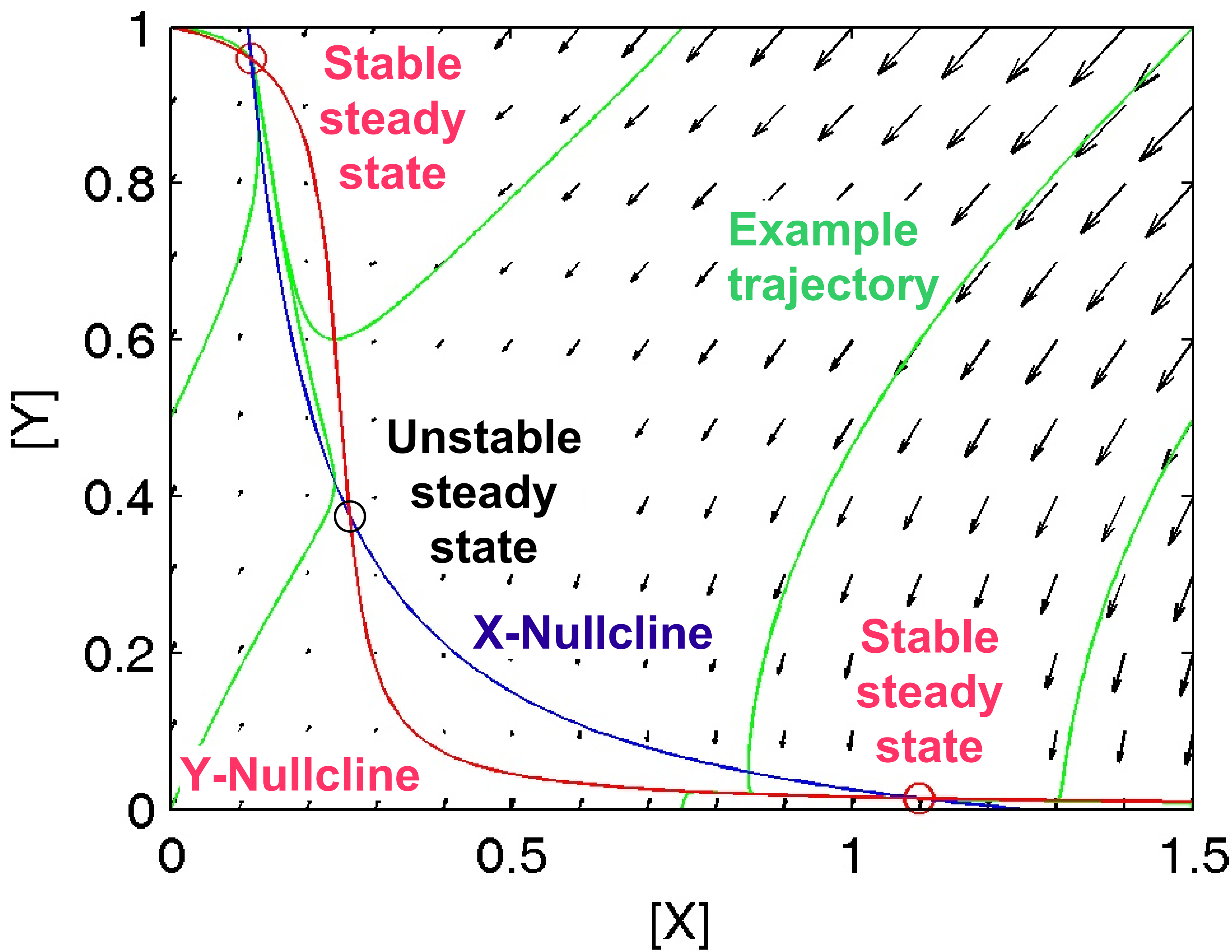
$$\frac{d[Y]}{dt} = \frac{k_3 \cdot [E]\left([Y]^T - [Y]\right)}{K_{M3} + [Y]^T - [Y]} - \frac{k_4[X][Y]}{K_{M4} + [Y]}$$

- Determination of nullclines → Zero velocity (derivatives):

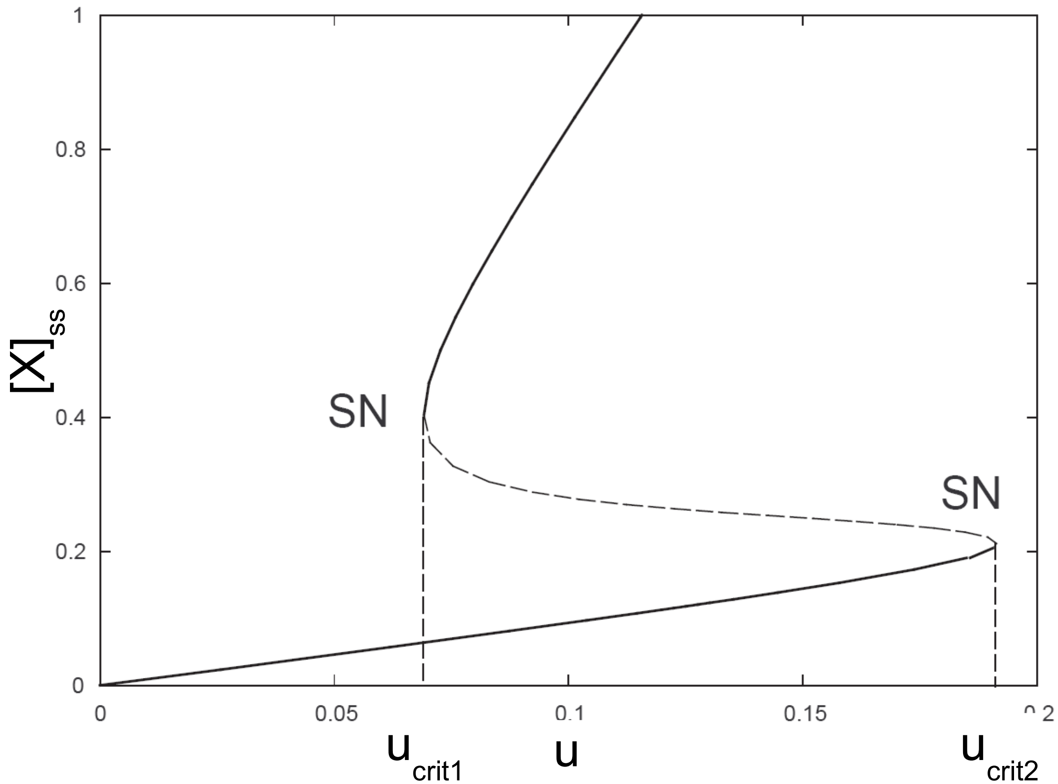
$$\frac{d[X]}{dt} = 0 \quad \Rightarrow \quad [Y] = \frac{k_1 \cdot u - k_2' \cdot [X]}{k_2 \cdot [X]}$$

$$\frac{d[Y]}{dt} = 0 \quad \Rightarrow \quad [Y] = [Y]^T \cdot G\left(k_3[E], k_4[X], K_{M3}/[Y]^T, K_{M4}/[Y]^T\right)$$

