Bistability in biochemical signaling models

Part 6
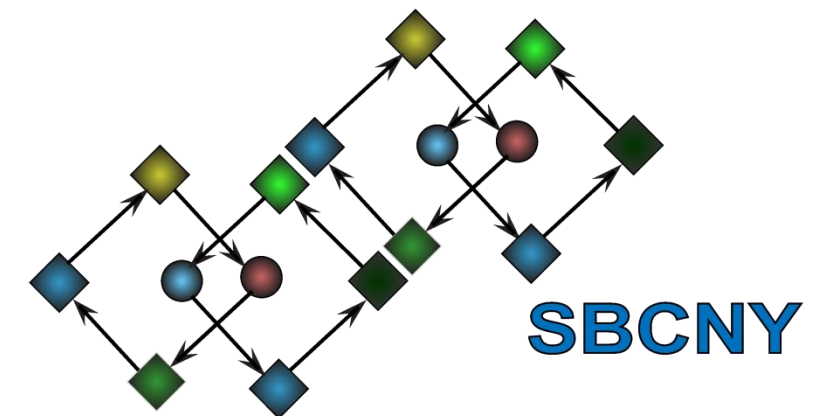
Review: what have we learned about bistability?

Bistable systems produce digital, all-or none, rather than graded responses.

Bistability is biologically useful when persistence is required: **apoptosis, cell division, differentiation**, etc.

Bistability is produced by complex regulation, e.g. mutual activation or mutual inhibition.

The presence or absence of bistability can be assessed mathematically and graphically **(rate balance plots, nullclines in the phase plane)**.

Outline: Part 6

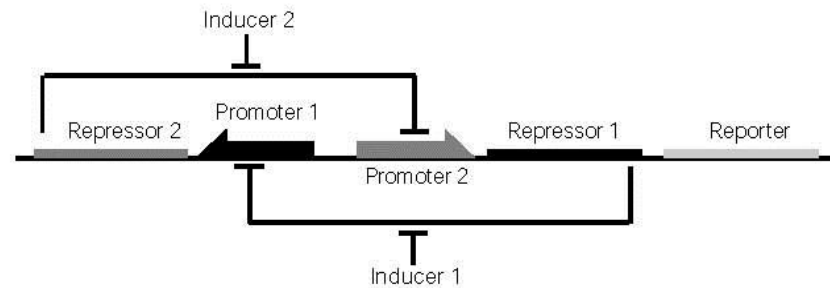## Examples of bistability

An artificial genetic "toggle switch"

