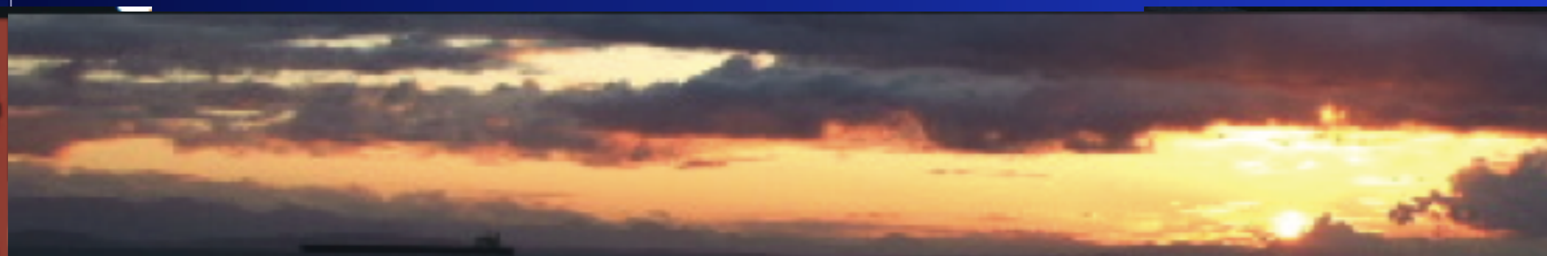
Mathematical Cell Biology Graduate Summer Course

University of British Columbia, May 1-31, 2012

Leah Edelstein-Keshet

Simple biochemical motifs (1)



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www.math.ubc.ca/~keshet/MCB2012/

Biochemical (and gene) circuits

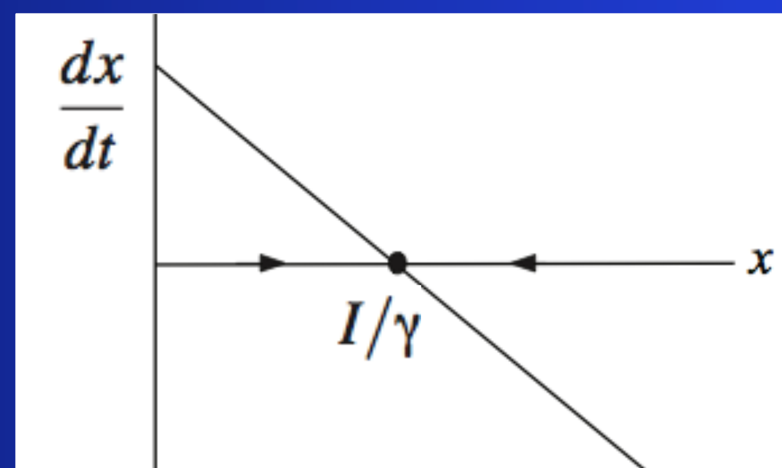
Switches, oscillators, adaptation, and amplification circuits

Production-decay at constant rates

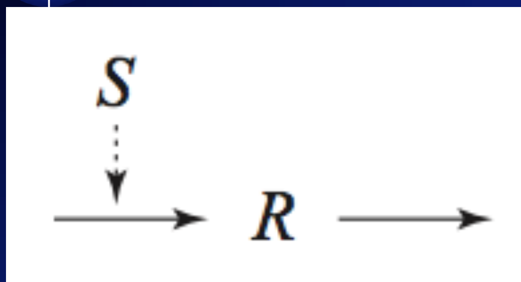
$$\frac{dx}{dt} = I - \gamma x$$

$I, \gamma > 0$ constants.