Mutual Antagonism: Phase Plane Analysis



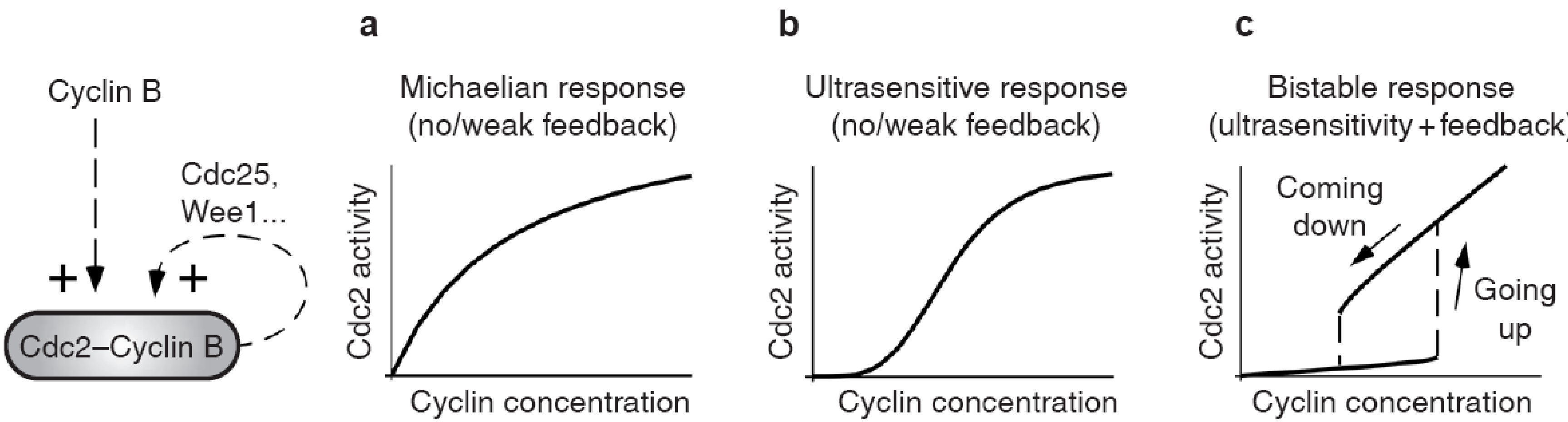
Mutual Antagonism: Bifurcation Diagram



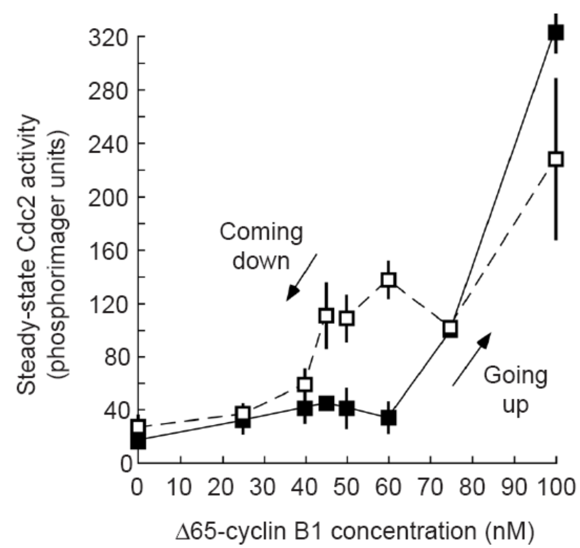
- Bifurcation produced by variation of input signal →
  Function equivalent to positive feedback circuit.

Positive Feedback: Application

- Potential behaviors of a circuit involved in cell cycle control:



- Experimental analysis based on evaluation of models / hypotheses:



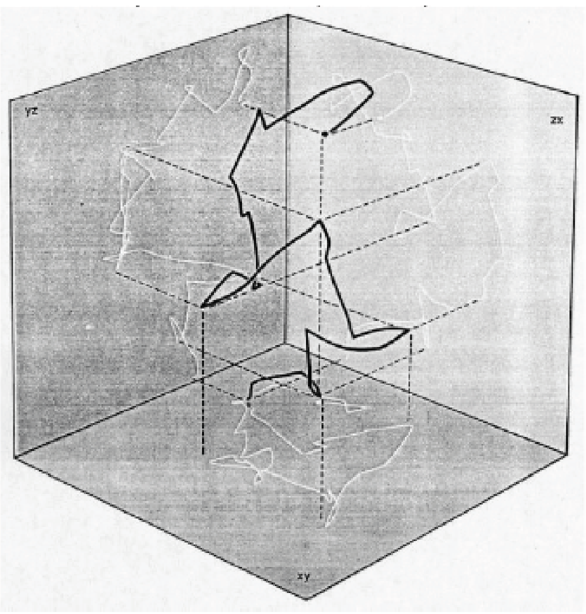
J. Pomerening et al. (2003) Nat Cell Biol **5:346.**

Positive Feedback: Functions

- **Simple positive feedback systems:**
  - Multiple (stable / unstable) steady states possible.
  - Phenomenon in nonlinear systems: Hysteresis.

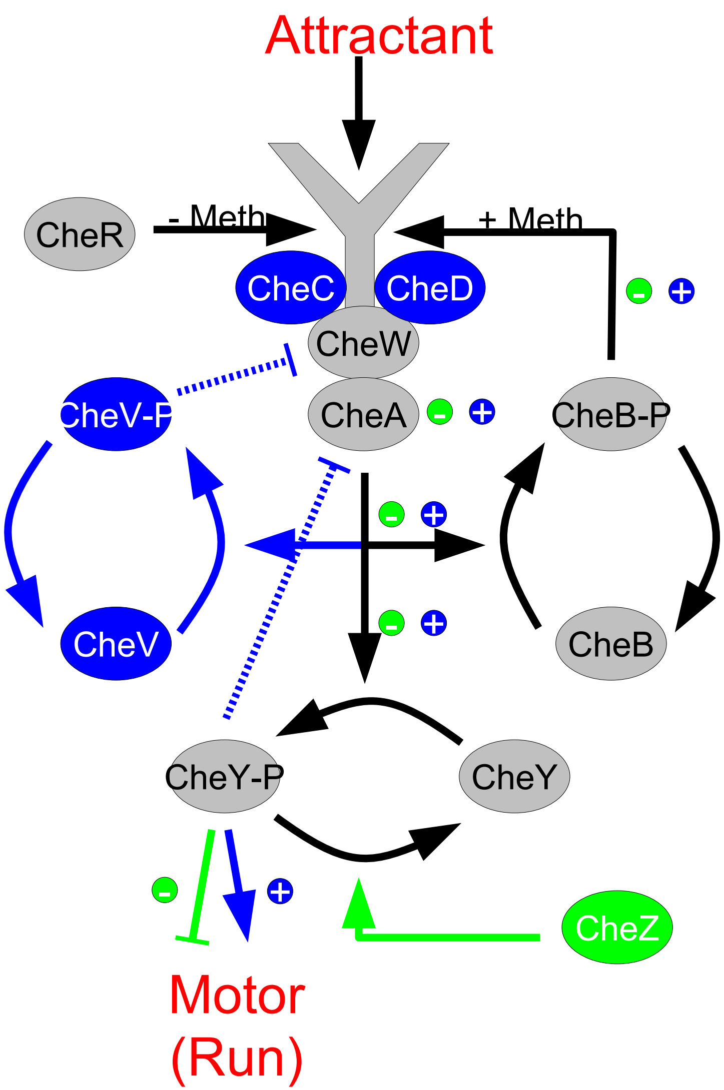
- **Functions in biological networks:**
  - Discrete decisions from continuous signals.
  - Irreversibility of decisions, e.g. in development.

Bacterial Chemotaxis: Application #1



- Random walk of bacterial cells: Run + tumble.
- Chemotaxis: Reduced tumbling frequency while going up the gradient of a chemical attractant.

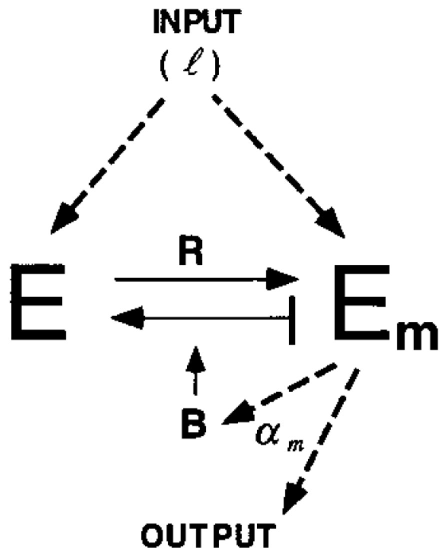
Bacterial Chemotaxis: Design vs. Implementation

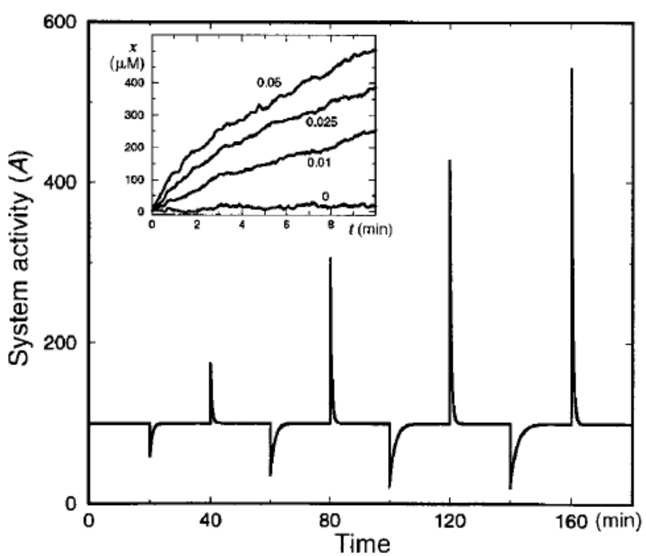


- Different implementations (connections, complexity) provide identical function:
  - *Escherichia coli*
  - *Bacillus subtilis*
- Common feature of robust perfect adaptation.

Bacterial Chemotaxis: Model Simplification

From: Barkai & Leibler (1997). Nature. **387**, 913-917





- Model simplifications:
  - System activity $A \sim [E_m]$.
  - Enzyme R works at saturation.
  - Enzyme B binds only to active receptor complexes.

