Bistability in biochemical signaling models

Part 4

Icahn School of Medicine at Mount Sinai

SBCNY

Outline: Part 4

Bistability in two variable systems

- Can occur by mutual activation or mutual repression
- Dynamic simulations can demonstrate bistability
- Bifurcation plots establish bistable regime

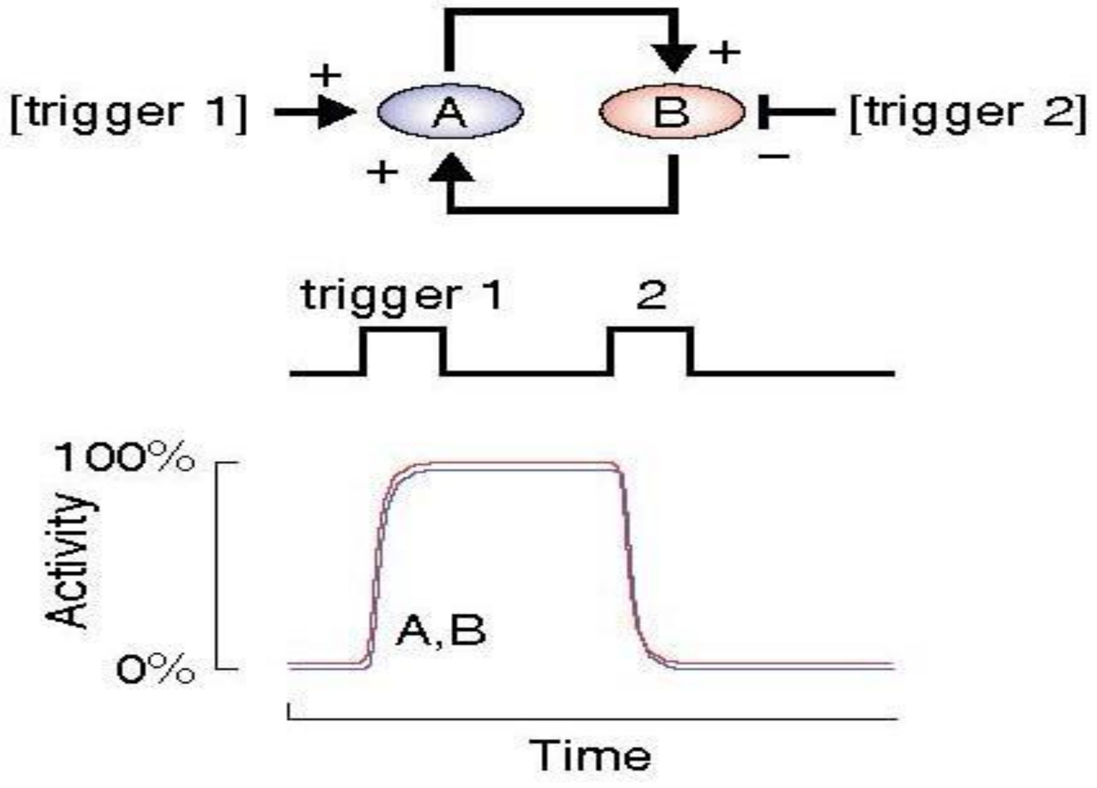
How to predict where bistability will be present?