Unique positive Steady state

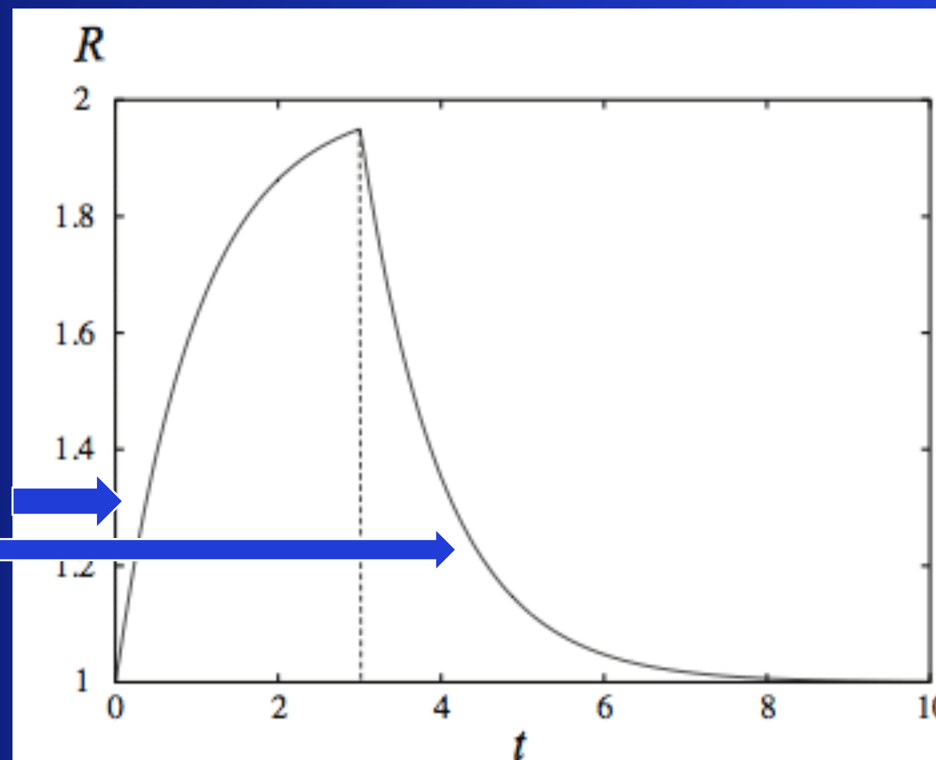


Signal-induced Production

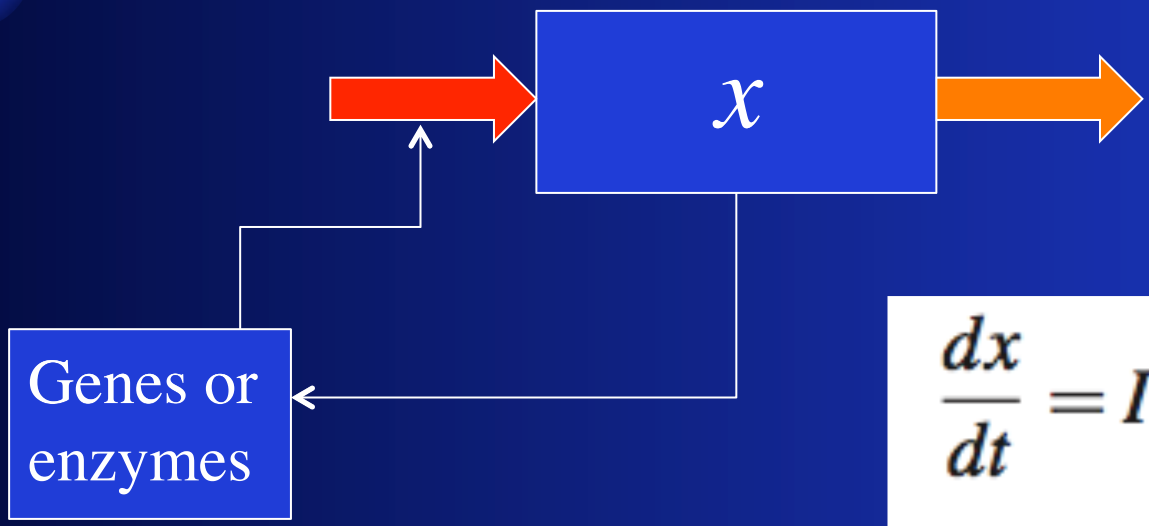


$$\frac{dR}{dt} = k_0 + k_1 S - k_2 R.$$

Note typical "1-exp($-k_2t$)" rise and exponential decay tail



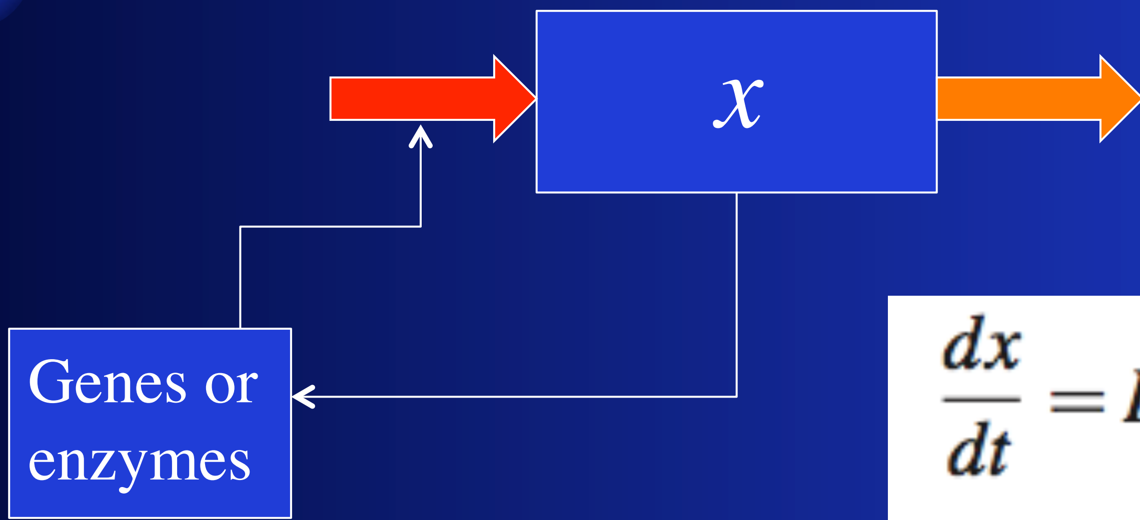
Feedback to production



$$\frac{dx}{dt} = I - \gamma x$$

I is now a function of *x*

Michaelian Feedback to production



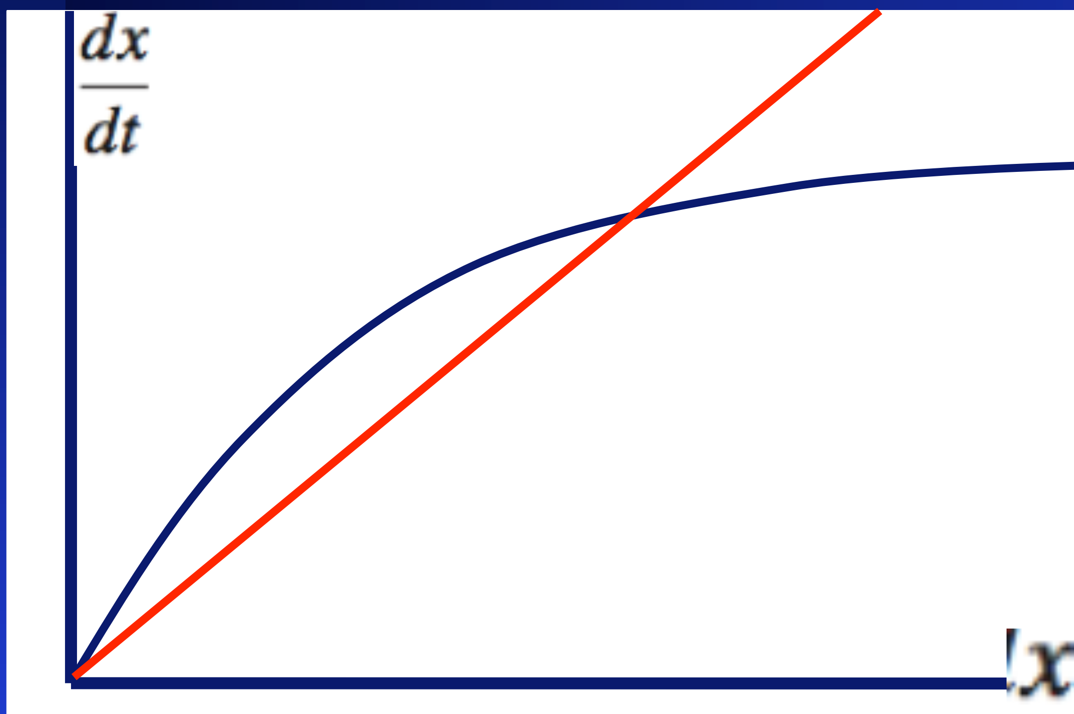
$$\frac{dx}{dt} = I - \gamma x$$

$$I(x) = I_0 + \frac{I_{max} \; x}{k_n + x}$$

Michaelian Feedback to production

$$I(x) = I_0 + \frac{I_{max}\ x}{k_n + x}$$

$$\frac{dx}{dt} = I - \gamma x$$

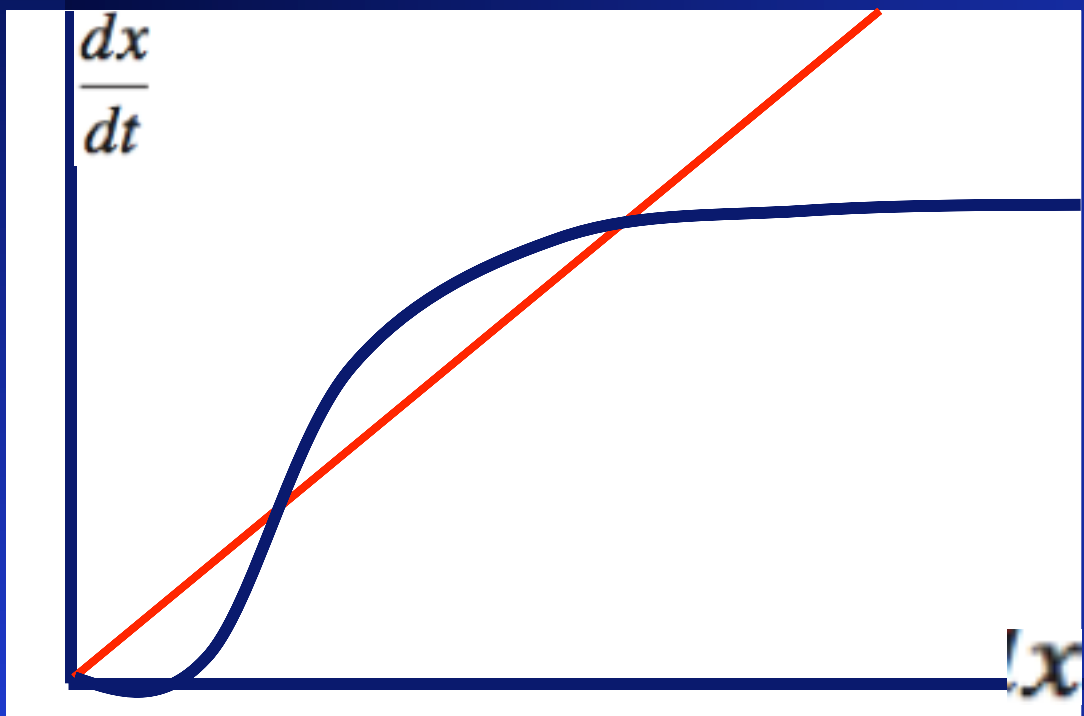


At most 2 steady states, one stable.

Sigmoidal Feedback to production

$$I(x) = I_0 + \frac{I_{max}\ x^2}{k_n^{\ 2} + x^2}$$

$$\frac{dx}{dt} = I - \gamma x$$



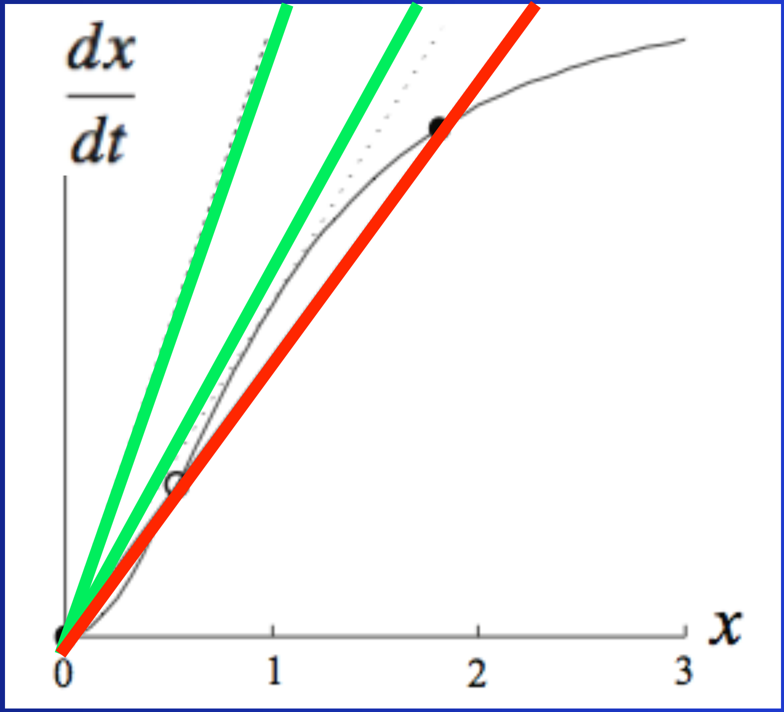
Up to 3 steady states, two stable.

"bistability"

Sigmoidal cont'd

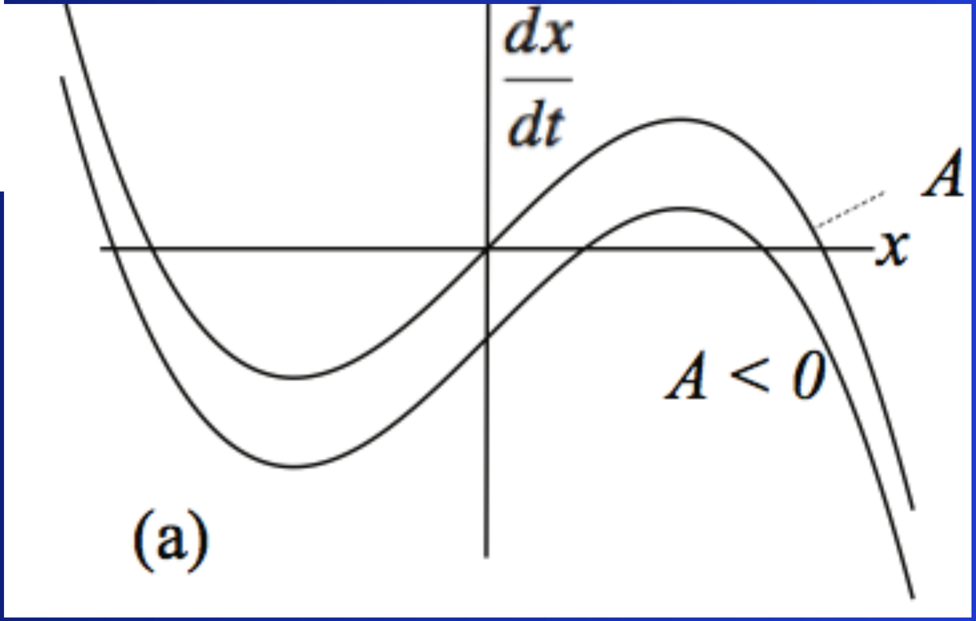
$$\frac{dx}{dt} = f(x) = \frac{x^2}{1+x^2} - mx + b$$

Actual number of steady states depends on parameters, e.g. on slope *m* (decay rate of *x*)