MAP-kinase pathway in oocyte maturation

MAP-kinase pathway in mammalian cells
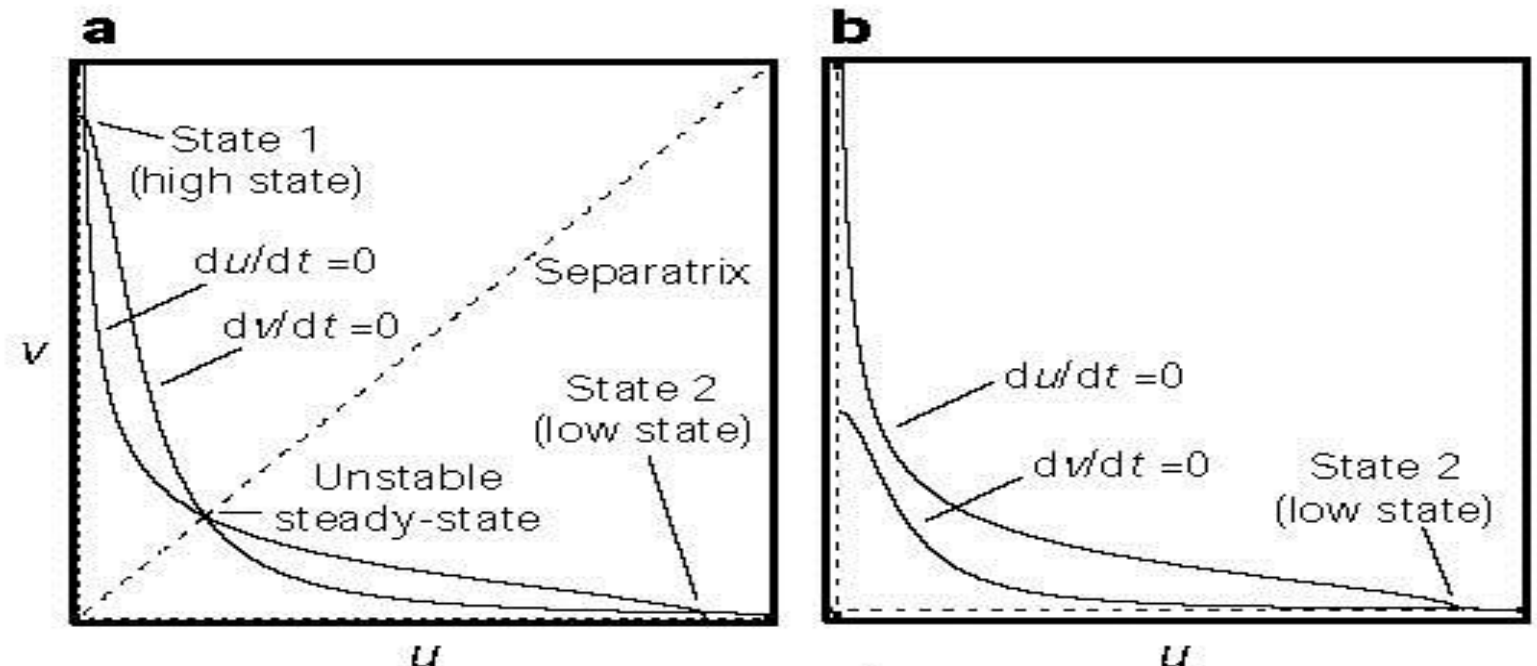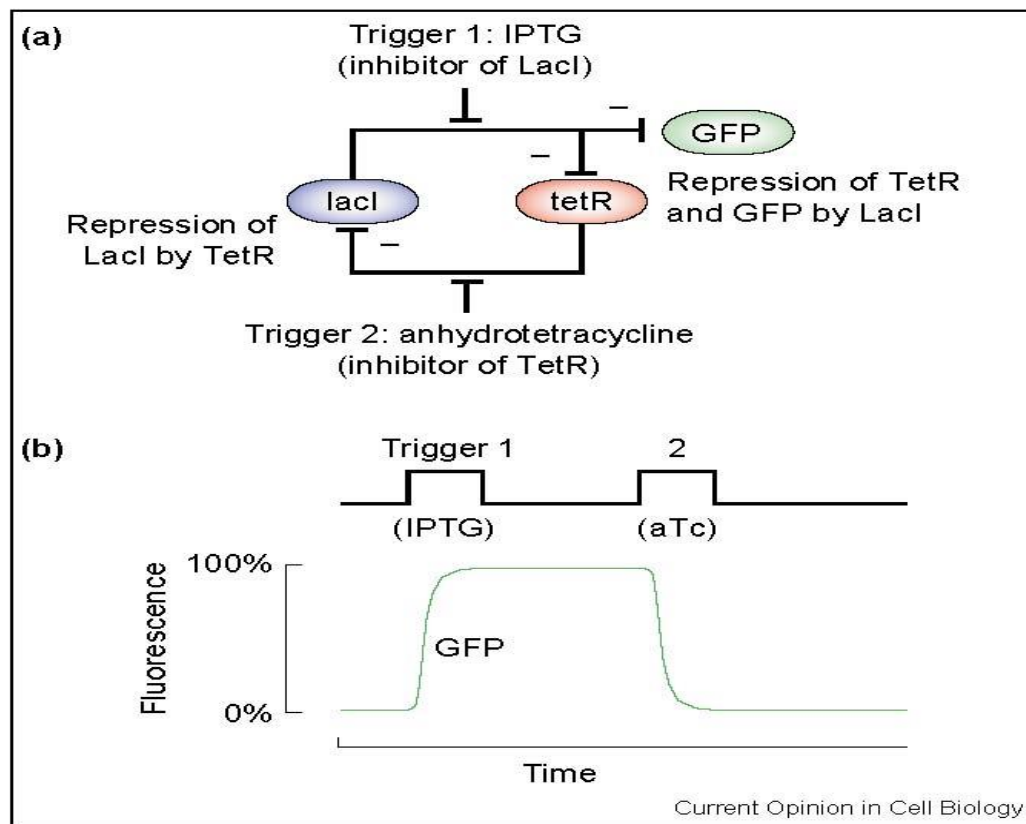
Lac operon