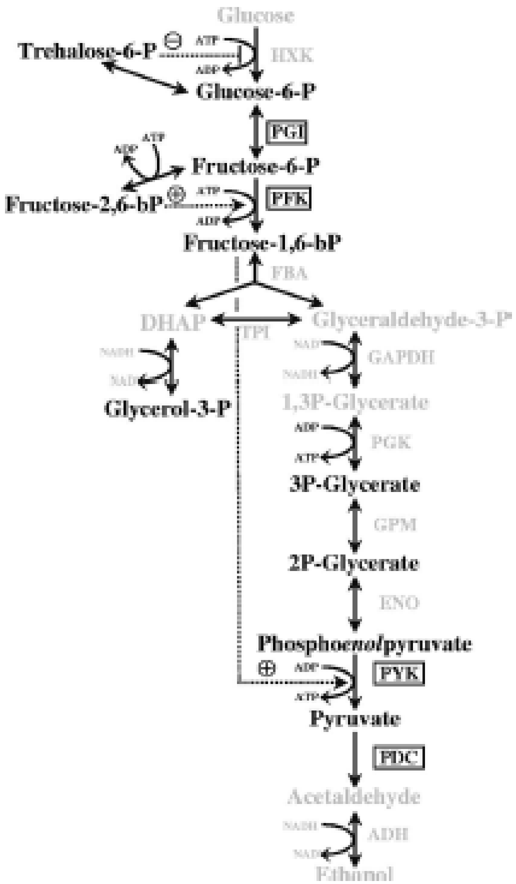
- **Adaptive system:**

$$\frac{d\,A}{dt} = V_{max}^{R} - \frac{V_{max}^{B} \cdot A}{K_b + A}$$

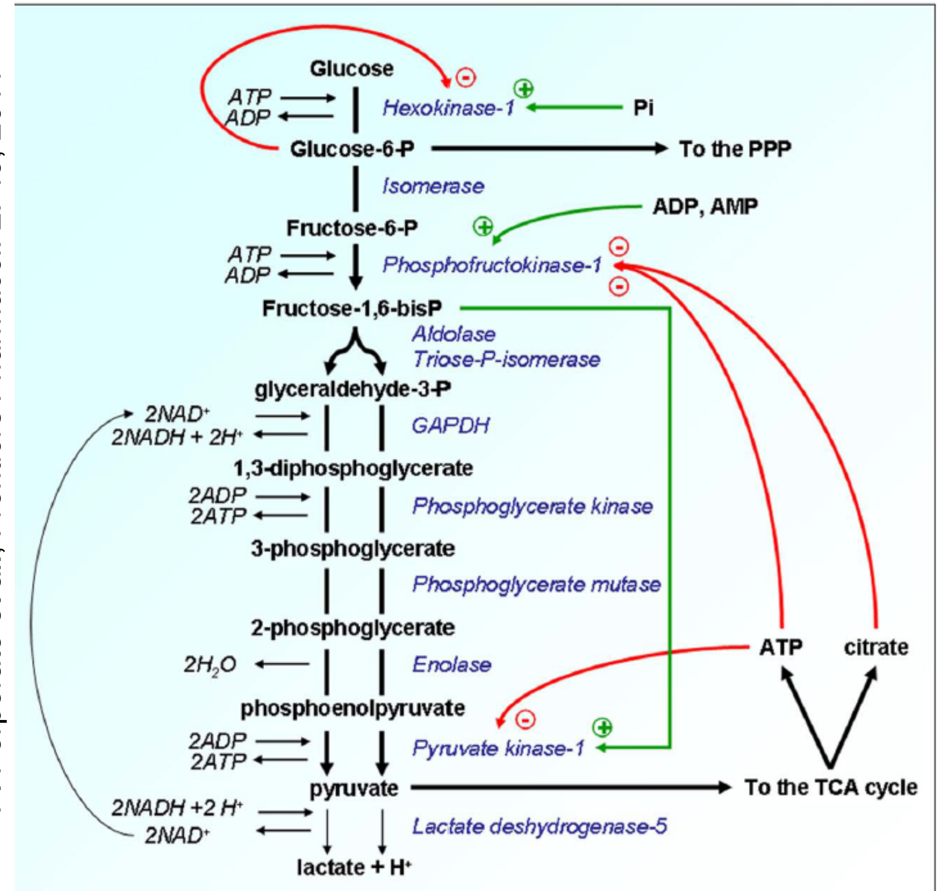
$$\Rightarrow \quad A^{ss} = K_b \cdot \frac{V_{max}^{R}}{V_{max}^{R} - V_{max}^{B}}$$

Glycolytic Regulation: Application #2

J. van den Brink et al., *Appl. Env. Microbiol.* 74: 5710, 2008

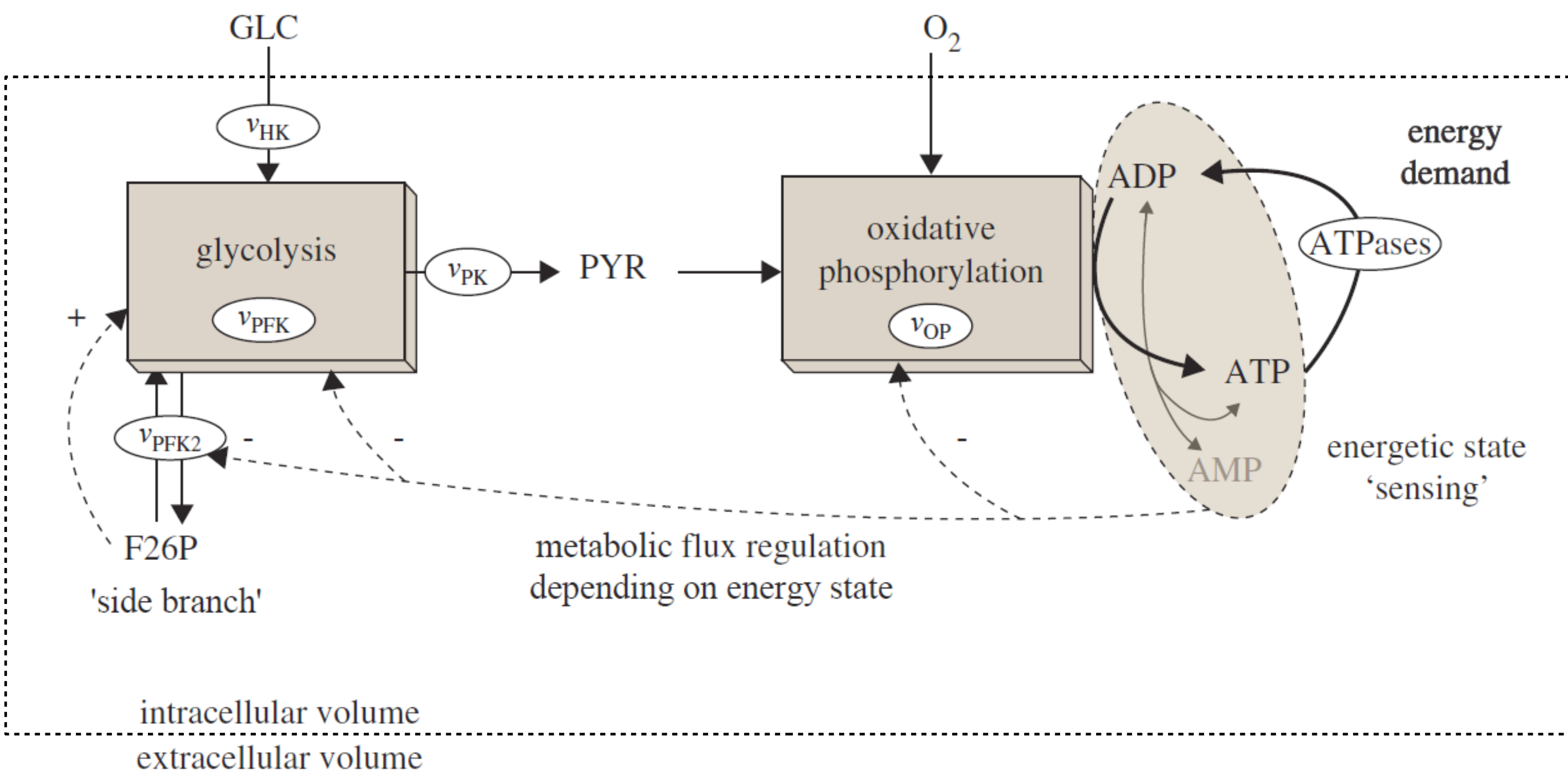


P. Porporato et al., *Frontiers Pharmacol.* 2: 49, 2011



- Glycolytic regulation: There is not a single (biological) model → Standardize and focus.