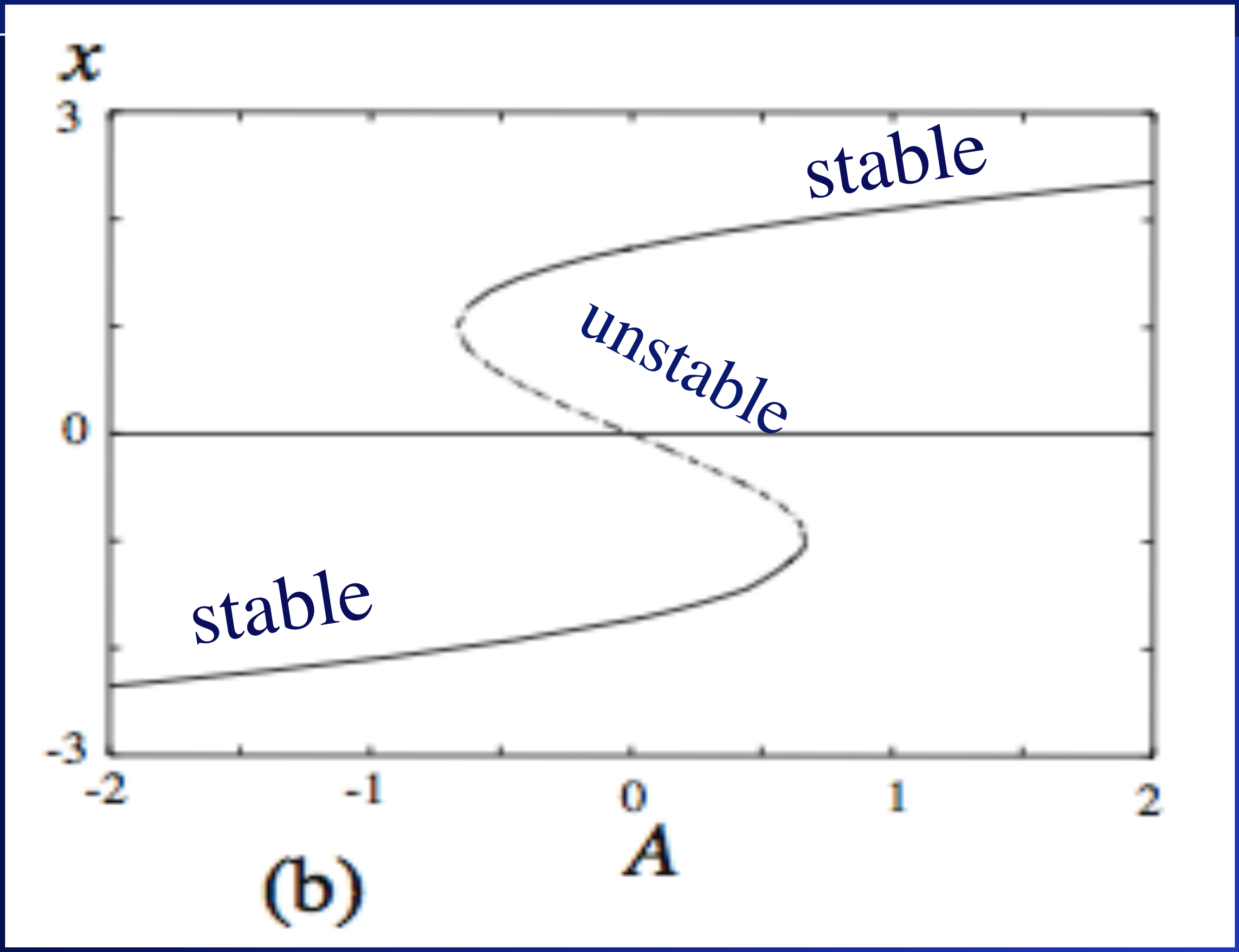


Generic bistability

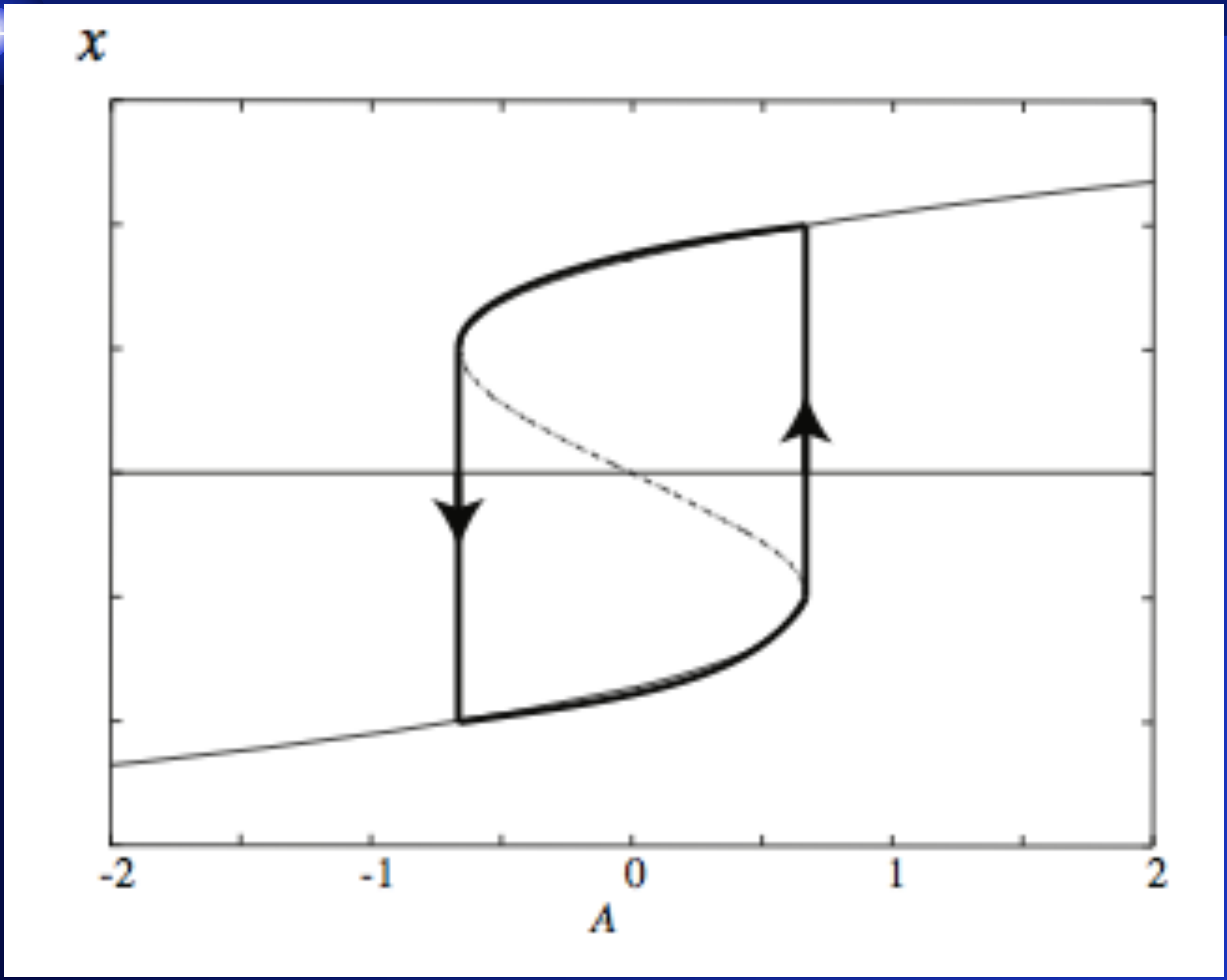
$$\frac{dx}{dt} = c\left(x - \frac{1}{3}x^3 + A\right)$$



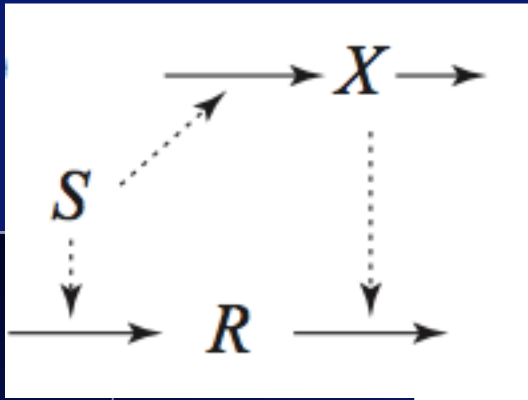
Bifurcation Diagram



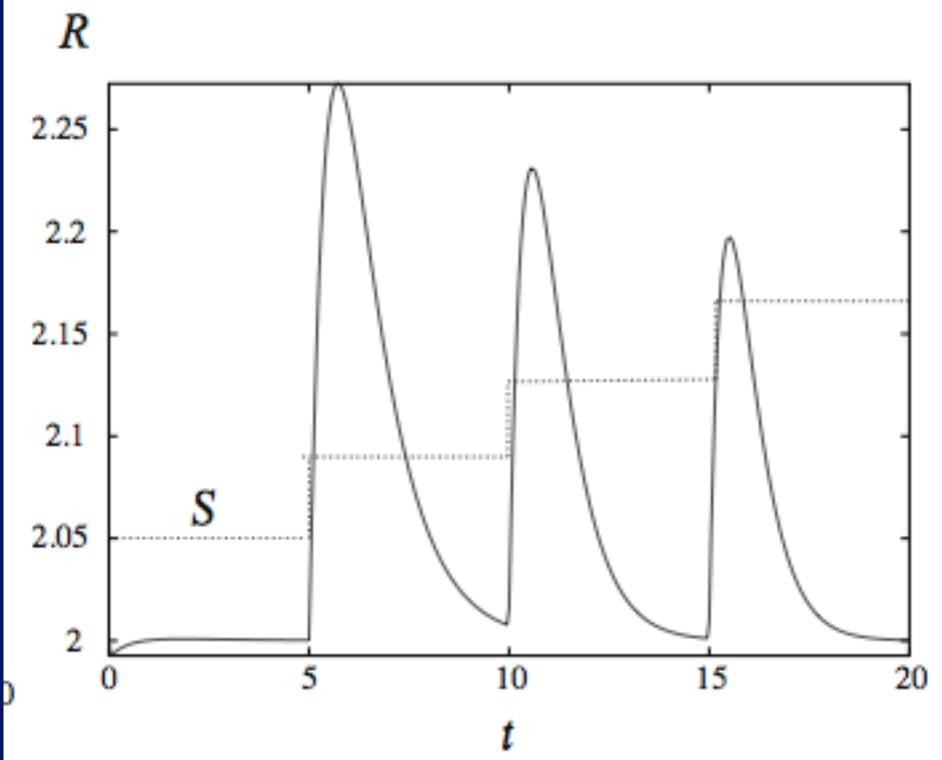
Hysteresis



Adaptation



$$\frac{dR}{dt} = k_1 S - k_2 X R,$$
$$\frac{dX}{dt} = k_3 S - k_4 X.$$



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Simple biochemical motifs (2)