Examples of bistable systems
An artificial "toggle switch"

Gardner, Cantor, & Collins (2000) *Nature* **339-342**

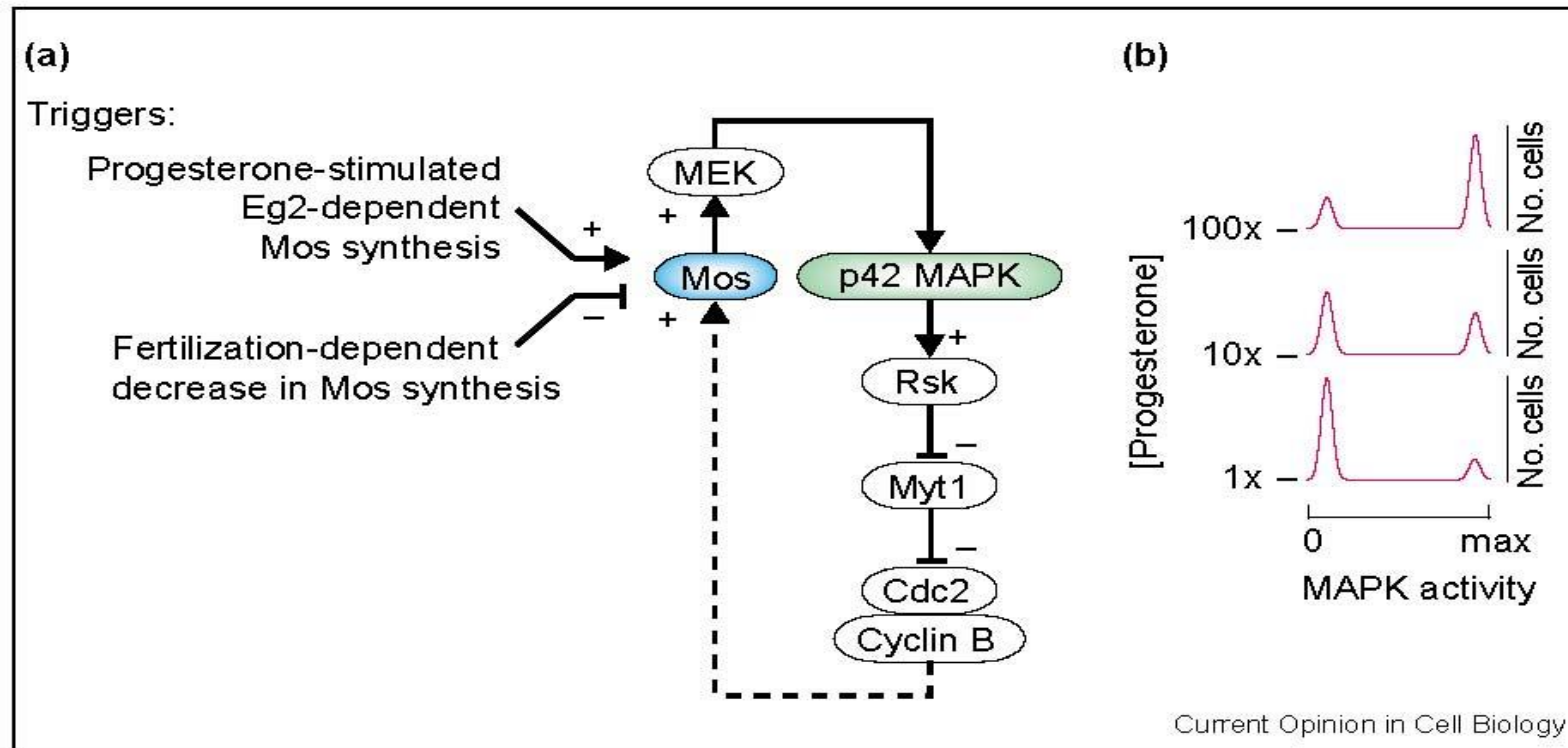$$\frac{du}{dt} = \frac{\alpha_1}{1+v^\beta} - u$$