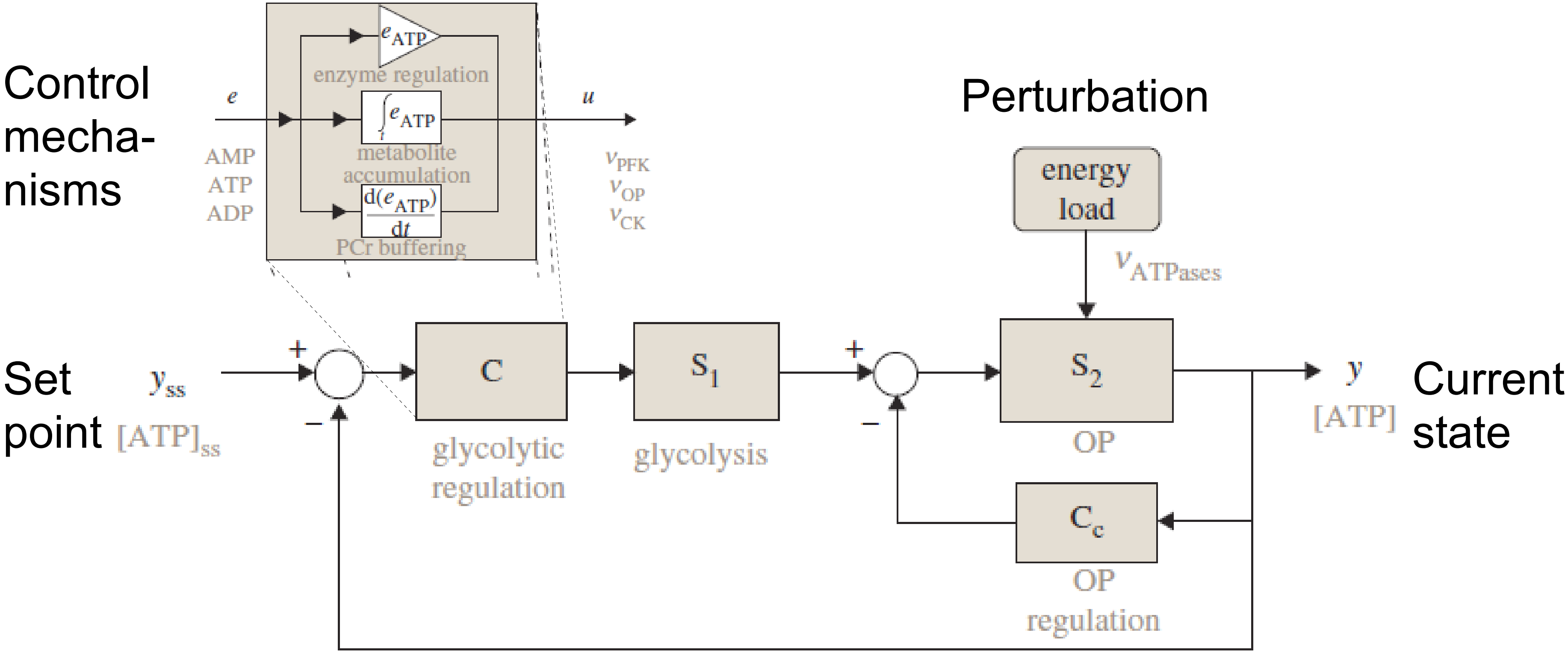
A Simplified Model of Energy Metabolism



Adapted from M. Cloutier & P. Wellstead, *J. R. Soc. Interface*, 2009.

- Feedback control of energy (ATP) homeostasis despite fluctuating demand → Why so many feedback loops?

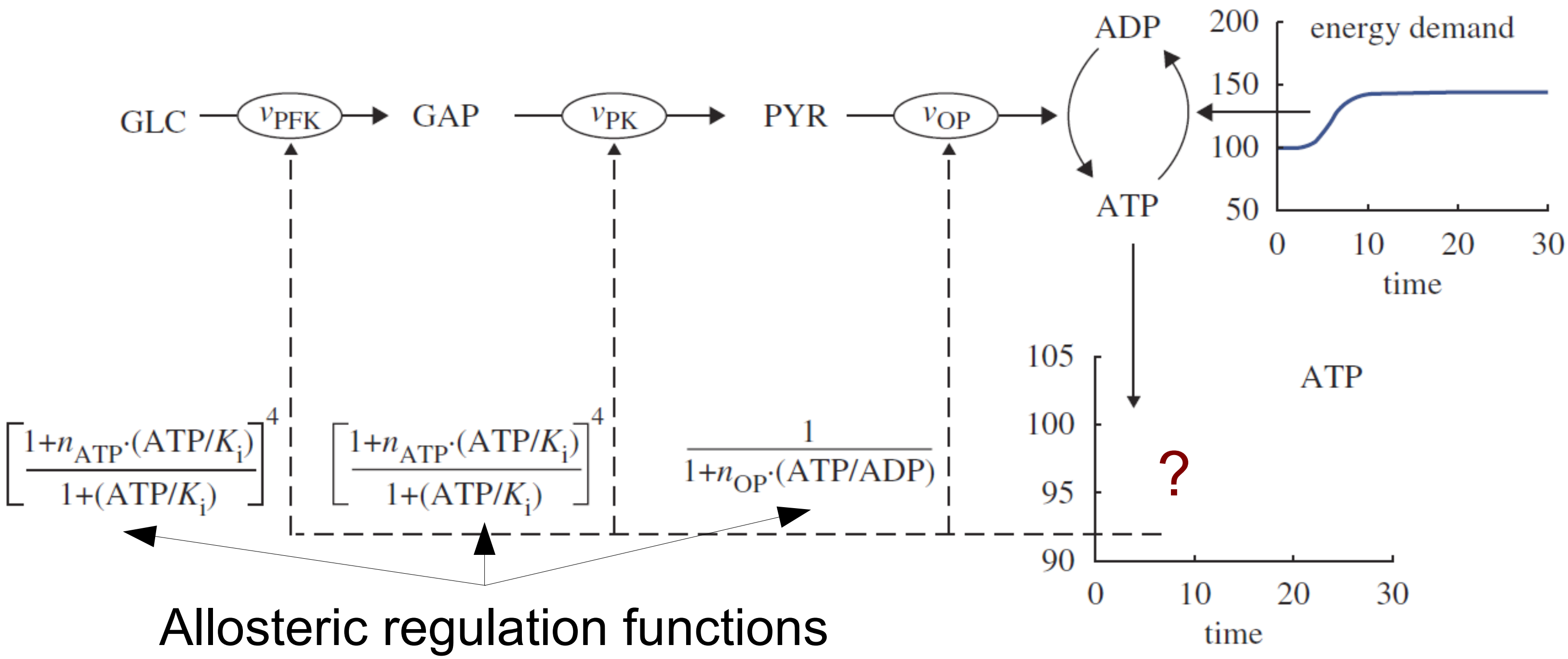
Energy Metabolism: An Engineer's View



Adapted from M. Cloutier & P. Wellstead, *J. R. Soc. Interface*, 2009.

- Different types of (negative) feedback have different functions in controlling energy states.

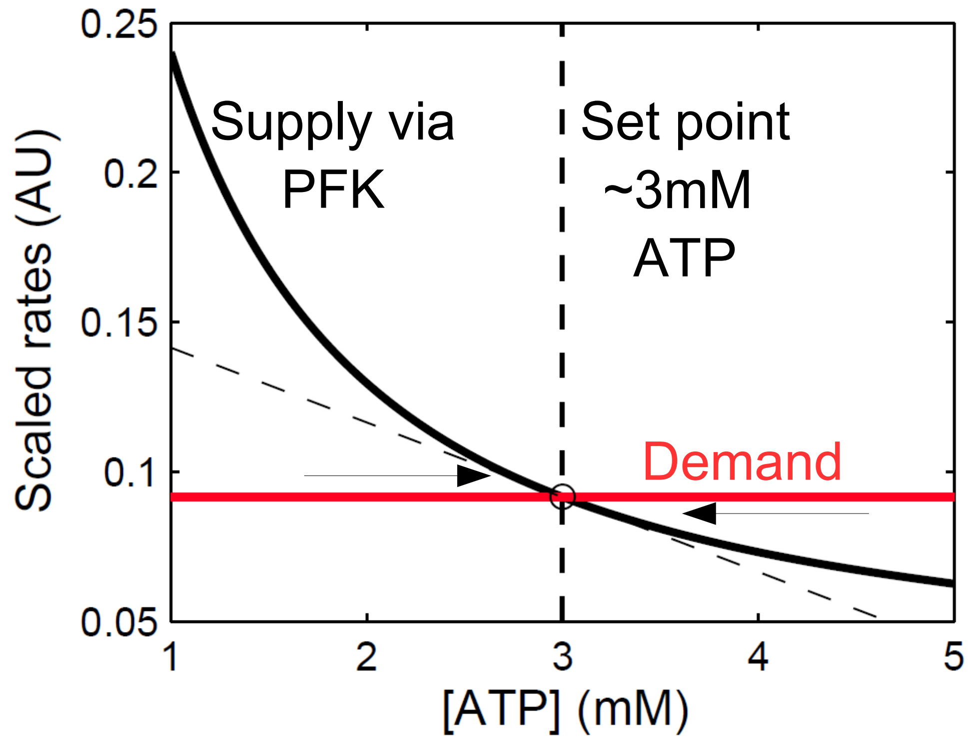
What Does Allosteric Regulation Achieve?