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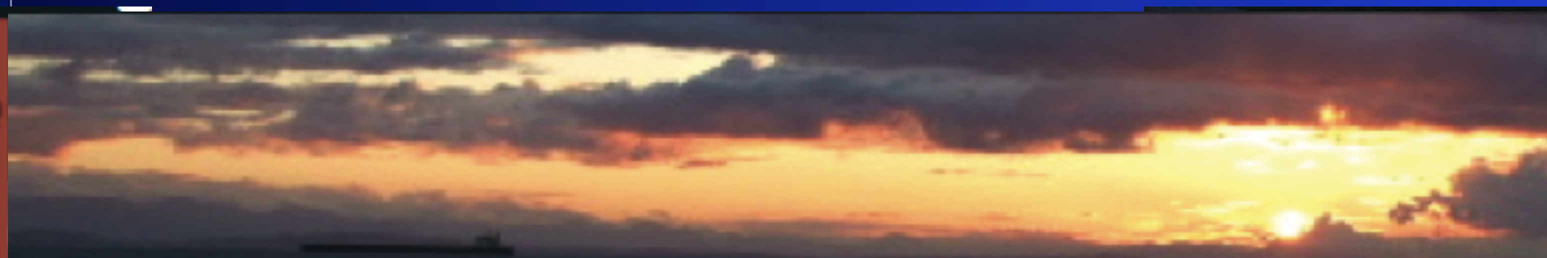

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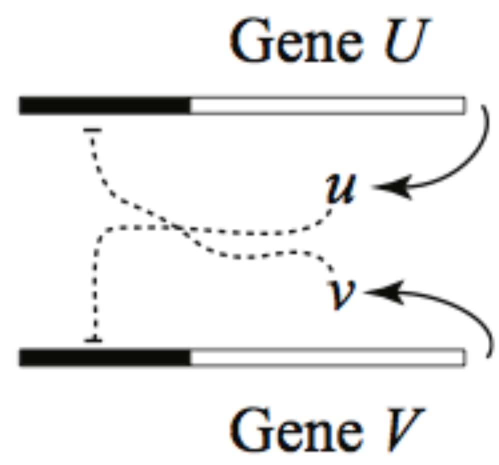
Genetic toggle switch

Construction of a genetic toggle switch in *Escherichia coli*

Timothy S. Gardner*†, Charles R. Cantor* & James J. Collins*†

NATURE | VOL 403 | 20 JANUARY 2000 | www.nature.com

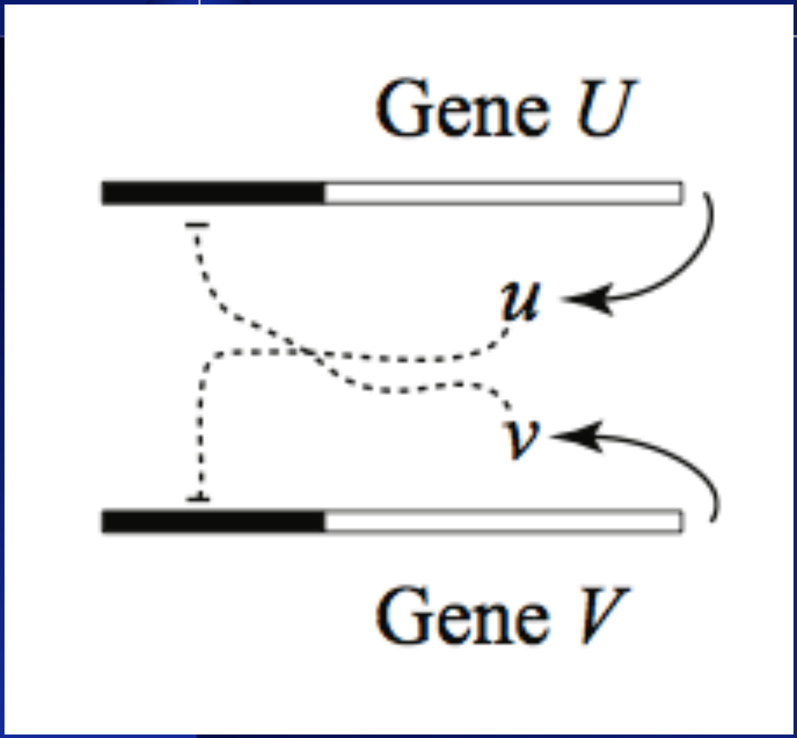
An actual "engineered genetic circuit" based on the concepts and models of biochemical switches.



Genetic toggle switch

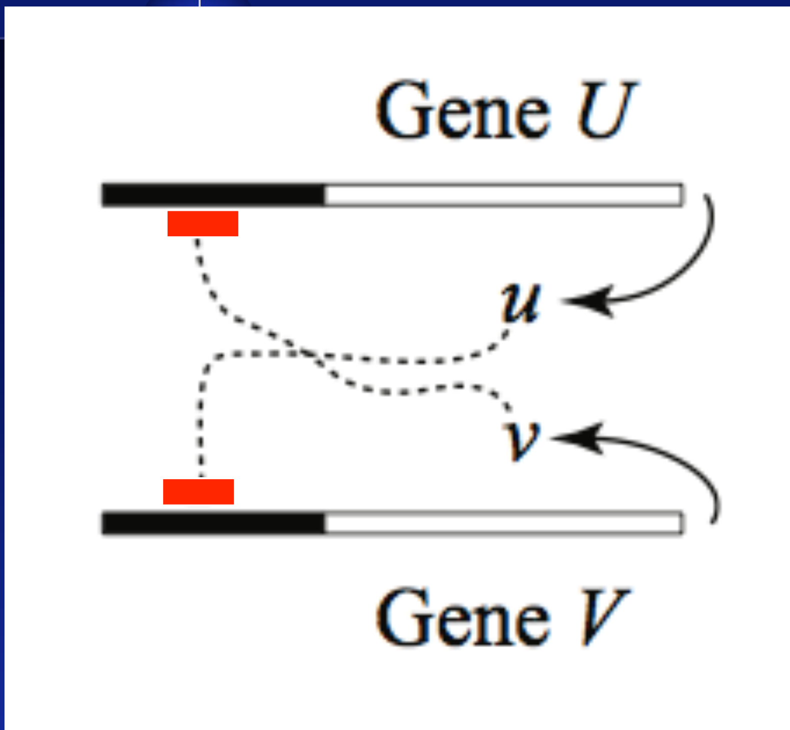
"Here we present the construction of a genetic toggle switch: a synthetic, bistable gene-regulatory network in E. coli and provide .. theory that predicts conditions for bistability."