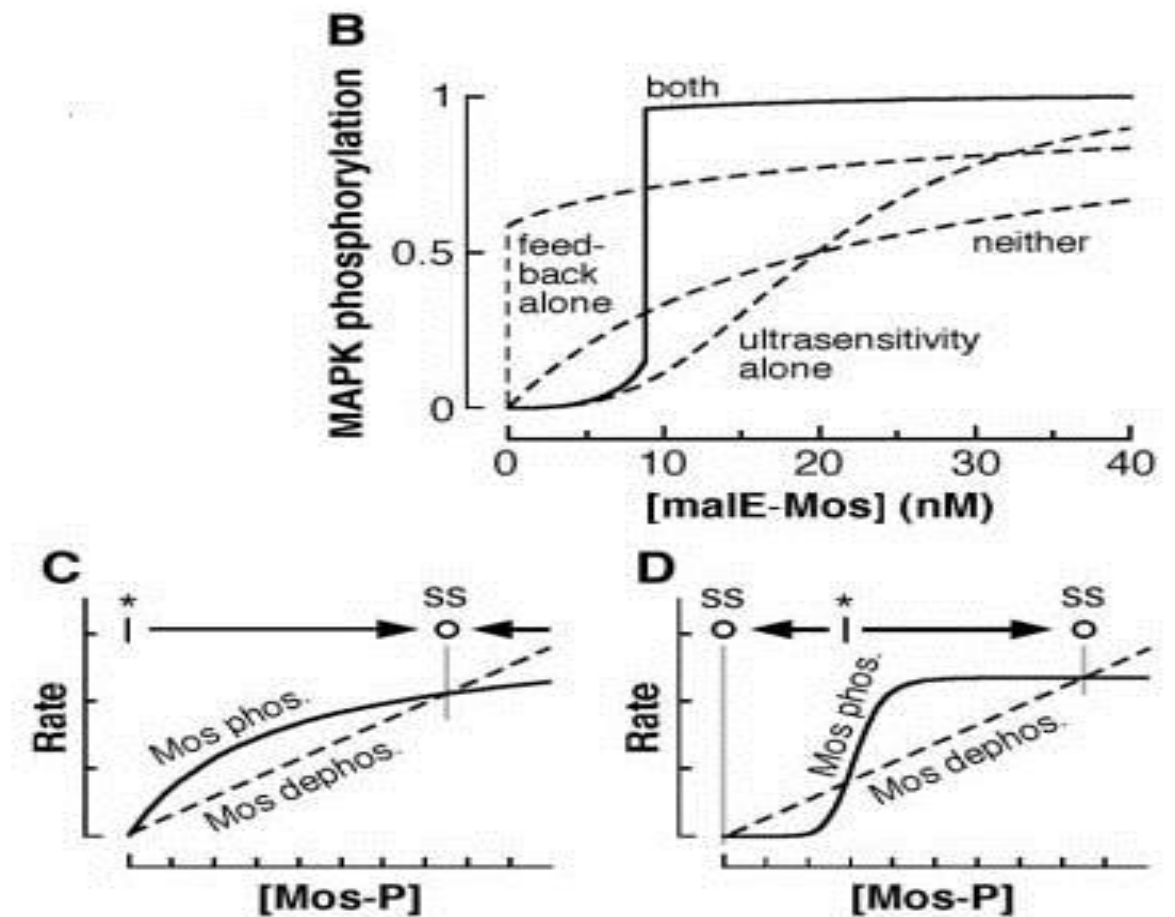$$\frac{dv}{dt} = \frac{\alpha_2}{1+u^\gamma} - v$$