Adapted from M. Cloutier & P. Wellstead, *J. R. Soc. Interface*, 2009.

- Allosteric flux regulation depending on ATP concentration.
- Why three different control targets in energy metabolism?

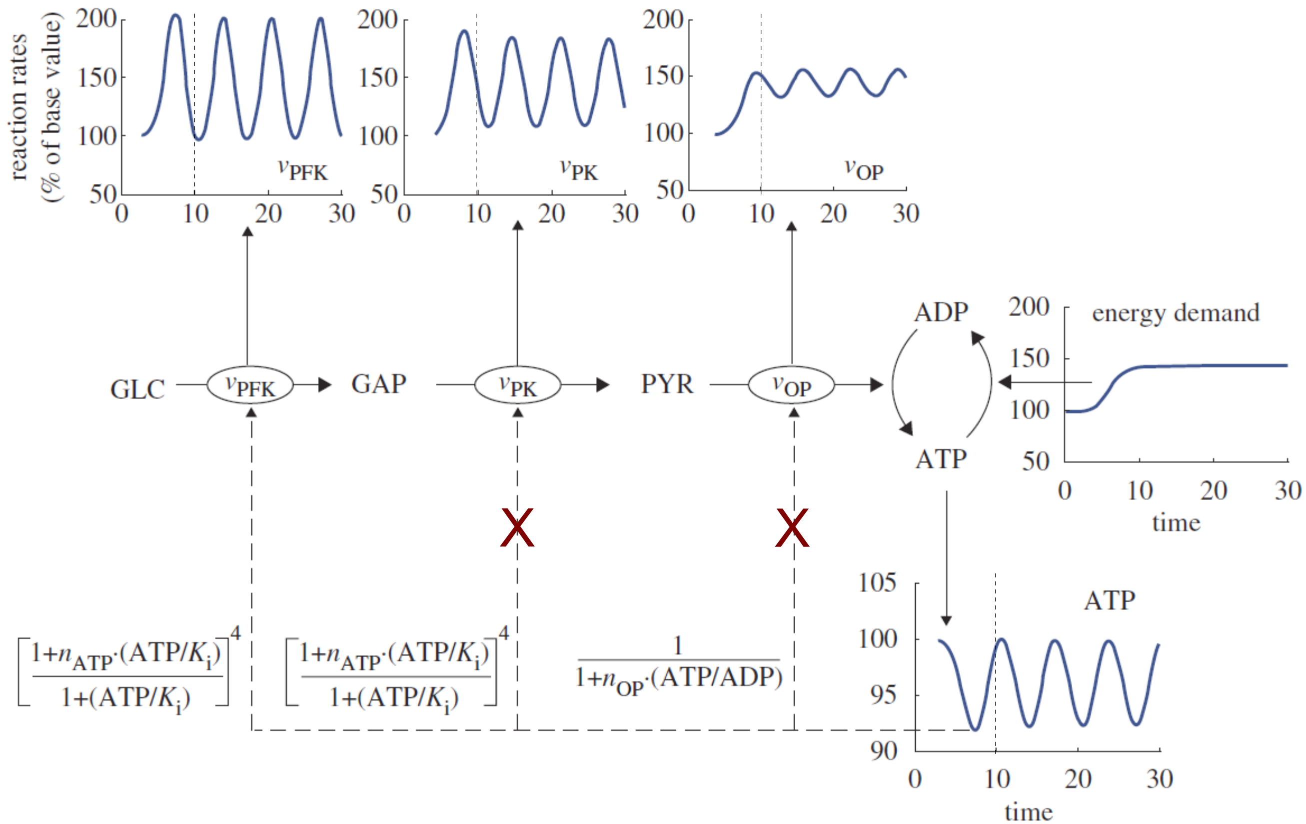
What Does Allosteric Regulation Achieve?



- Allosteric regulation represses flux with $\left[\dfrac{1+n_{\mathrm{ATP}}\cdot(\mathrm{ATP}/K_{\mathrm{i}})}{1+(\mathrm{ATP}/K_{\mathrm{i}})}\right]^4$.
- Approximately **proportional** negative feedback on ATP.

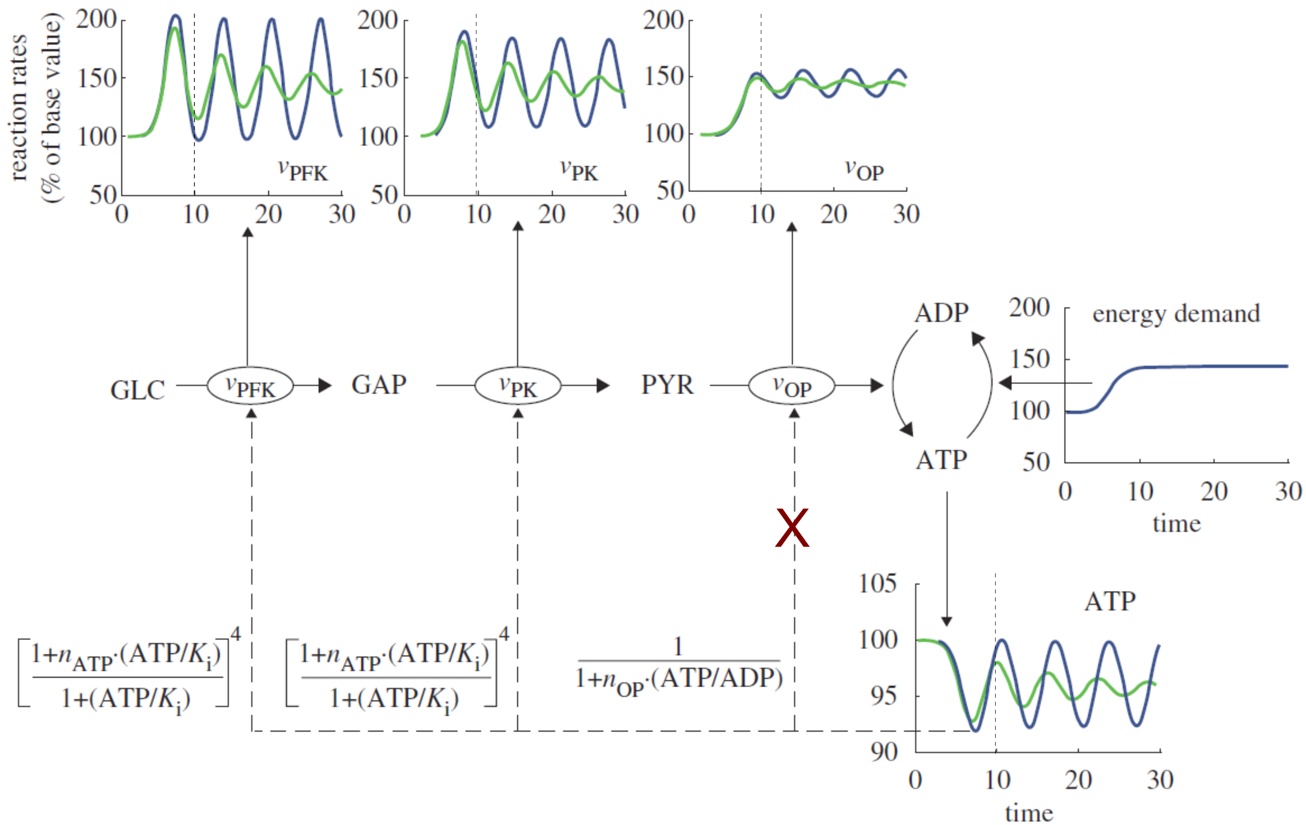
What Does Allosteric Regulation Achieve?

Adapted from M. Cloutier & P. Wellstead, *J. R. Soc. Interface*, 2009.



- Test of individual feedbacks: Different model structures.
- Only 'long' PFK feedback → Time delay → Instabilities!

