Mathematical Cell Biology Graduate Summer Course

University of British Columbia, May 1-31, 2012

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Simple biochemical motifs (2)

mprime

PIMS

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

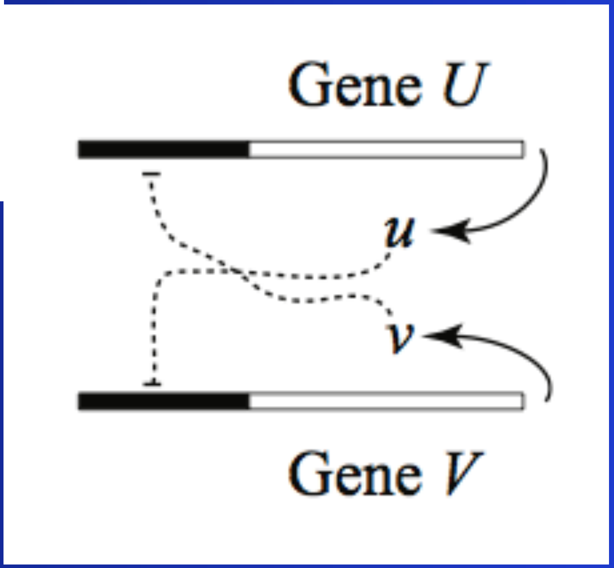
Genetic toggle switch

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

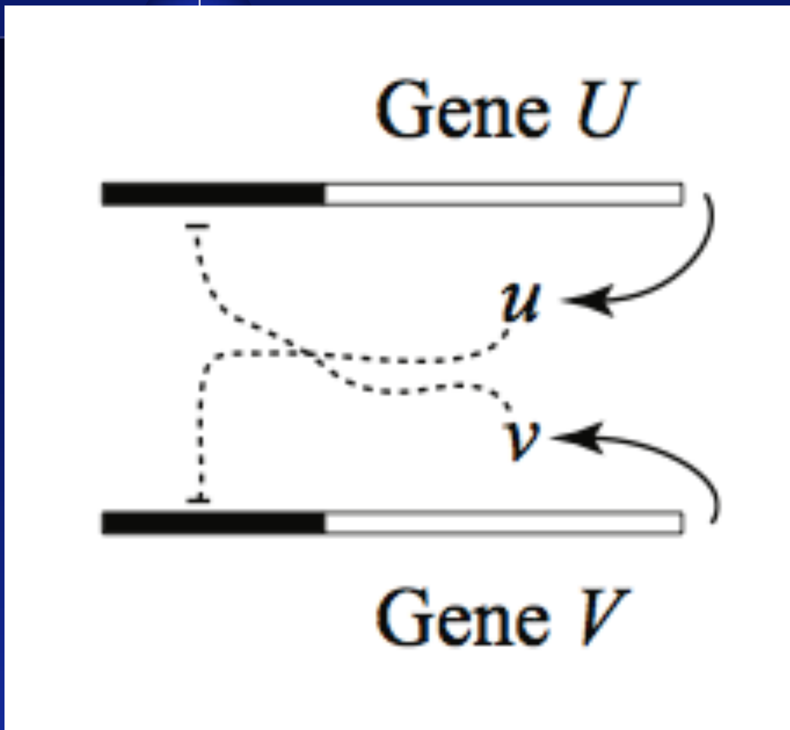
An actual “engineered genetic circuit” based on the concepts and models of biochemical switches.



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.”