Ferrell (2002) *Curr. Op. Cell Biol.* **14:140–148.**

Examples of bistable systems
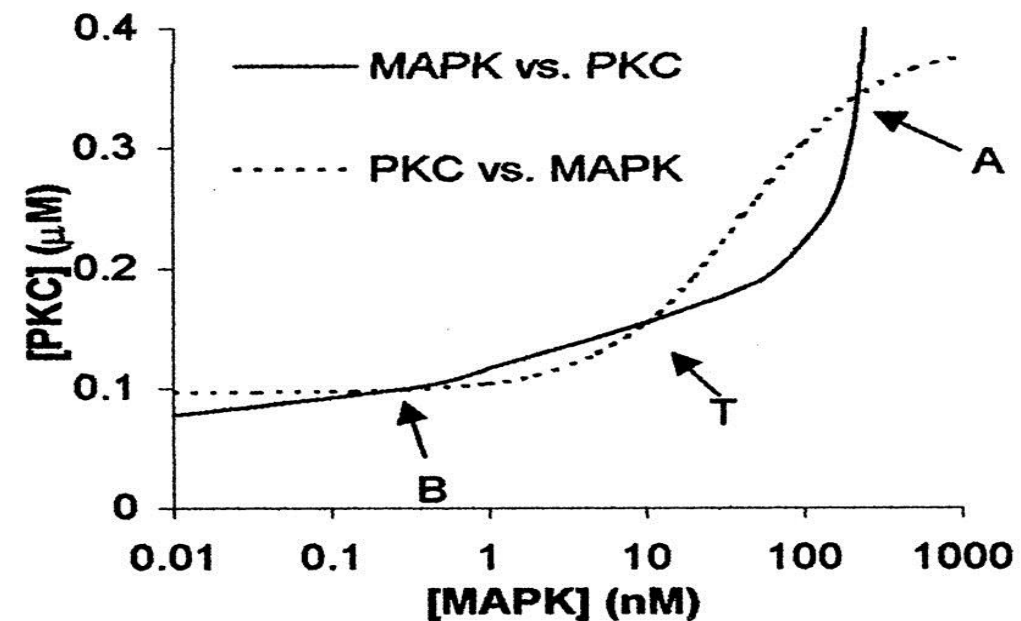