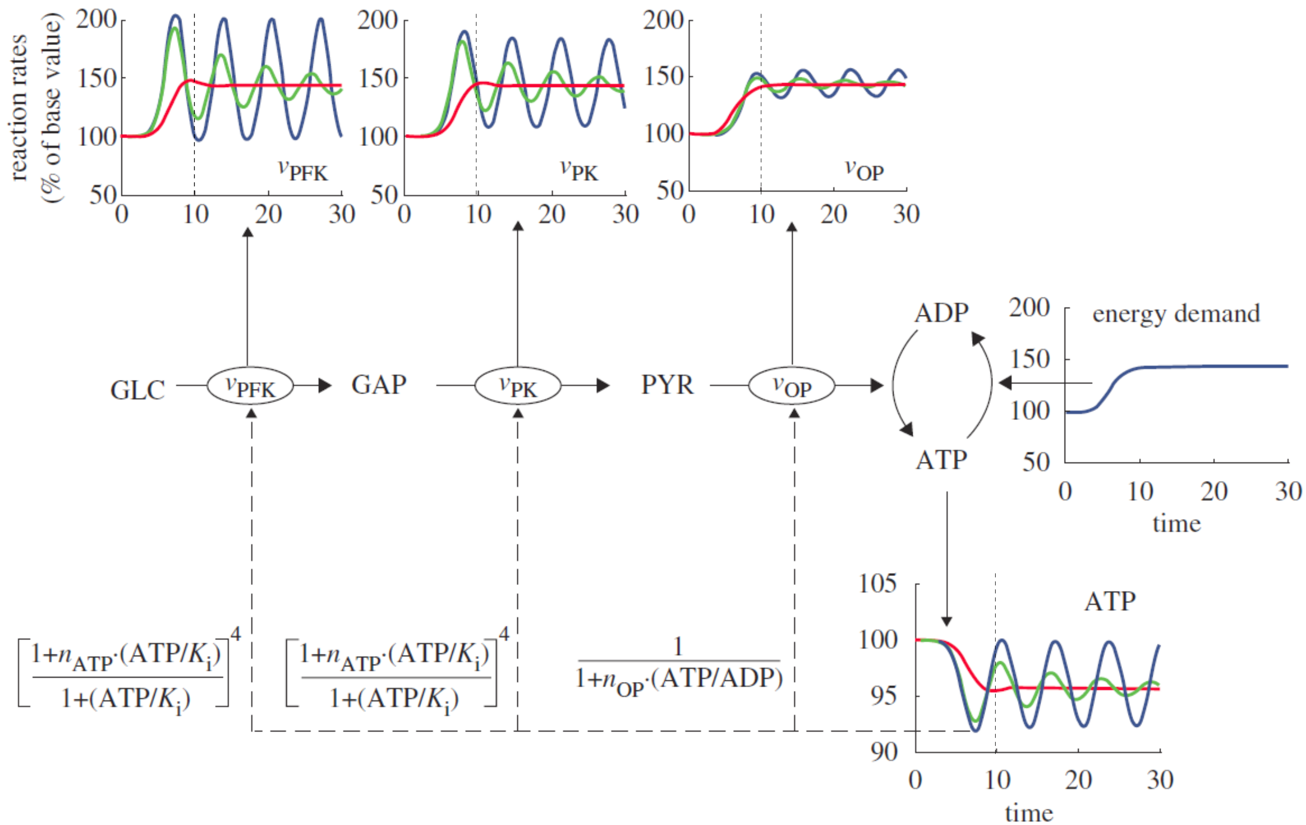
What Does Allosteric Regulation Achieve?



Adapted from M. Cloutier & P. Wellstead, *J. R. Soc. Interface*, 2009.

- Test of individual feedbacks: Different model structures.
- Two (cascaded) feedbacks → Reduced instabilities.

What Does Allosteric Regulation Achieve?

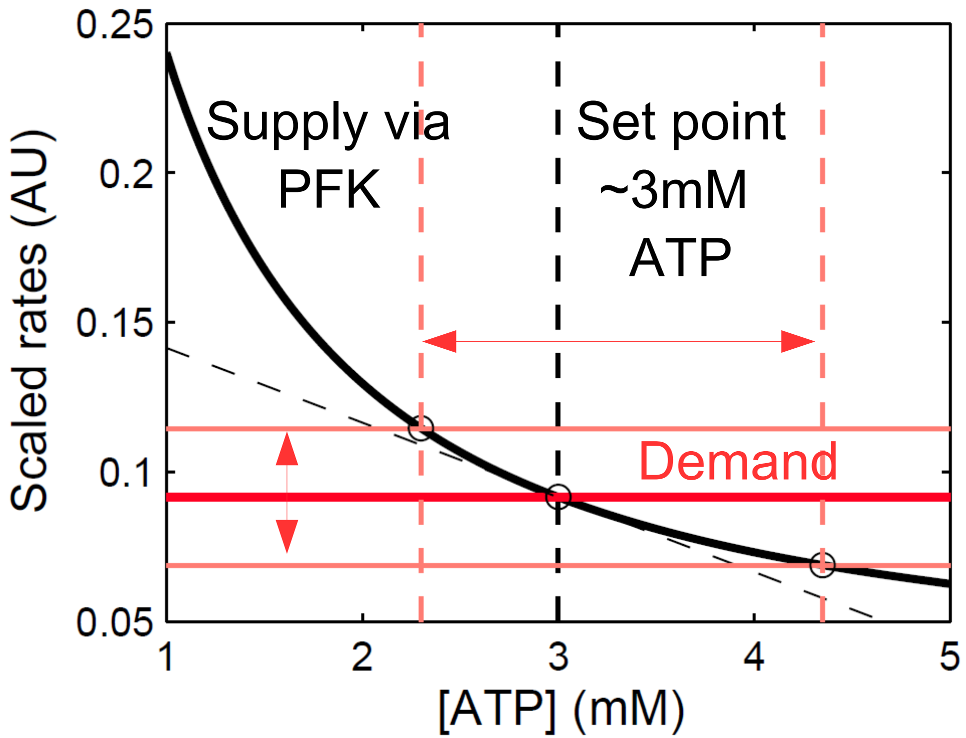


Adapted from M. Cloutier & P. Wellstead, *J. R. Soc. Interface*, 2009.

- Three (cascaded) feedbacks → Homeostasis achieved.

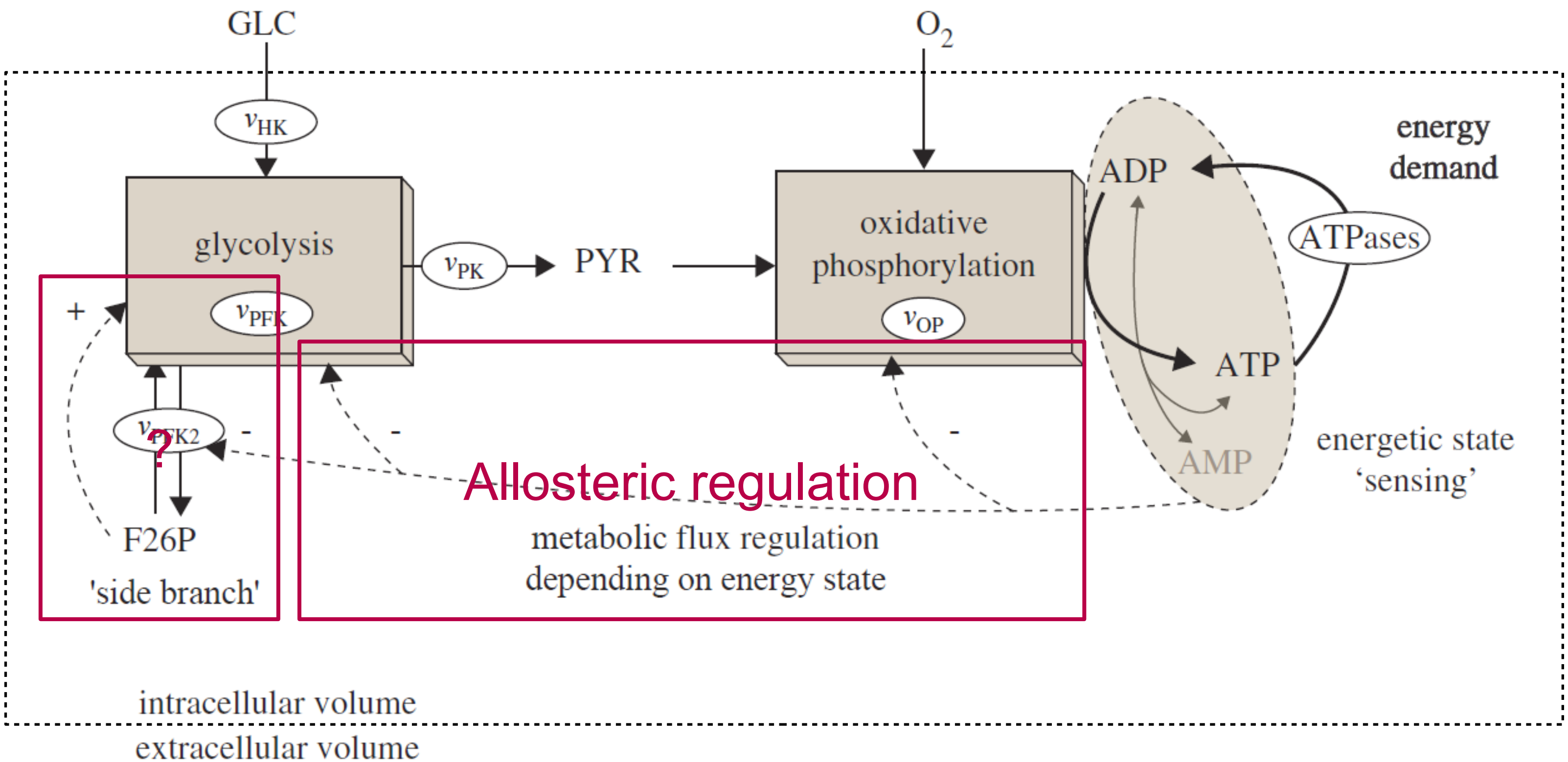
- But what is biologically 'wrong' with the ATP response?