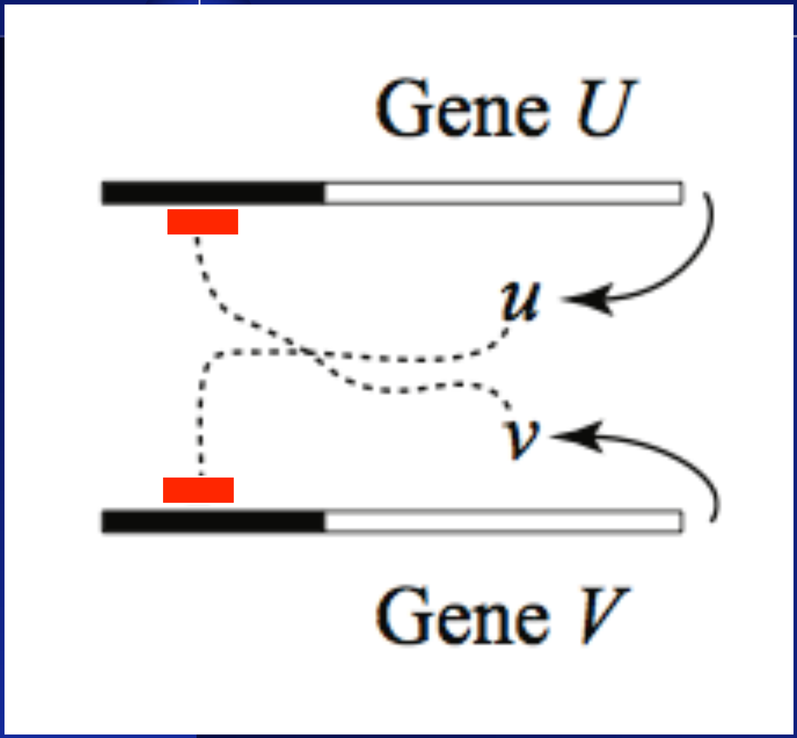
Production-decay of two proteins



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

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

Negative feedback



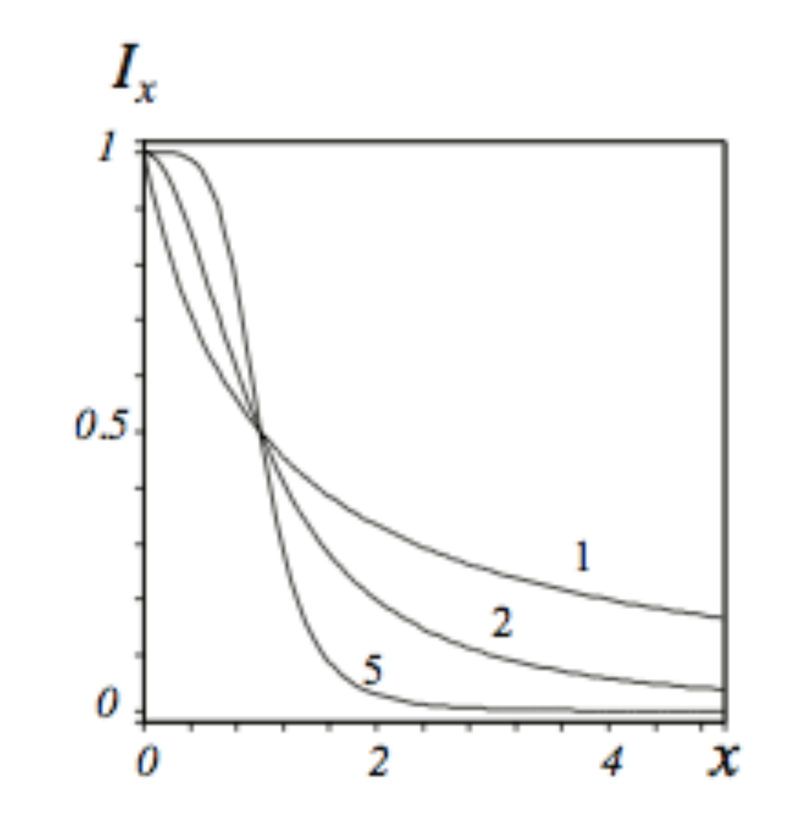
$$\frac{du}{dt} = I_u - d_u u,$$
$$\frac{dv}{dt} = I_v - d_v v.$$