Production-decay of two proteins



$$\frac{du}{dt} = I_u - d_u u,$$
$$\frac{dv}{dt} = I_v - d_v v.$$

Negative feedback



$$\frac{du}{dt} = I_u - d_u u,$$

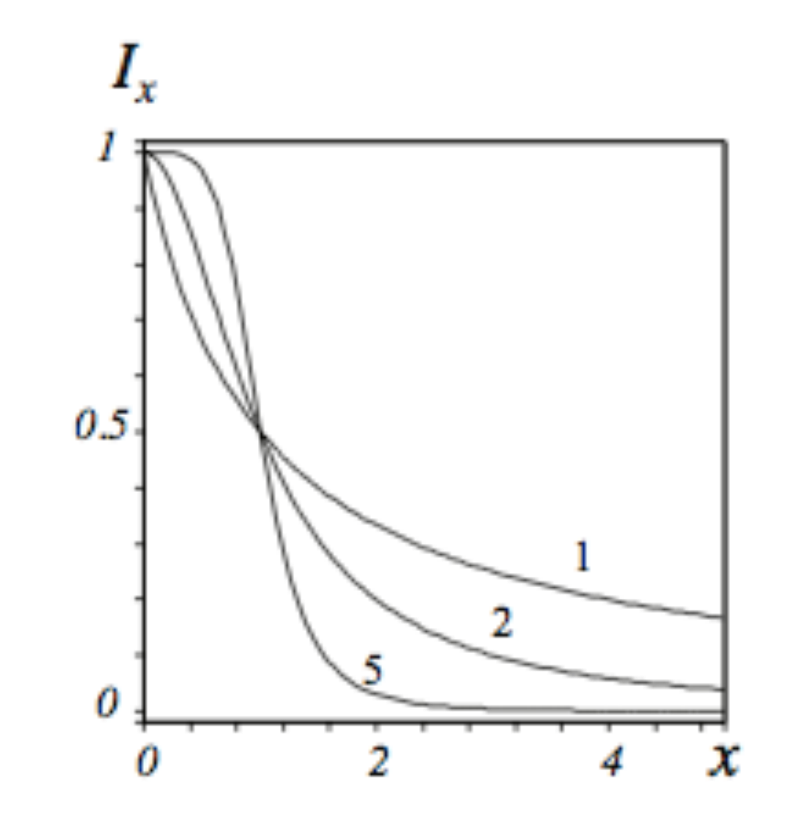
$$\frac{dv}{dt} = I_v - d_v v.$$

$$I_x = \frac{\alpha}{1 + x^n}.$$

Negative feedback function

$$I_x = \frac{\alpha}{1 + x^n}.$$

Higher n means sharper response with increasing x



Mutual inhibition

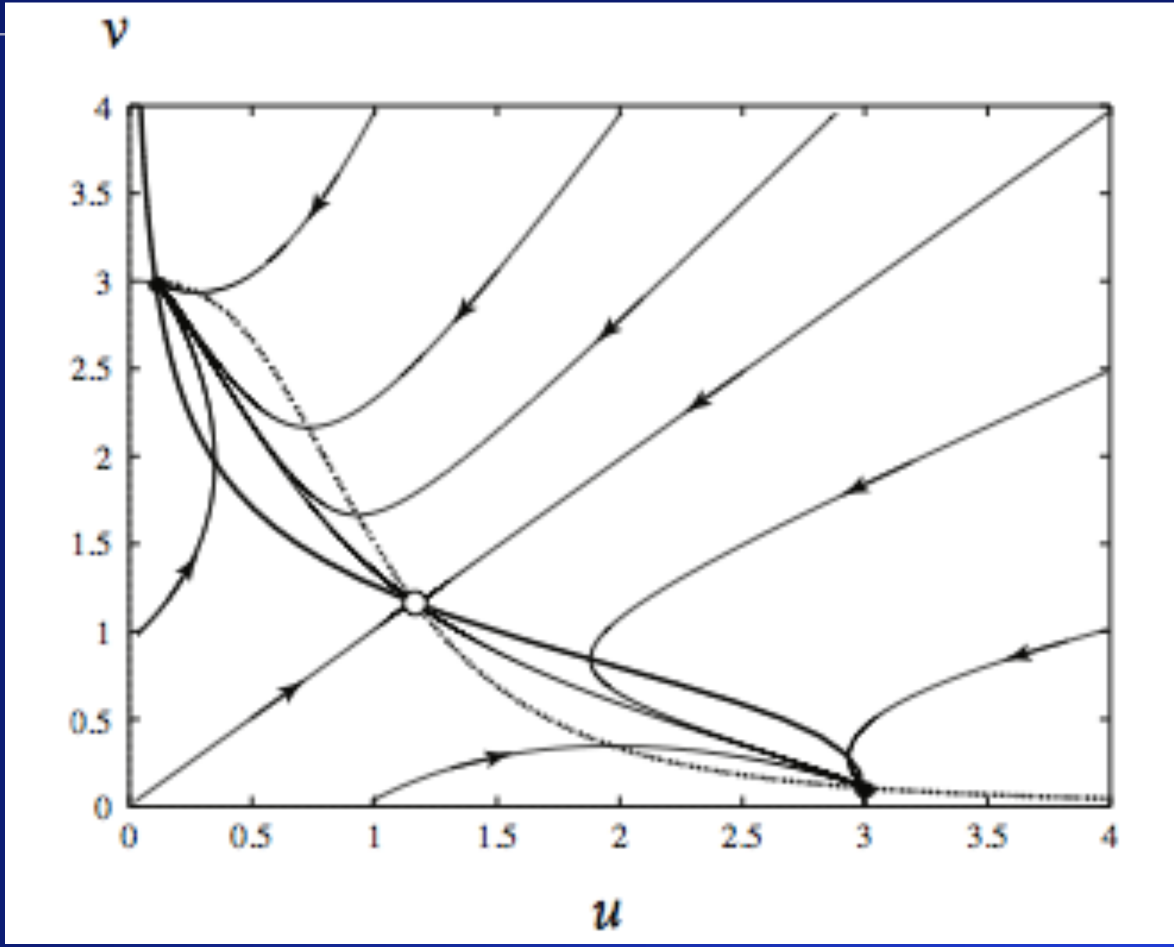
$$\frac{du}{dt} = \frac{\alpha_1}{1+v^n} - u,$$
$$\frac{dv}{dt} = \frac{\alpha_2}{1+u^m} - v.$$

Each gene product inhibits the other gene.

"… the toggle equations have 2 fundamental aspects: cooperative repression and degradation .. of the repressors"

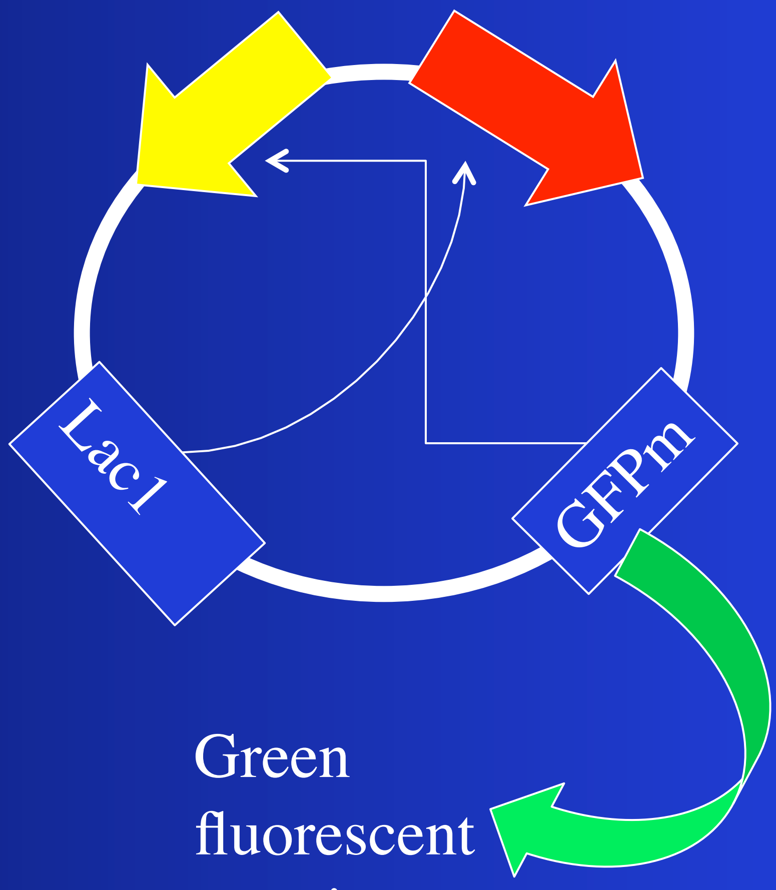
Switch-like behaviour

$$\frac{du}{dt} = \frac{\alpha_1}{1+v^n} - u,$$
$$\frac{dv}{dt} = \frac{\alpha_2}{1+u^m} - v.$$



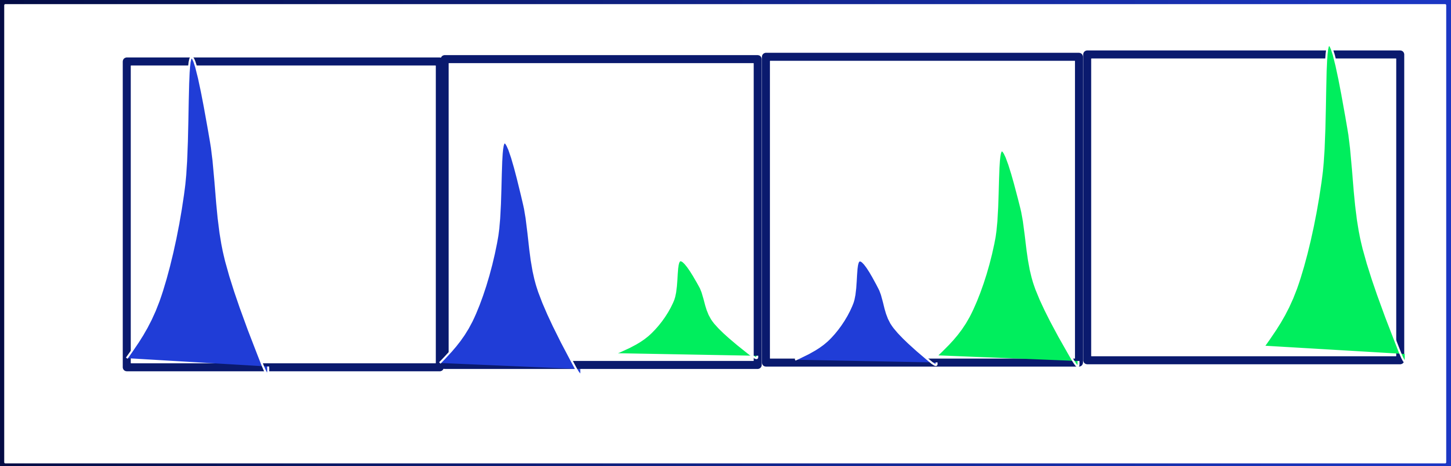
Plasmid circuit

a synthetic, bistable gene-regulatory network in E. coli



Cells switching can be induced

3hrs 4hrs 5hrs 6hrs



fluorescence

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Simple biochemical motifs (2.5)

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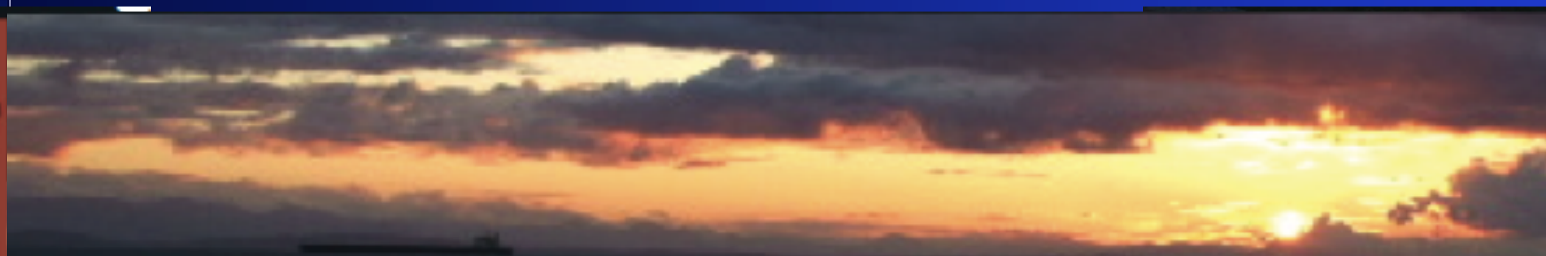