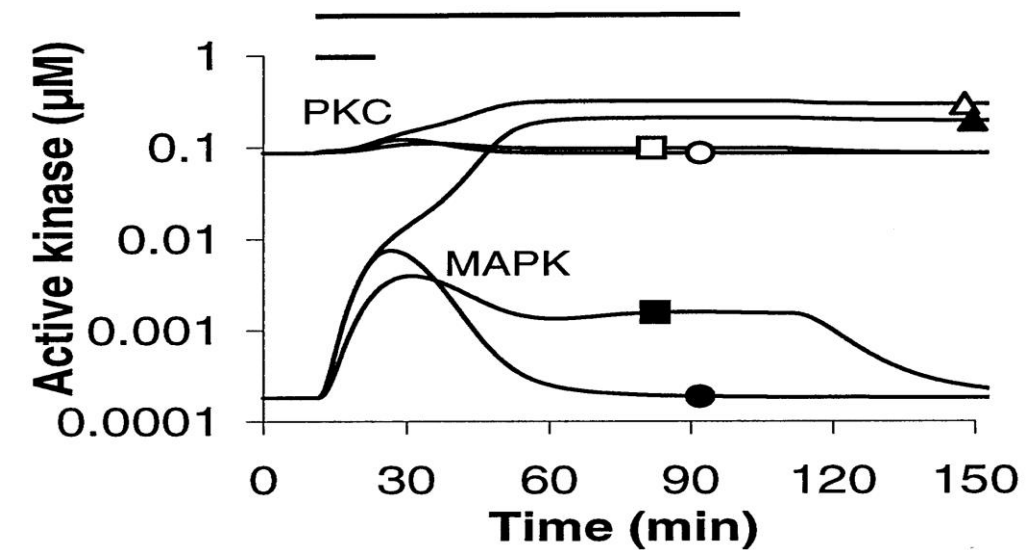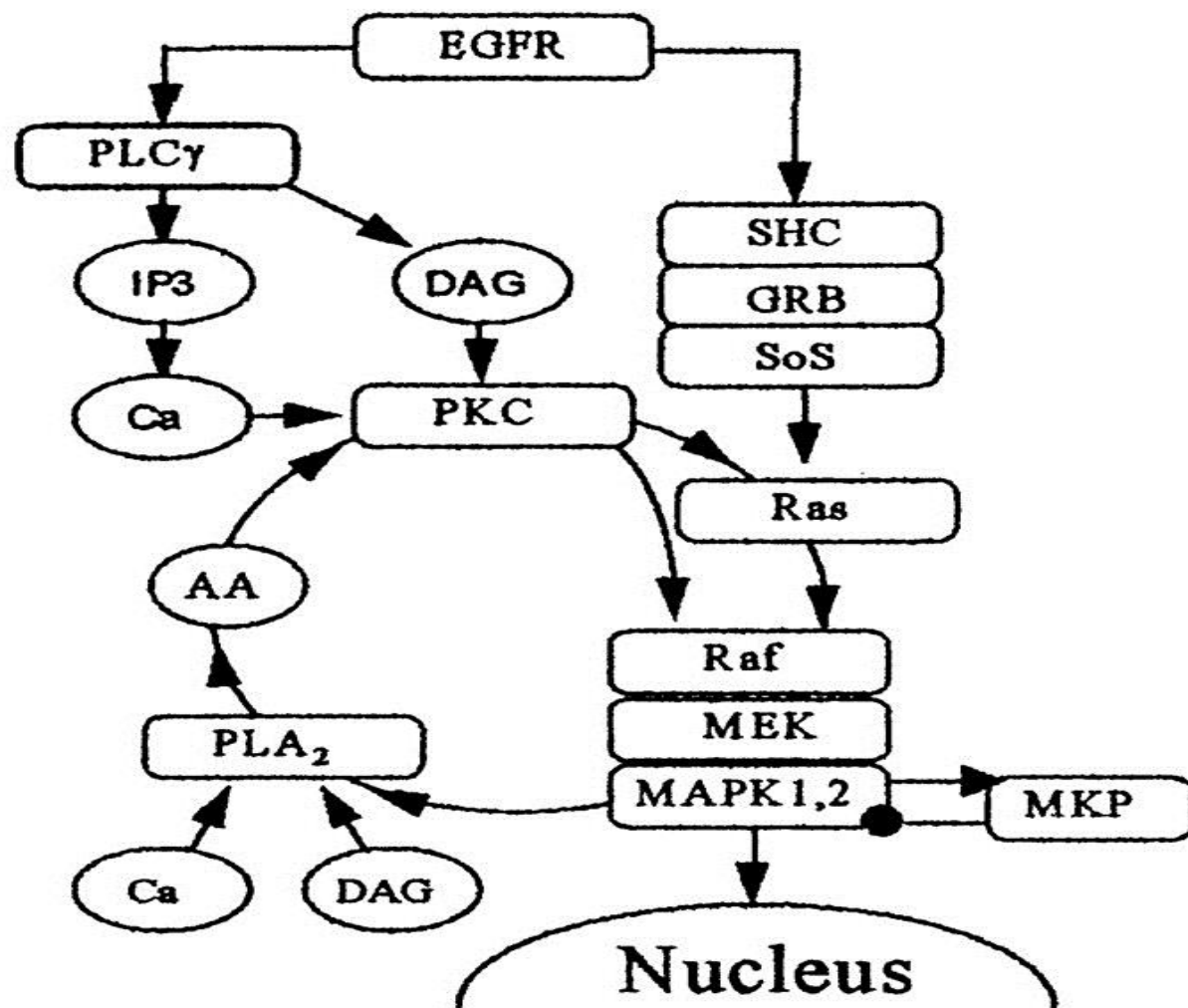## MAPK cascade in oocyte maturation