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

Negative feedback function

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

Higher n means sharper response with increasing x



Mutual inhibition

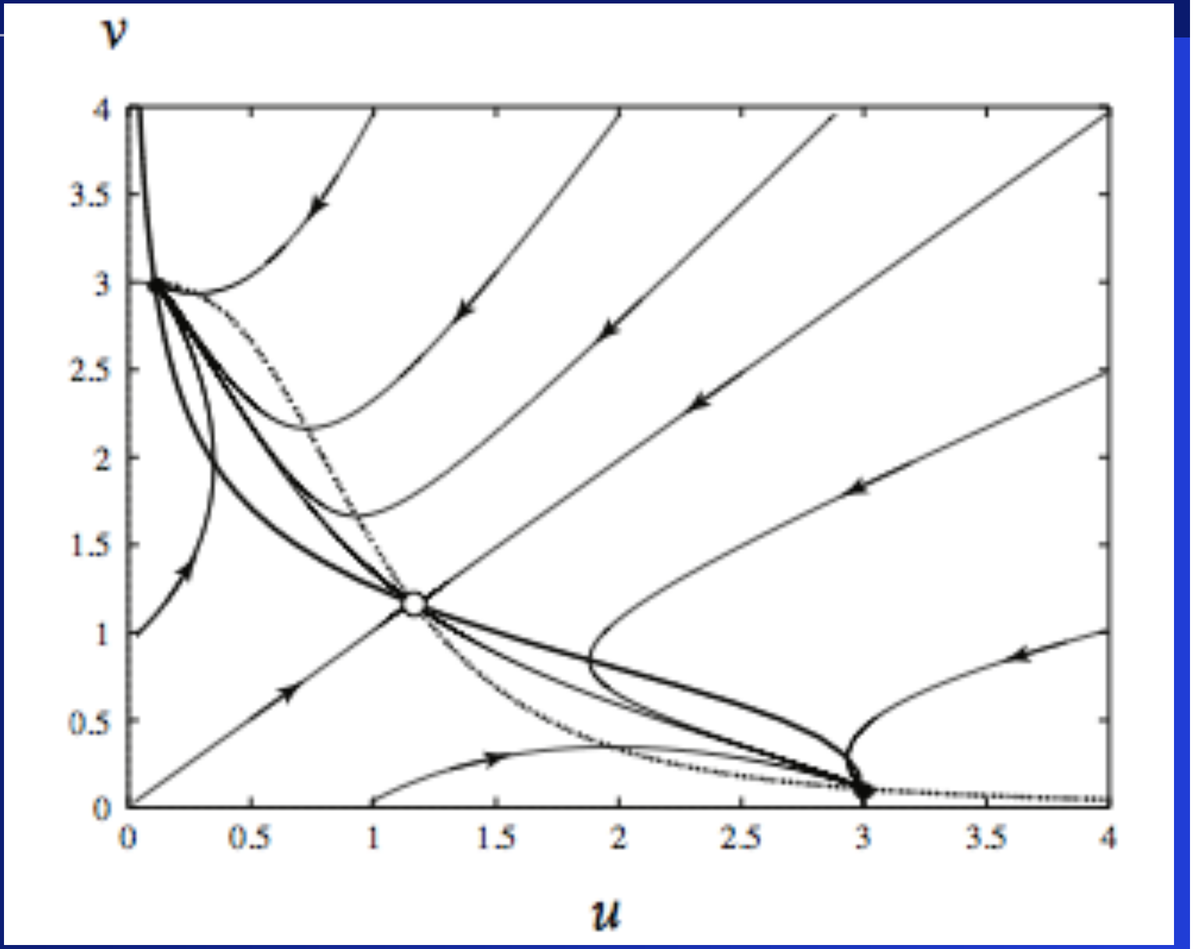
$$\frac{du}{dt} = \frac{\alpha_1}{1+v^n} - u,$$
$$\frac{dv}{dt} = \frac{\alpha_2}{1+u^m} - v.$$

Each gene product inhibits the other gene.