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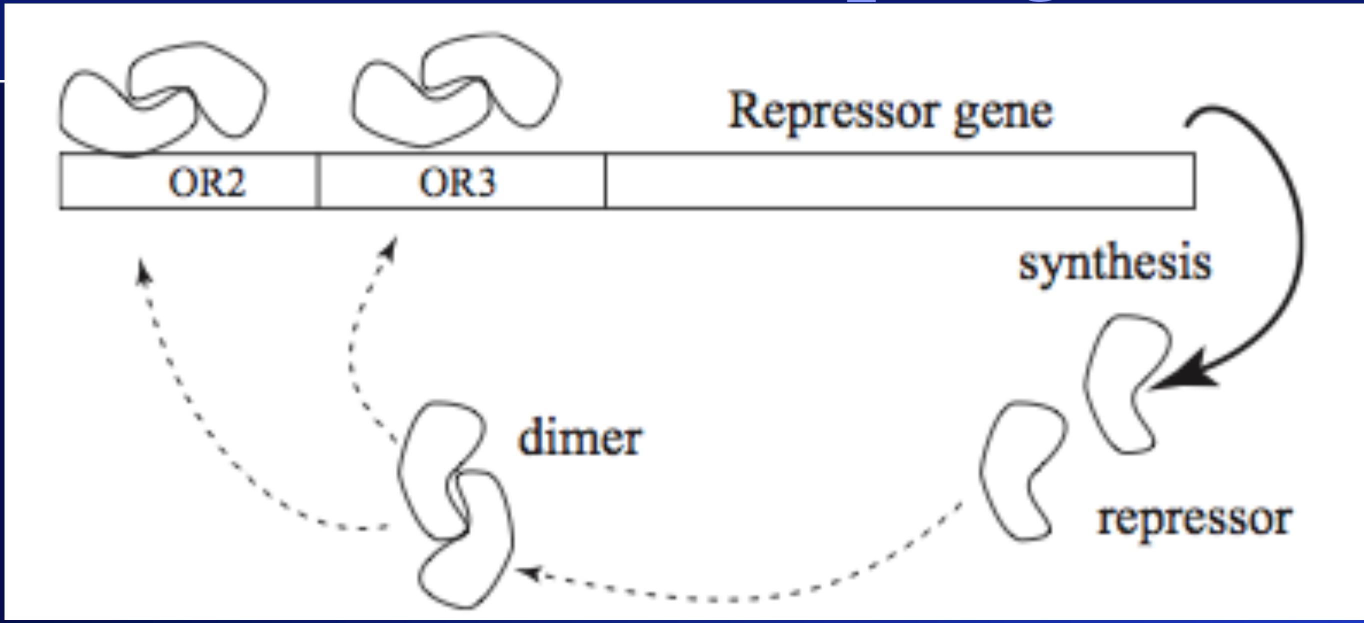
www.math.ubc.ca/~keshet/MCB2012/

Noise-based switches and amplifiers for gene expression

Jeff Hasty*†, Joel Pradines*, Milos Dolnik*‡, and J. J. Collins*

PNAS | February 29, 2000 | vol. 97 | no. 5 | 2075–2080

Dimerization and the phage lambda



- The phage λ gene encodes for protein (conc x)
- Protein dimerizes (conc of dimers y).
- Dimers bind to regulatory sites on the gene.
- Binding to OR2 activates transcription.
- Biding to OR3 inhibits transcription.

Reaction scheme

Dimerization: $2X \overset{K_1}{\rightleftarrows} X_2$

Binding to DNA (OR2): $D + X_2 \overset{K_2}{\rightleftarrows} DX_2$

Binding to DNA (OR3): $D + X_2 \overset{K_3}{\rightleftarrows} DX_2^*$

Double binding (OR2 and OR3): $DX_2 + X_2 \overset{K_4}{\rightleftarrows} DX_2X_2$

DX_2= the dimerized repressor bound to site OR2

DX_2 = the dimerized repressor bound to site OR3,*

DX_2X_2 = both OR2 and OR3 are bound by dimers

QSS

$$y = K_1 x^2,$$
$$u = K_2 d y = K_1 K_2 d x^2,$$
$$v = \sigma_1 K_2 d y = \sigma_1 K_1 K_2 d x^2,$$
$$z = \sigma_2 K_2 u y = \sigma_2 (K_1 K_2)^2 d x^4.$$

The "fast variables" assumed to equilibrate rapidly with the variable x.

Slower timescale

Protein synthesis: $DX_2 + P \xrightarrow{k_1} DX_2 + P + nX$

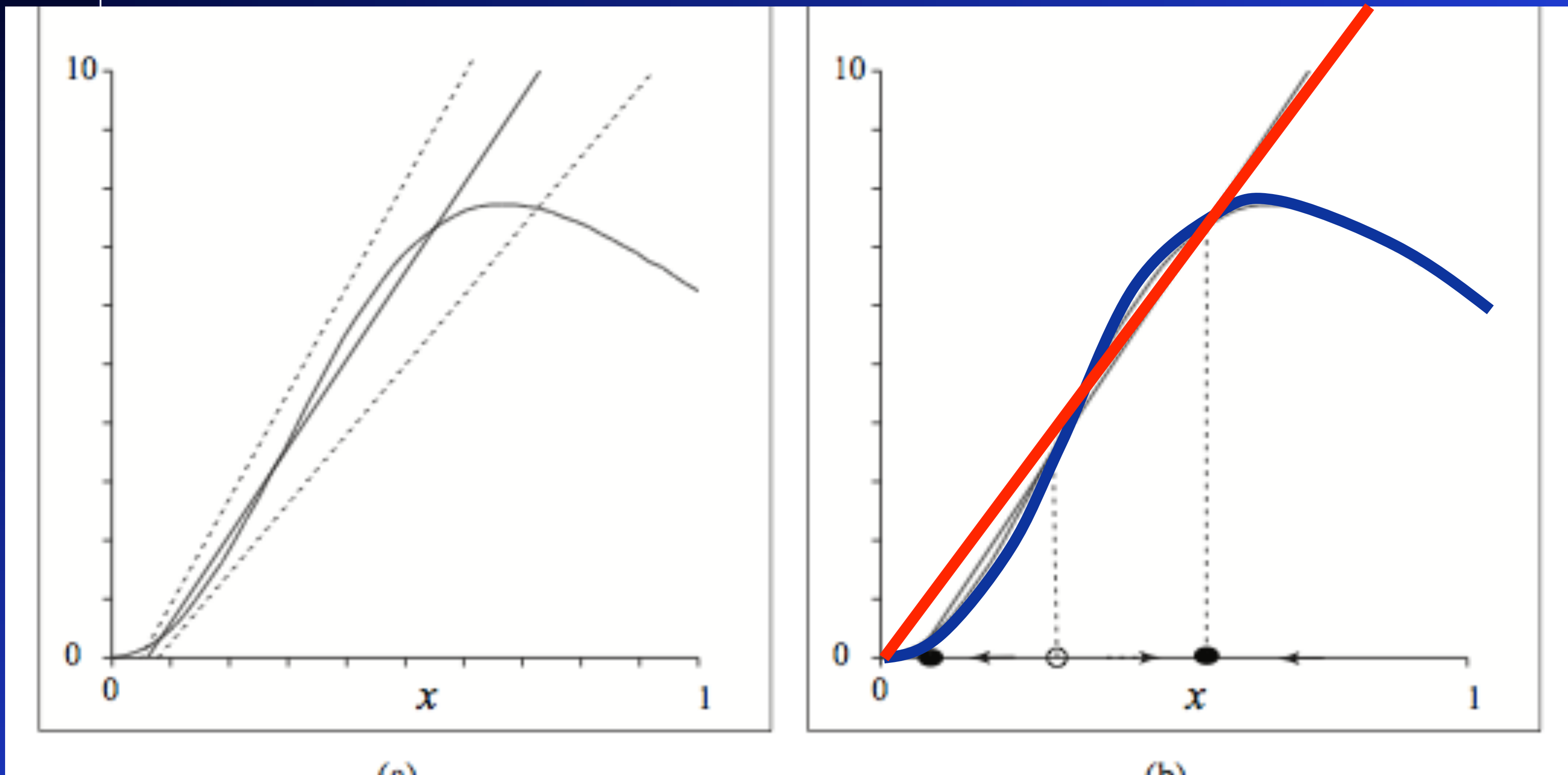
Protein degradation: $X \xrightarrow{k_d} A$

QSS and scaling the equations: system collapses to one variable, amt of synthesized protein, *x*:

$$\frac{dx}{dt} = \frac{\alpha x^2}{1 + (1+\sigma_1)x^2 + \sigma_2 x^4} - \gamma x + 1.$$

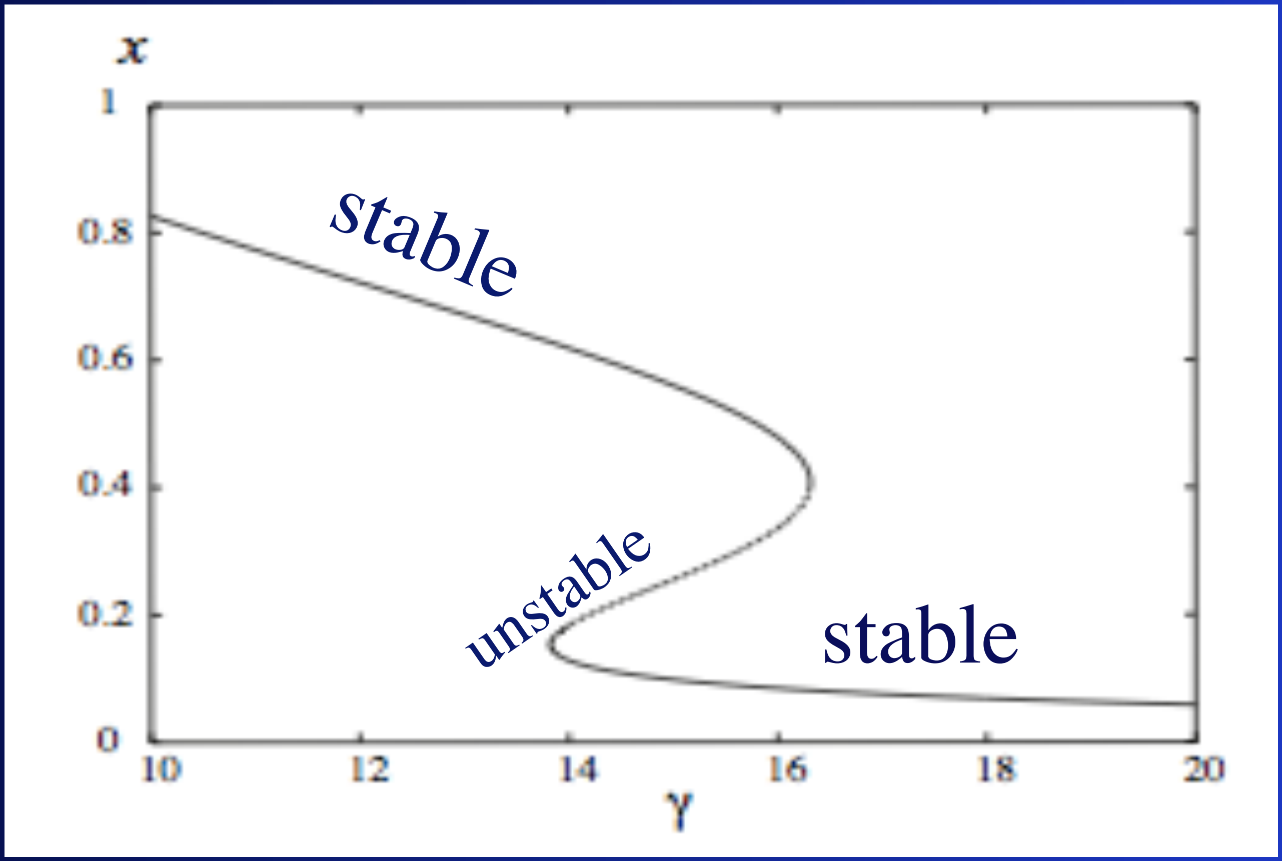
bistability

$$\frac{dx}{dt} = \frac{\alpha x^2}{1+(1+\sigma_1)x^2+\sigma_2 x^4} - \gamma x + 1.$$



Bifurcation:

$$\frac{dx}{dt} = \frac{\alpha x^2}{1+(1+\sigma_1)x^2+\sigma_2 x^4} - \gamma x + 1.$$



Comments

Combination of scaling, time scale considerations, and various simplifications can often reduce larger networks to effective dynamics of simpler systems.