Ferrell (2002) *Curr. Op. Cell Biol.* 14:140–148.

Ferrell & Machleder (1998) *Science* 280:895-898
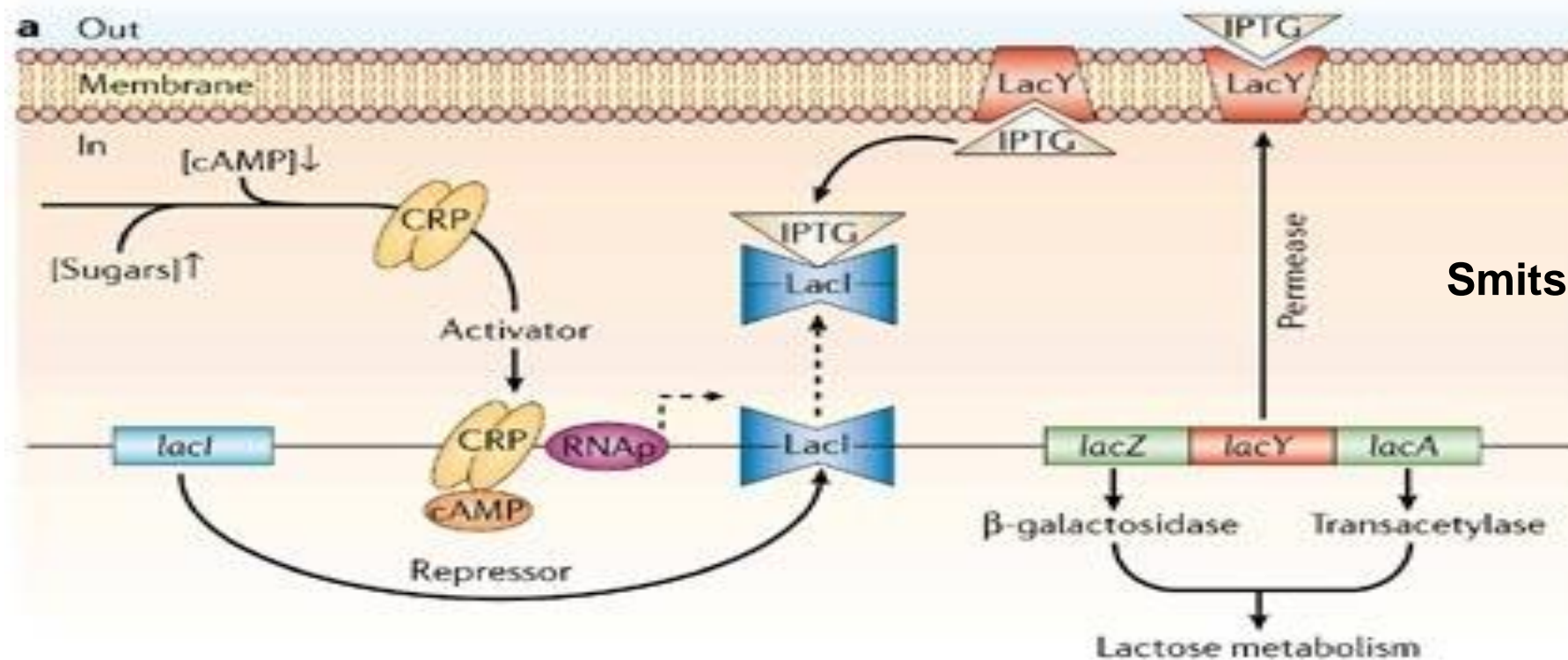
Examples of bistable systems
MAPK cascade in mammalian cells

Bhalla & Iyengar (1999) *Science* 283:381-387

Examples of bistable systems

The *lac* operon in *E. coli*

Smits et al. (2006) *Nat. Rev. Micro.* 4:259-271

With low nutrient levels, LacI will repress transcription of the the LacA, LacY, and LacZ genes.

Lactose, allolactose, or IPTG will bind to LacI, relieve repression.

LacY encodes a "permease", which allows lactose into the cell.

Examples of bistable systems

A minimal model of the *lac* operon

$$\frac{dl}{dt} = \beta l_{ext} LacY - \gamma l$$

$$\frac{dLacY}{dt} = \delta + p \frac{l^4}{l^4 + l_0^4} - \sigma LacY$$

l = intracellular lactose

$LacY$ = expression of LacY/permease
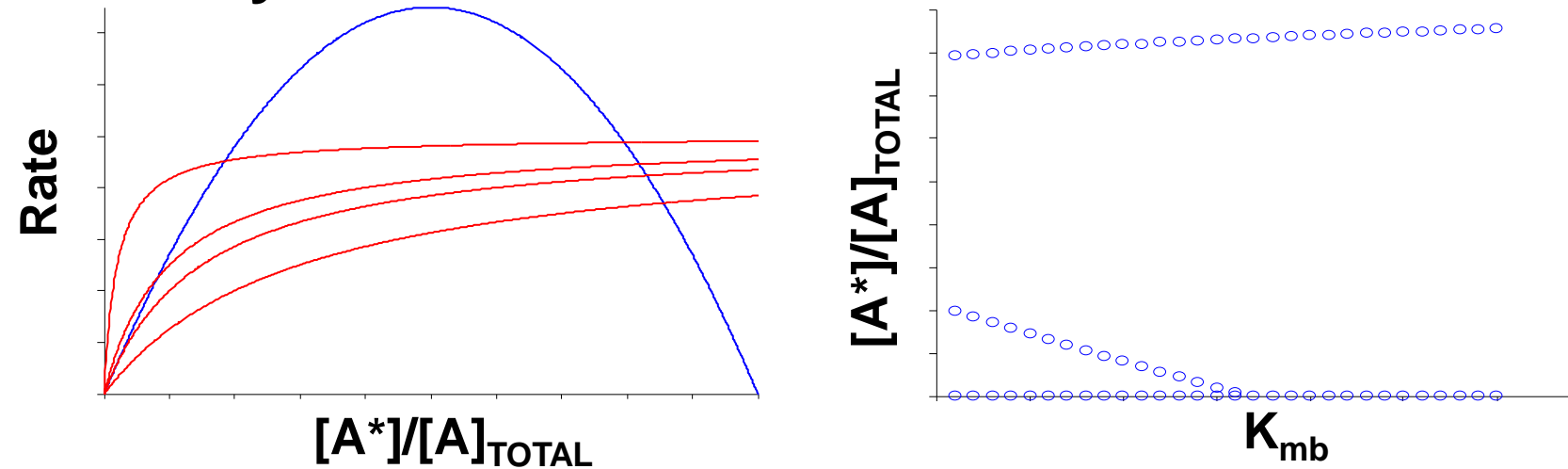
$\beta, \gamma, \delta, \sigma, p, l_0$ = constants