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

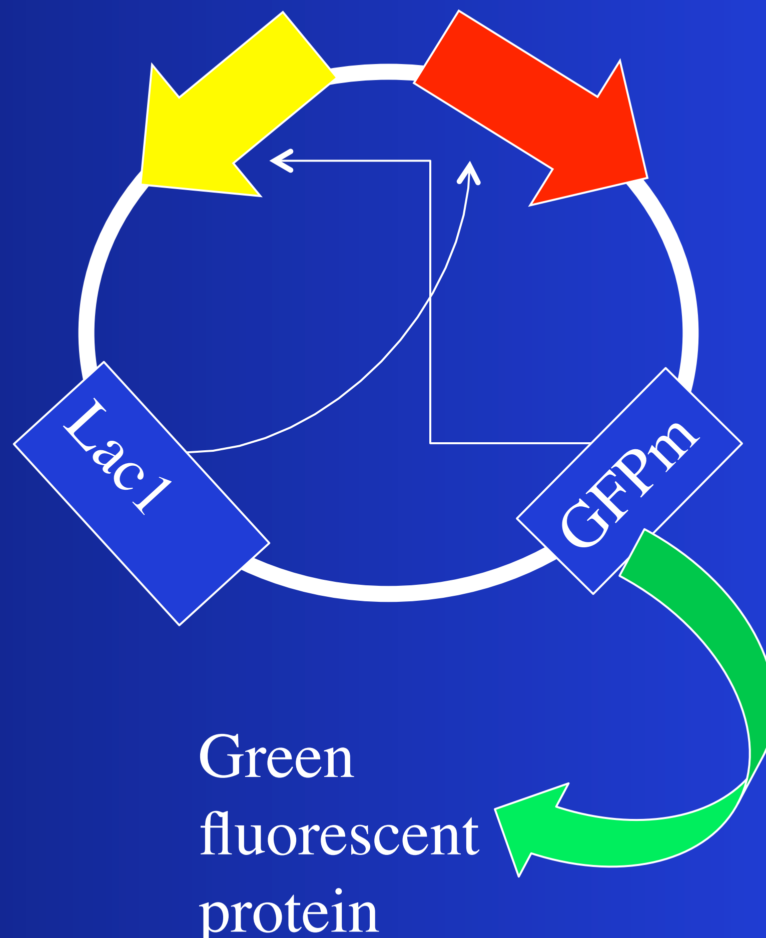
Switch-like behaviour

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

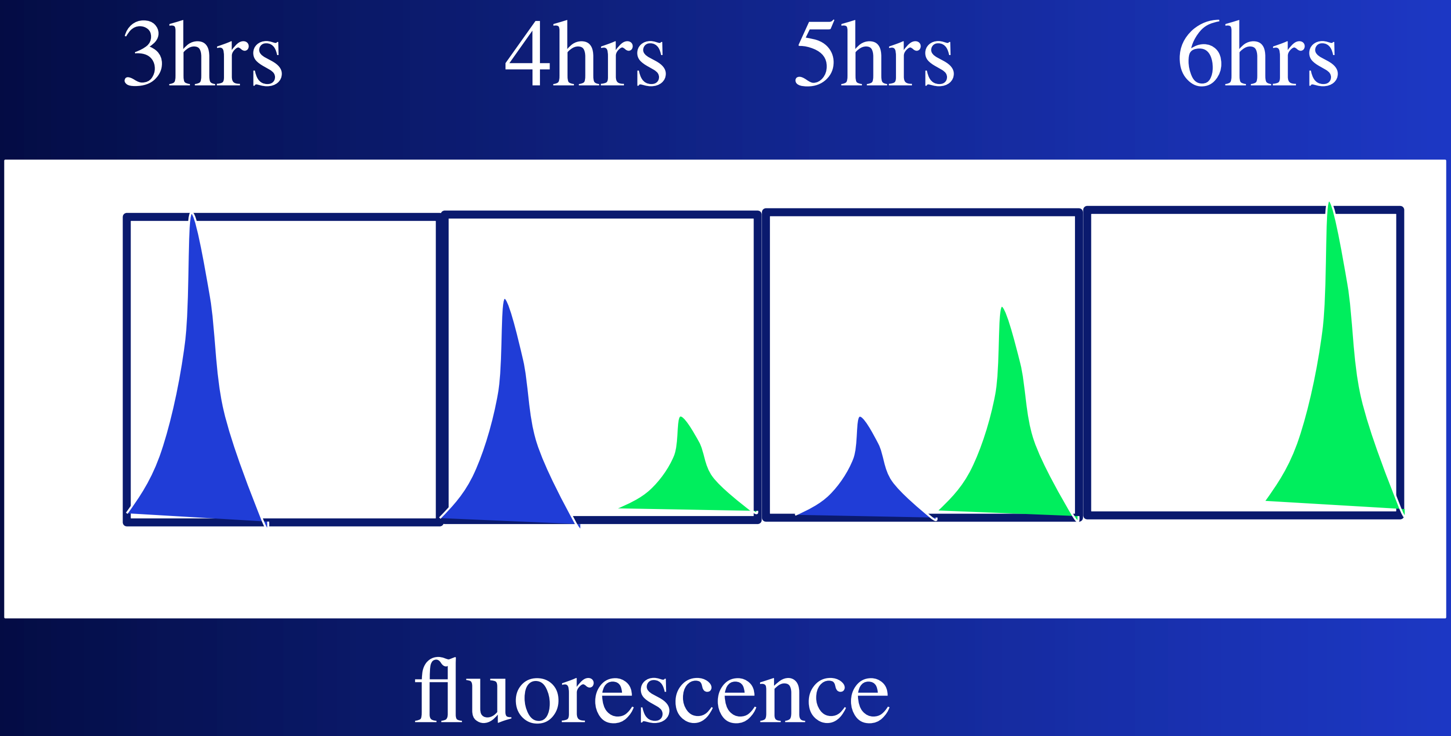


Plasmid circuit