What Does Allosteric Regulation Achieve?



- **Problem:** Proportional feedback does not lead to the same steady-state ATP concentration for different demands → Large deviations from set point possible.

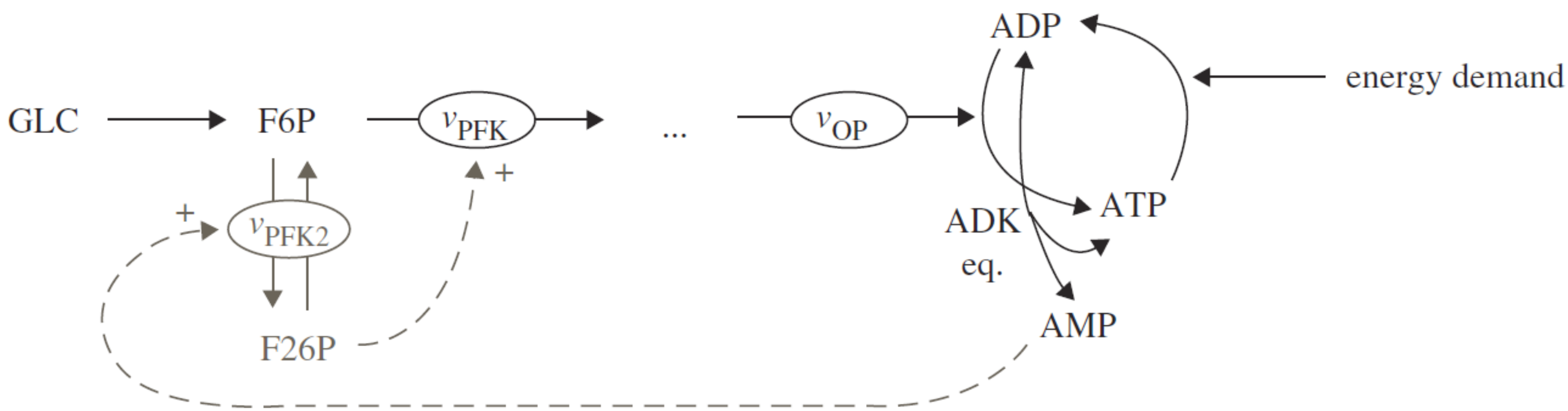
Back to the Simplified Model



Adapted from M. Cloutier & P. Wellstead, *J. R. Soc. Interface*, 2009.

- 'Glycolysis is usually presented as a linear pathway with nine reactions. However, this representation neglects a very important side reaction, the PFK2. This reaction allows the accumulation of F26P, one of the strongest activators of glycolysis.'

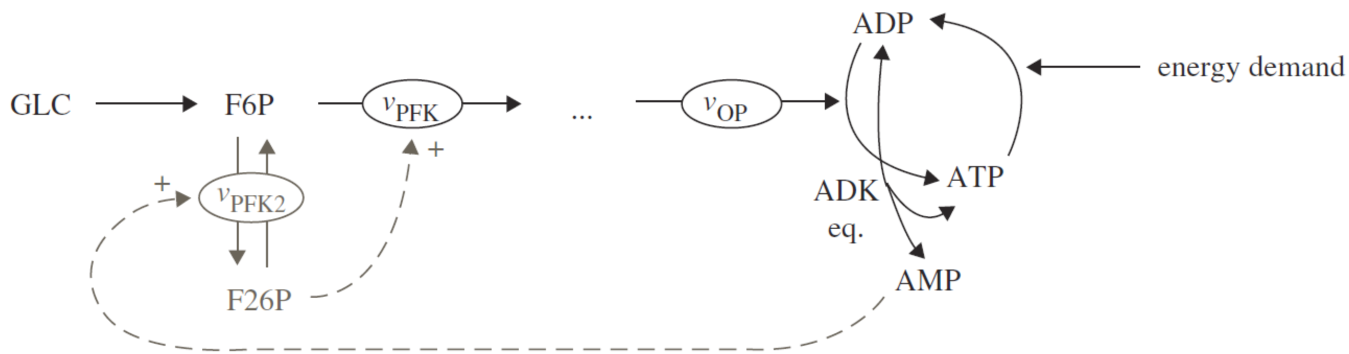
Control by PFK2



Adapted from M. Cloutier & P. Wellstead, *J. R. Soc. Interface*, 2009.

- AMP activates F26P production, which activates PFK → Another feedback loop in the system.
- Which type of feedback? Why different from the allosteric feedback loops already discussed?

Integral Negative Feedback by PFK2



Adapted from M. Cloutier & P. Wellstead, *J. R. Soc. Interface*, 2009.

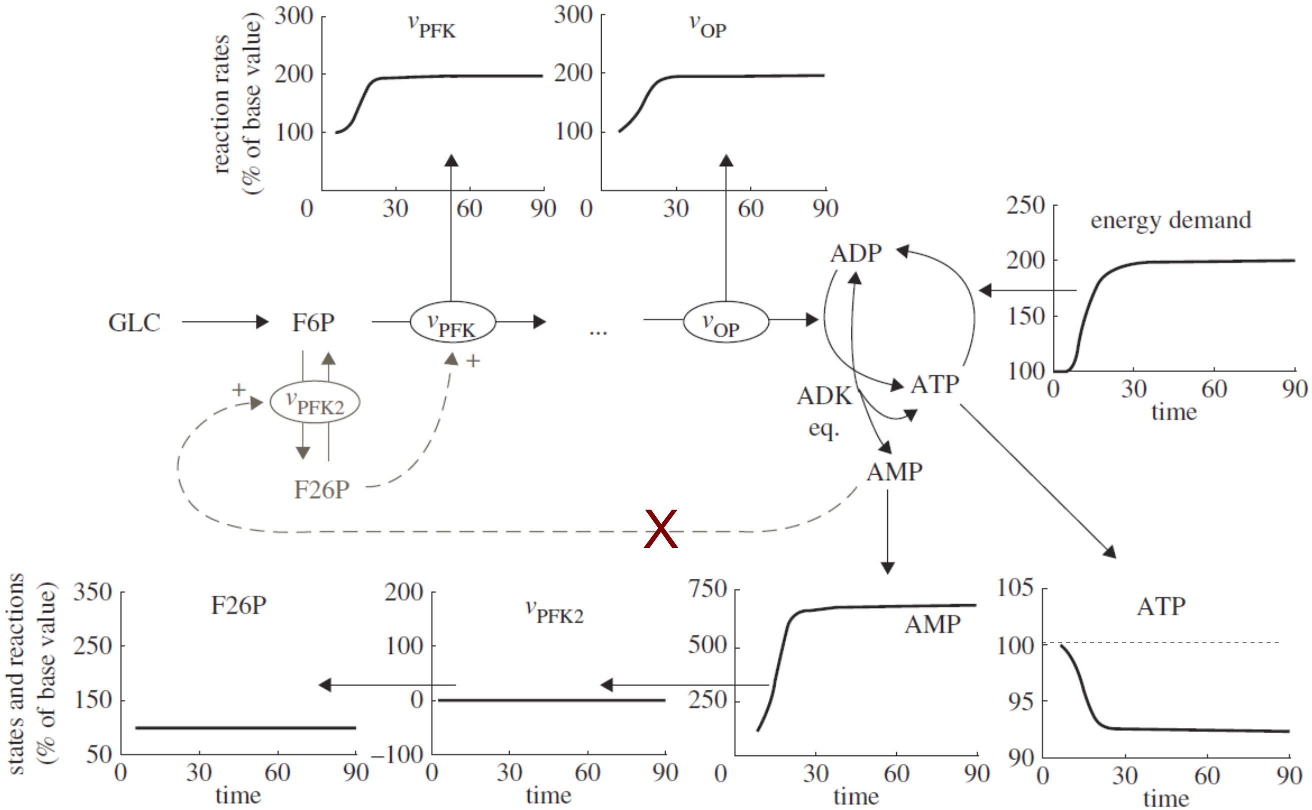
- If total AXP is conserved then $[AMP]$ represents the '$error$' in the current energy (ATP) state.