Other examples will be provided.

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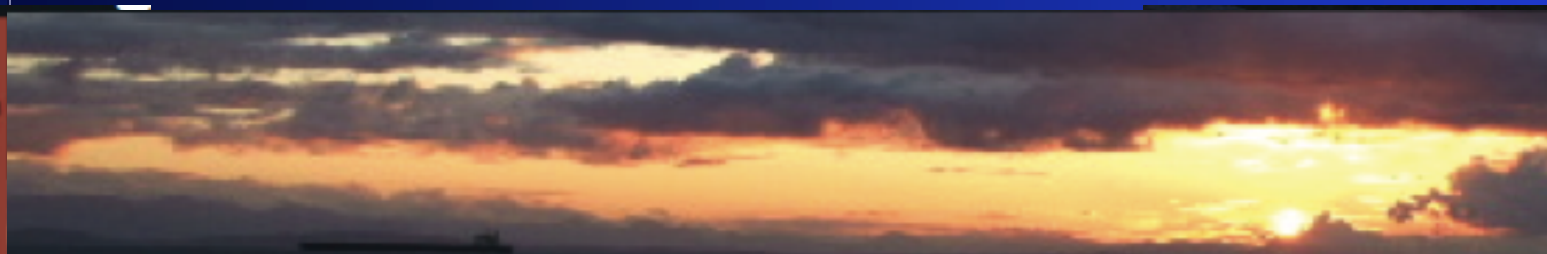
Simple biochemical motifs (3)



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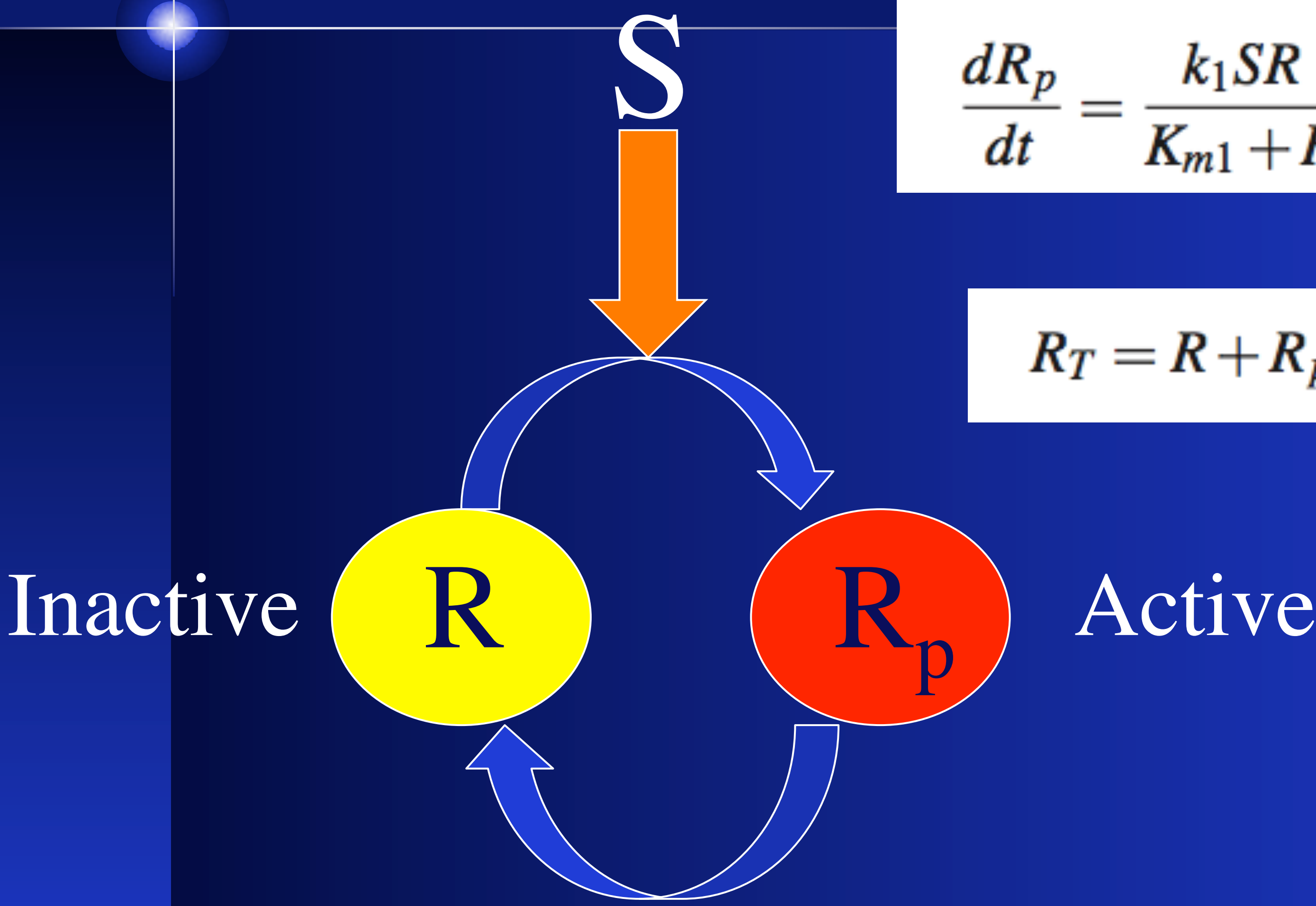
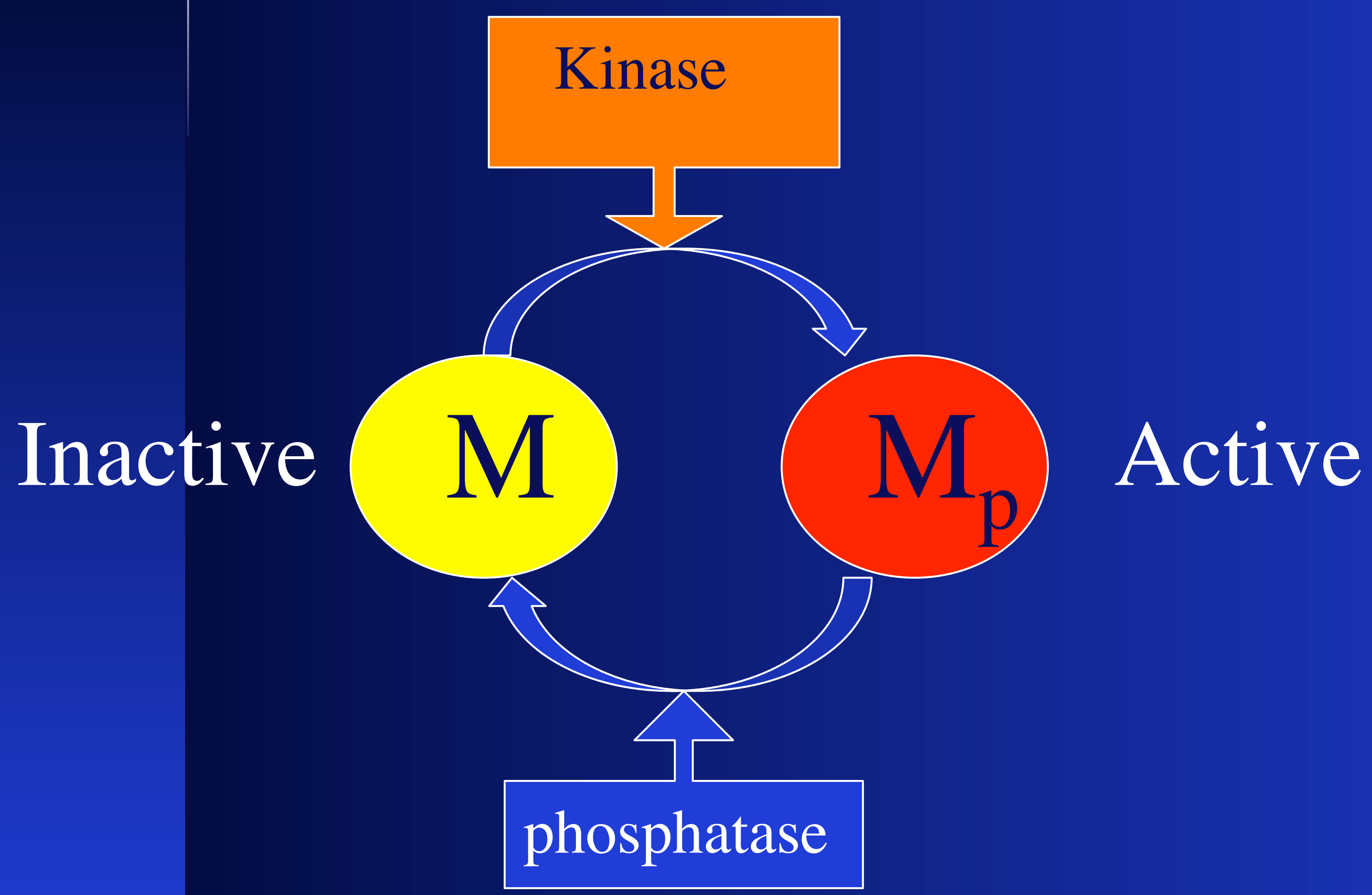
Activation-inactivation