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



Cells switching can be induced

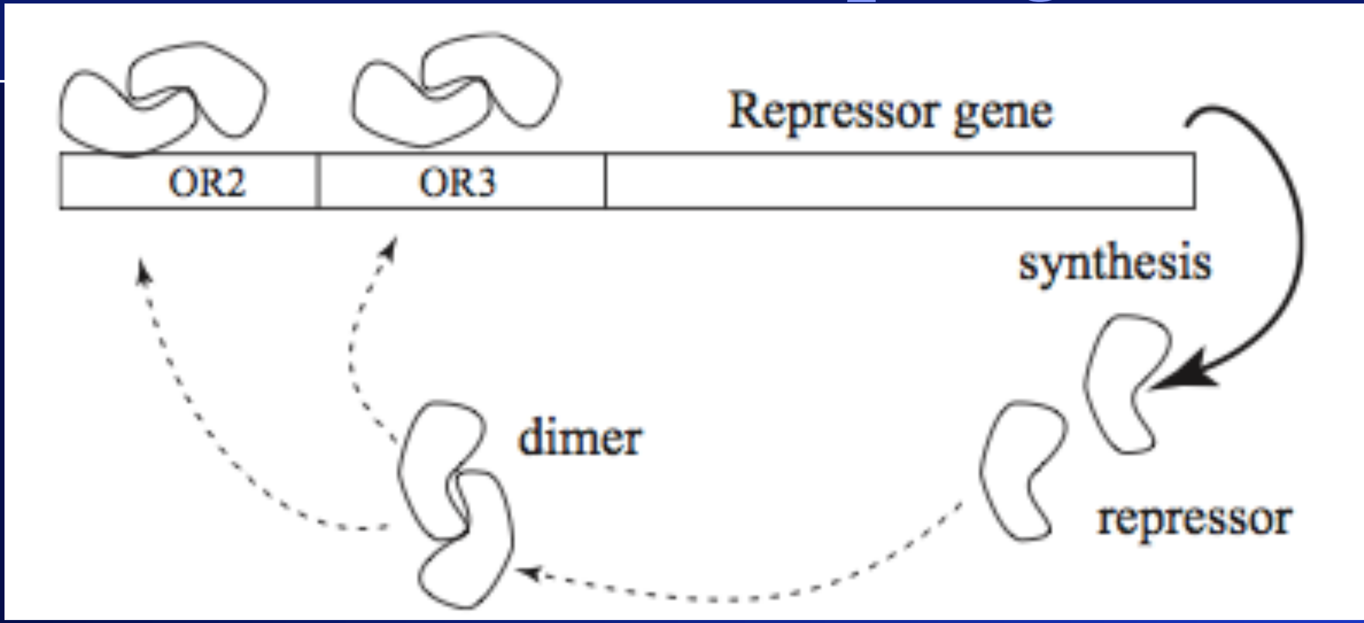


Noise-based switches and amplifiers for gene expression

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: $2X \overset{K_1}{\longleftrightarrow} X_2$