l_{ext} = external lactose

(Note: in most models, dLacY/dt depends on [lactose]^2. We have assumed a dependence on [lactose]^4 to improve the nullcline plots.)
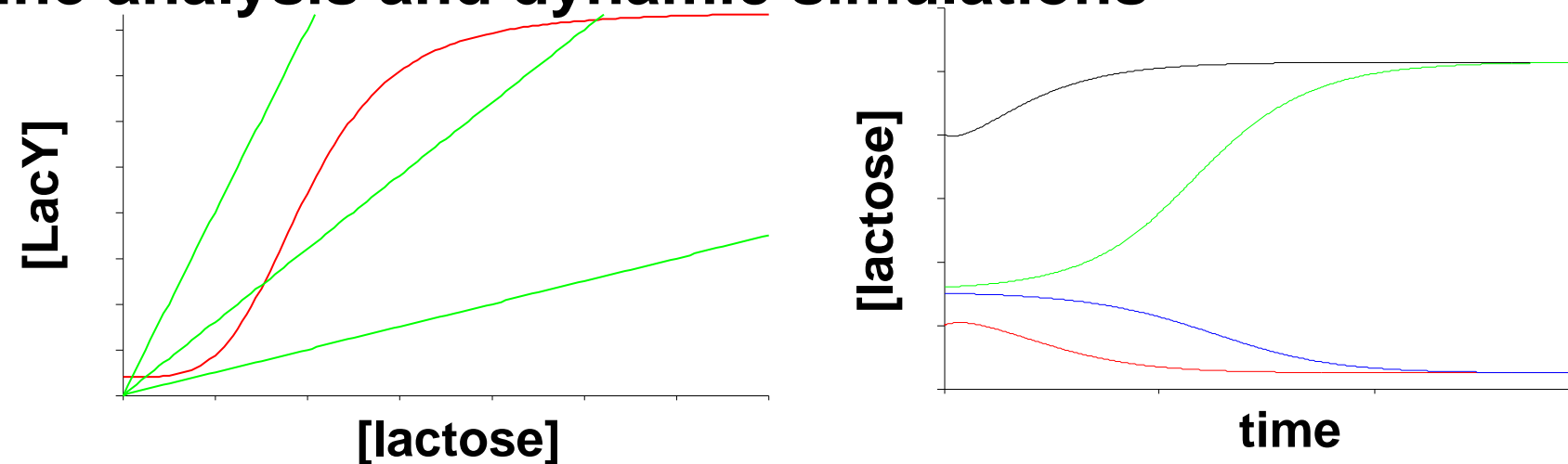
Homework assignment

1) Rate balance plots

Linear autocatalytic feedback & saturation of back reaction

2) Model of *lac* operon

Nullcline analysis and dynamic simulations

Summary

Bistability is observed in biological systems when mutual activation or mutual inhibition is present

MAP-kinase signaling

The *lac* operon in *E. coli*

Mutual activation/inhibition can occur through post-translational modifications (e.g. phosphorylation) or through changes in gene expression.

Mutual activation/inhibition can be direct or can occur through intermediates.