- The negative feedback loop **integrates** the error:

$$\frac{d[F26P]}{dt} = v_{PFK2} \propto error \Rightarrow v_{PFK} \propto [F26P] \propto \int_t error$$

Integral Negative Feedback by PFK2

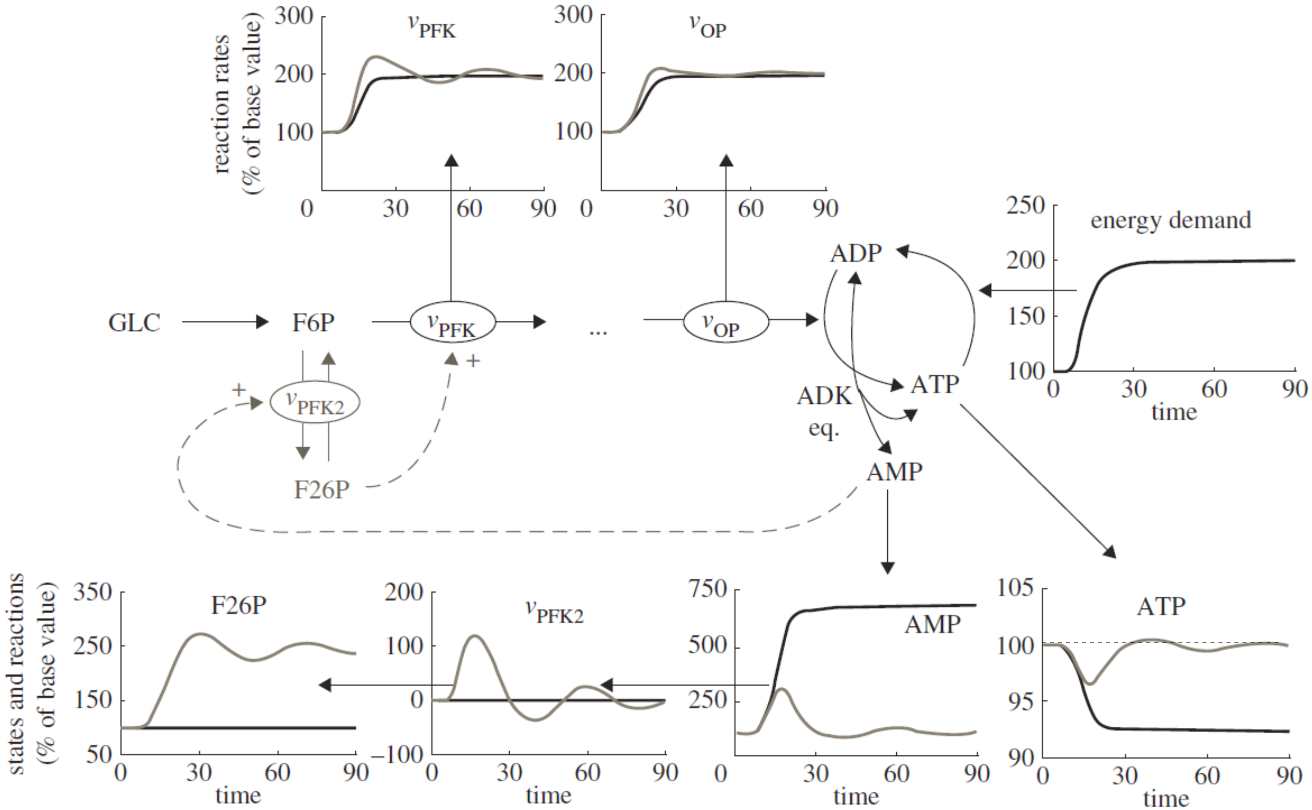
Adapted from M. Cloutier & P. Wellstead, *J. R. Soc. Interface*, 2009.



- Without integral feedback: Deviation from ATP set-point.

Integral Negative Feedback by PFK2

Adapted from M. Cloutier & P. Wellstead, *J. R. Soc. Interface*, 2009.



- Without integral feedback: Deviation from ATP set-point.
- With integral feedback: Perfect adaptation to demand.

Caveat #1: Limitations of ODE Models

- Underlying assumptions need not be fulfilled:
  - Spatial homogeneity (→ compartmentalization).
  - High numbers of molecules for all species.
- Closed solutions as well as graphical analysis only for limited model classes:
  - Recursion to numerical simulation / analysis.
  - Proofs for global system properties impossible.

Dynamic Systems (II): Summary

- Simple feedback circuits → Complicated behaviors possible.
- Basic circuits: Positive / negative feedback, antagonism.
- Dynamic systems fundamentals (qualitatively, so far): Attractors, stability, multi-stability, bifurcations, hysteresis.
- Graphical analysis: Vector fields, nullclines, steady states, ...
- Functions of simple nonlinear feedback circuits:
  - Negative: Homeostasis, adaptation.
  - Positive: (Irreversible) switches, decisions.

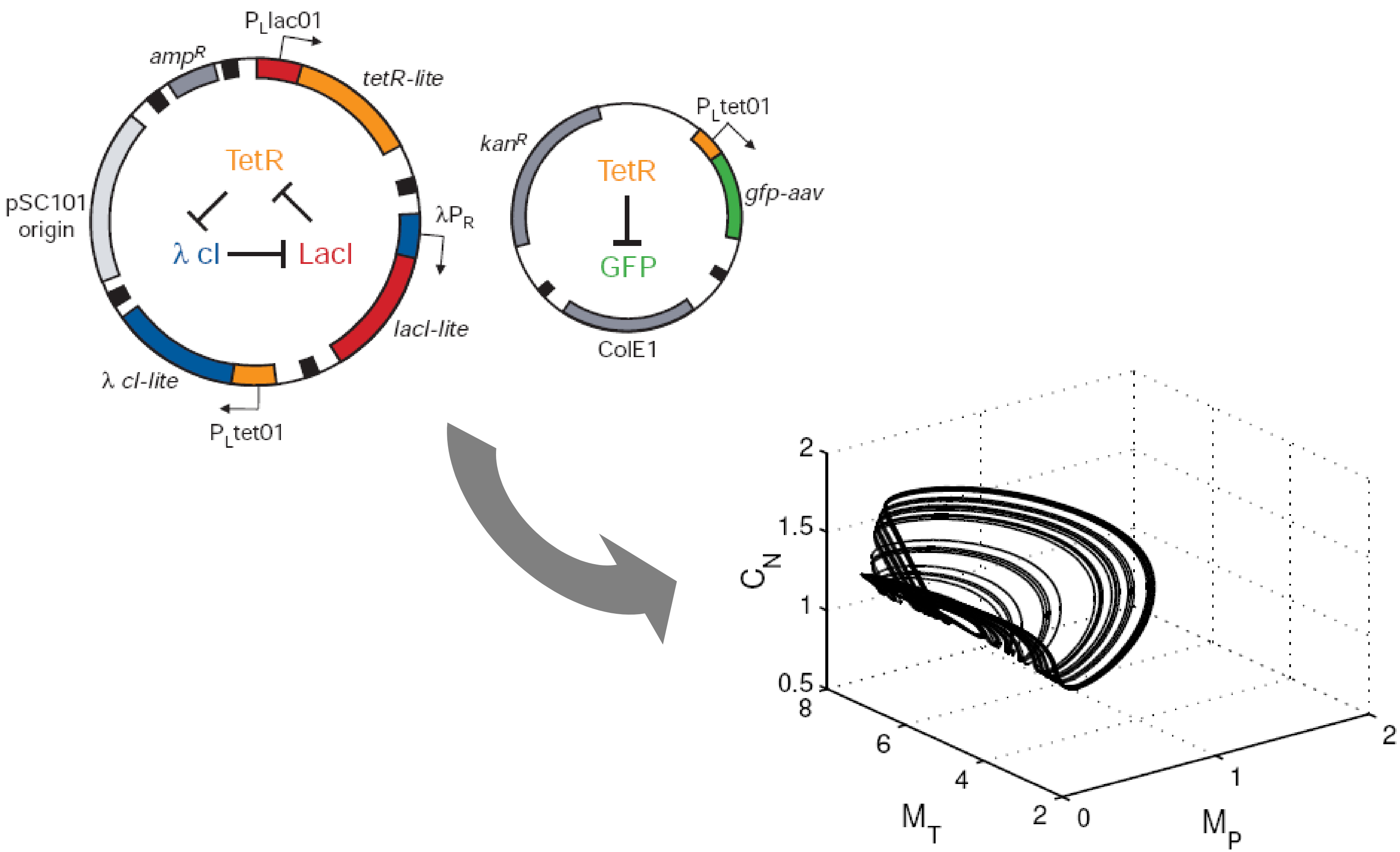
Further Reading

- J.J. Tyson, K.C. Chen & B. Novak. Sniffers, buzzers, toggles and blinkers: dynamics of regulatory and signaling pathways in the cell. Curr Opin Cell Biol. 15, 221 – 231 (2003).

- T.-M. Yi, Y. Huang, M.I. Simon & J.C. Doyle. Robust perfect adaptation in bacterial chemotaxis through integral feedback control. Proc. Natl. Acad. Sci. USA 97, 4649 – 4653 (2000).

- M. Khammash. An engineering viewpoint on biological robustness. BMC Biology 14, 22 (2016).

Next Week



P$_L$lac01
amp^R
tetR-lite
pSC101
origin
TetR
λ cI
LacI
λP$_R$
lacI-lite
λ cI-lite
P$_L$tet01
kan^R
P$_L$tet01
TetR
gfp-aav
GFP
ColE1
C$_N$
M$_T$
M$_P$