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

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

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

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

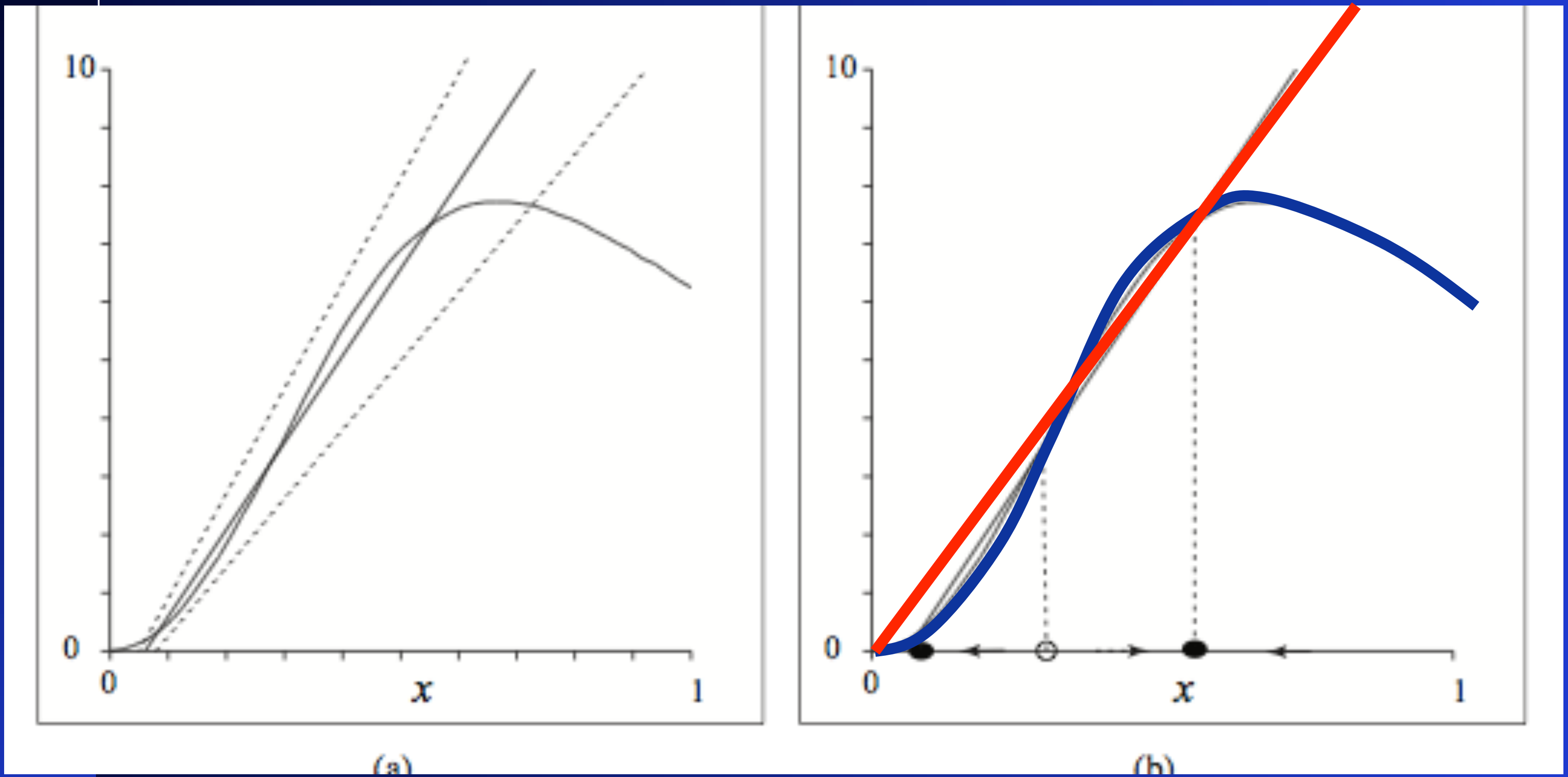
Protein degradation: $X \xrightarrow{k_d} A$