$$\frac{dR_p}{dt} = \frac{k_1 S R}{K_{m1} + R} - \frac{k_2 R_p}{K_{m2} + R_p}.$$

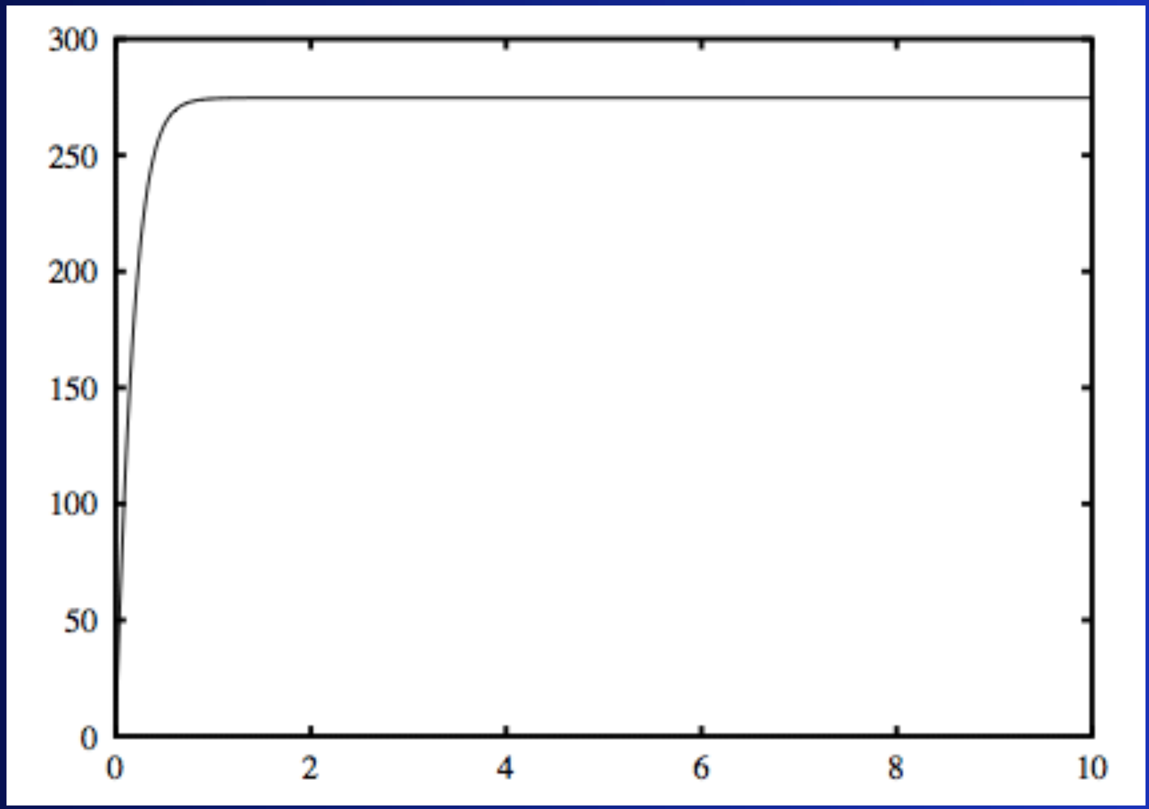
$$R_T = R + R_p = \text{ constant.}$$



GTPase cycle



Without feedback: Fast equilibration



M_p

Time (seconds)

System has a single biologically relevant steady state

Eliminate R, rescale

$$\frac{dR_p}{dt} = \frac{k_1 S R}{K_{m1} + R} - \frac{k_2 R_p}{K_{m2} + R_p}.$$

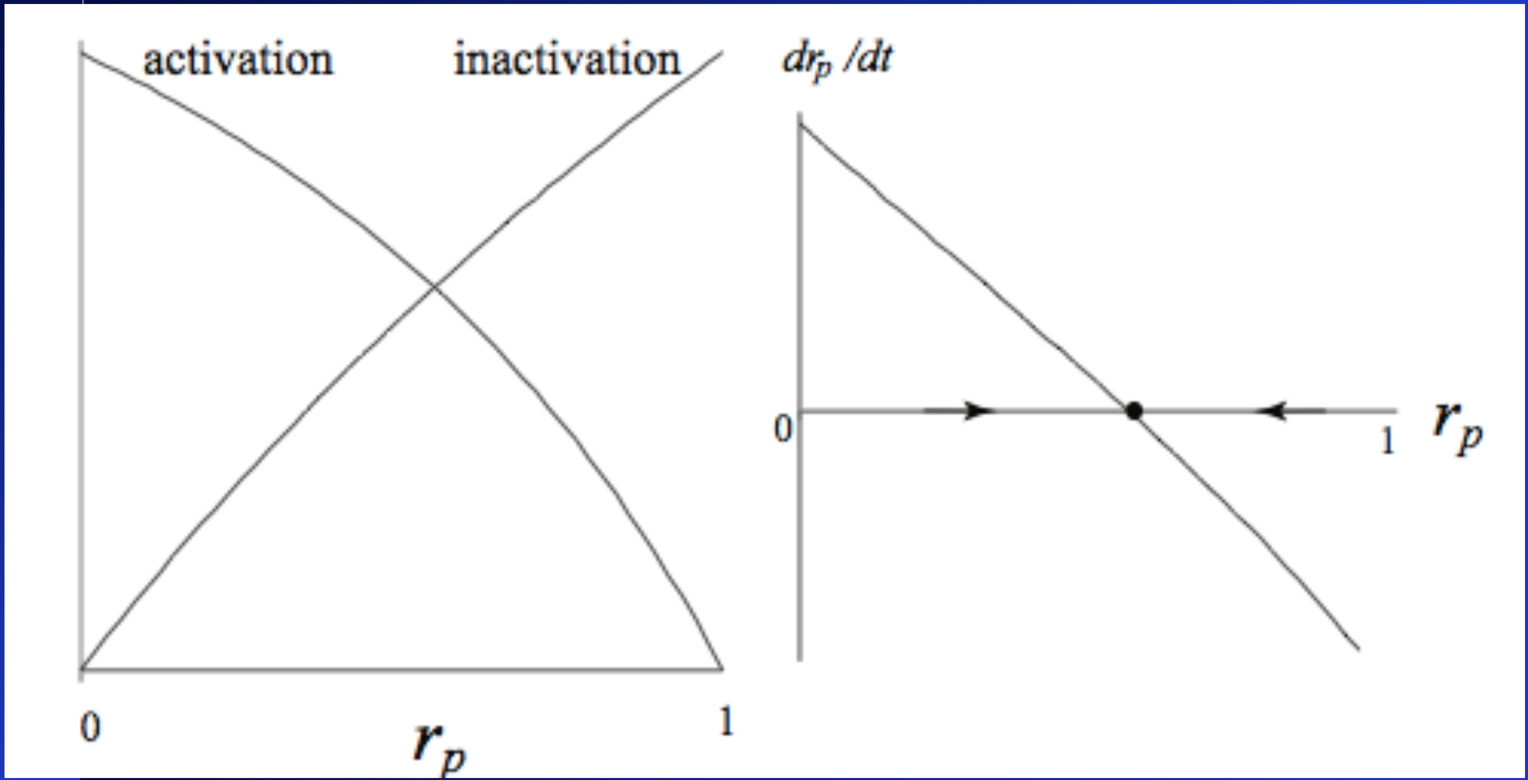
Use

$$R_T = R + R_p = \text{ constant.}$$

$$r_p = R_p / R_T$$

Rescaled

$$\frac{dr_p}{dt} = \frac{k_1 S(1-r_p)}{K'_{m1} + (1-r_p)} - \frac{k_2 r_p}{K'_{m2} + r_p}.$$



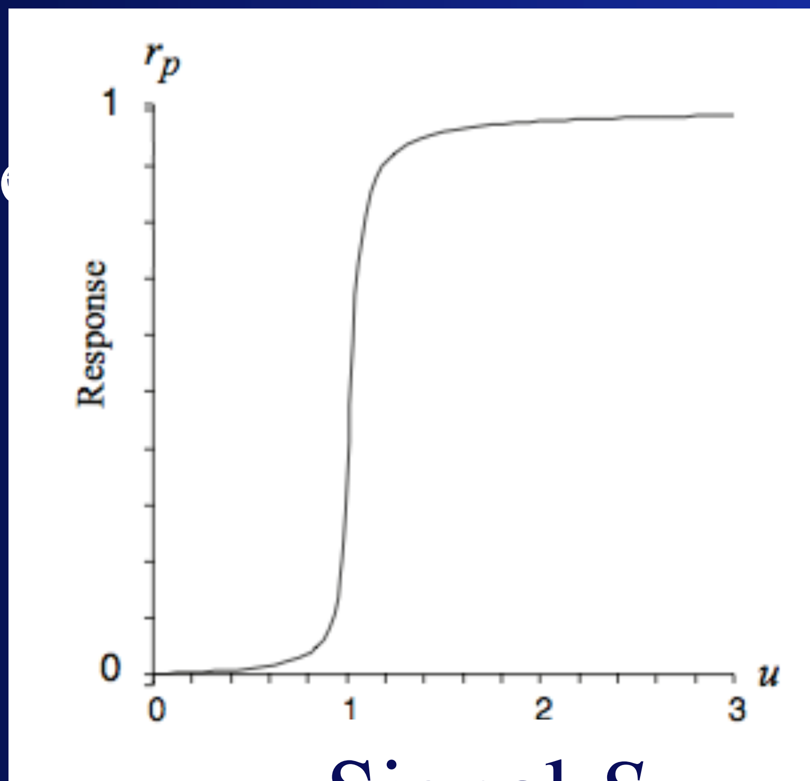
Steady states

$$\frac{dr_p}{dt} = \frac{k_1 S(1-r_p)}{K'_{m1} + (1-r_p)} - \frac{k_2 r_p}{K'_{m2} + r_p} = 0$$

The steady states can be shown to be solutions to a quadratic equation. Only one is positive and is called the "Goldbeter-Koshland function" of the stimulus.

"Zero order ultrasensitivity"

Steady state response



Signal *S*

response is minimal for low signal level, until some threshold. Then there is steep rise to full response. – *Goldbeter and Koshland*