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

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

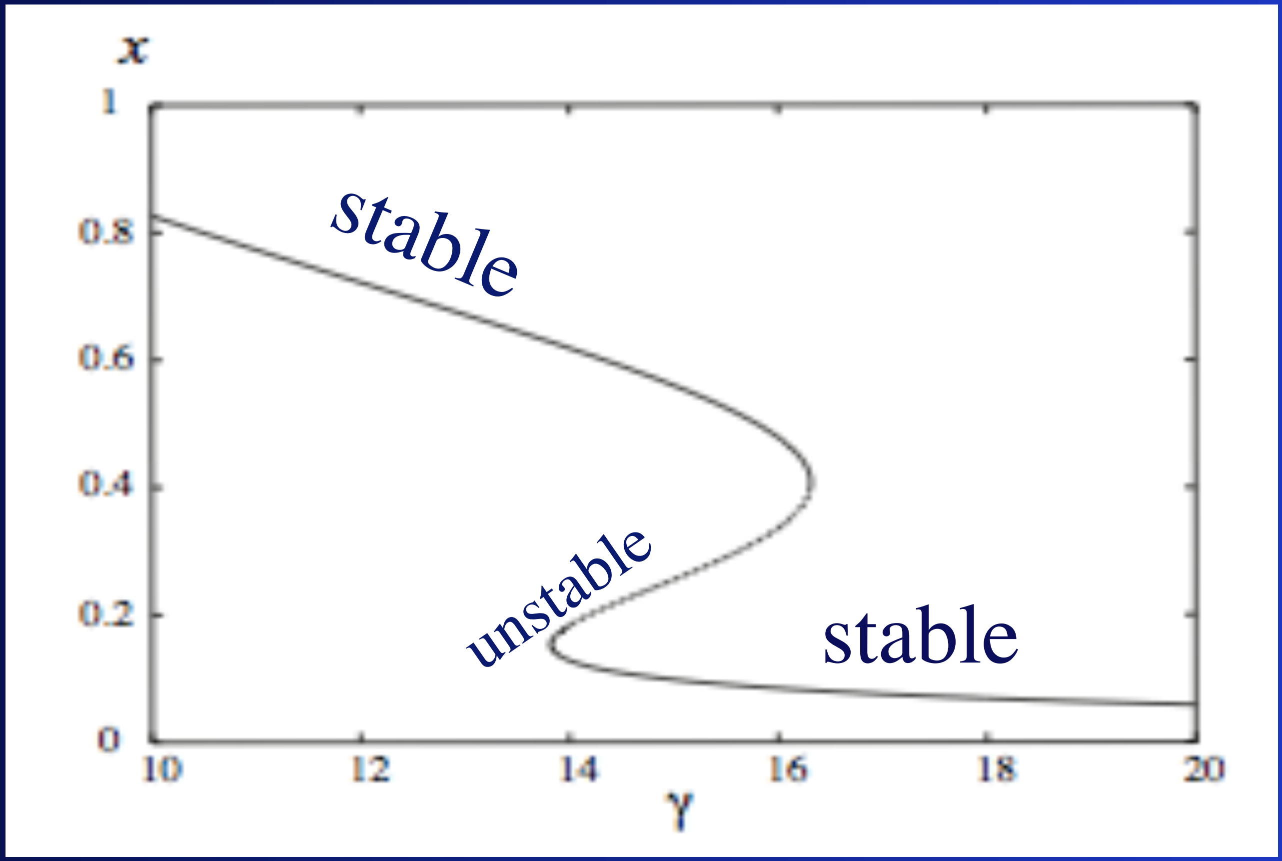
bistability

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



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.