- Plot nullclines in the phase plane

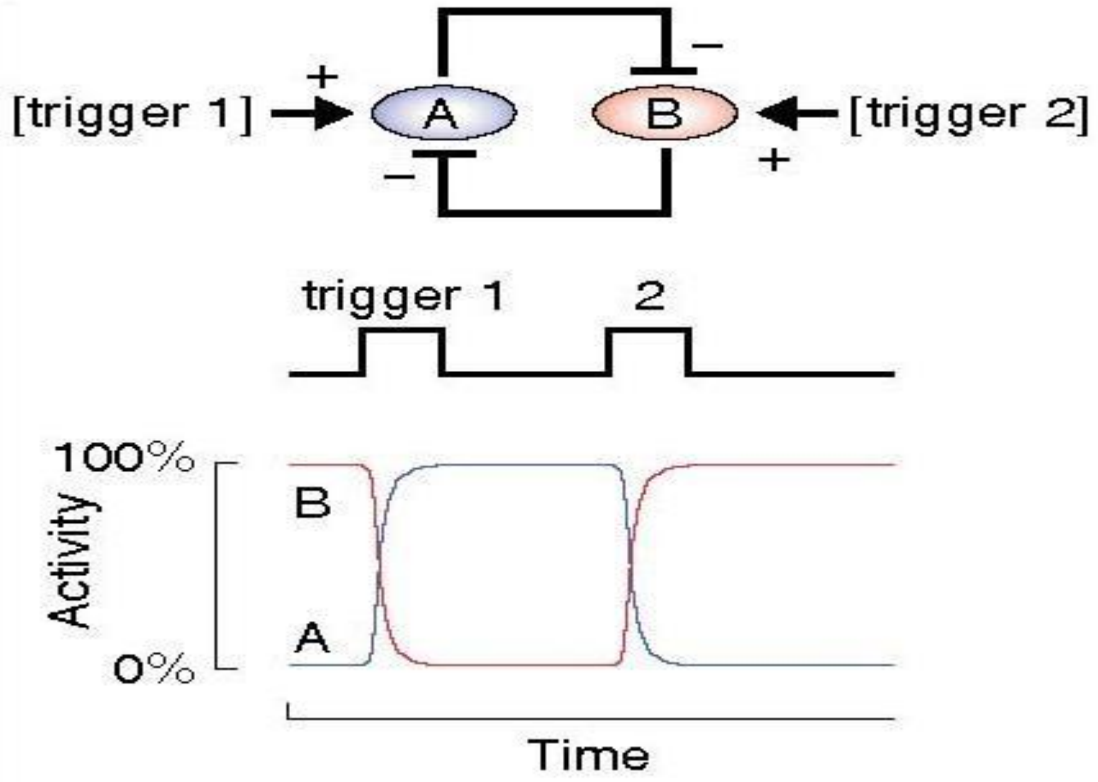
Bistability in a two variable system

Reminder: How can bistability arise in general?

Mutual activation



Mutual inhibition

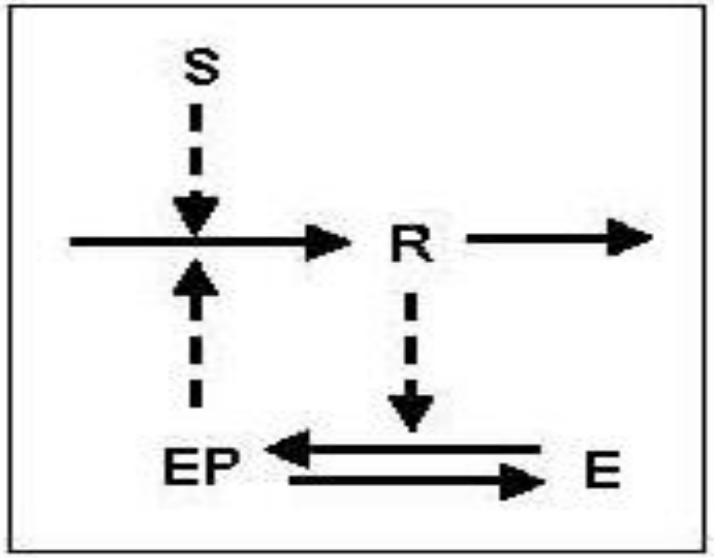


Ferrell (2002) *Curr. Op. Cell Biol.* 14:140–148.

Analysis of two variable systems

1) Generic example of mutual activation

R = response
S = stimulus
E = enzyme



Tyson (2003) *Curr. Op. Cell Biol.* 15:221-231

R causes phosphorylation of E, EP leads to synthesis of R

$$\frac{d[R]}{dt} = k_{1R}\left([E]_{TOTAL} - [E]\right) + k_{1R}[S] - k_{2R}[R]$$

$$\frac{d[E]}{dt} = -k_{2E}[R]\frac{[E]}{[E]+K_{m2E}} + k_{1E}\frac{[E]_{TOTAL} - [E]}{[E]_{TOTAL} - [E] + K_{m1E}}$$

Analysis of two variable systems

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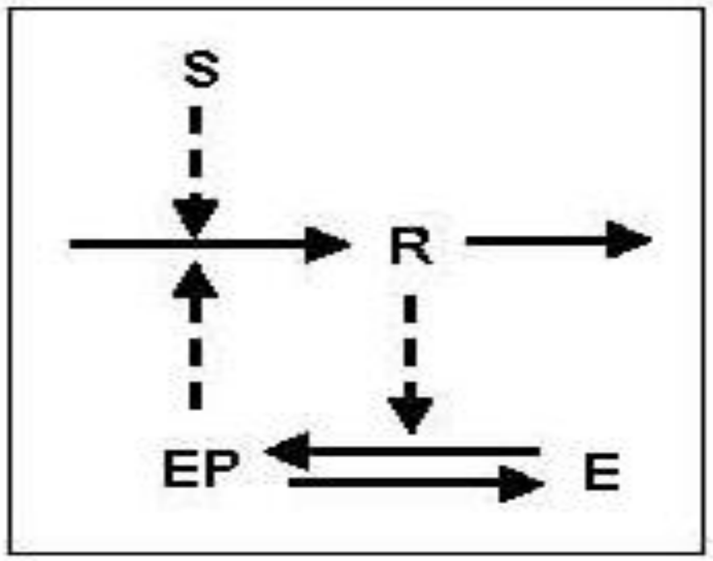

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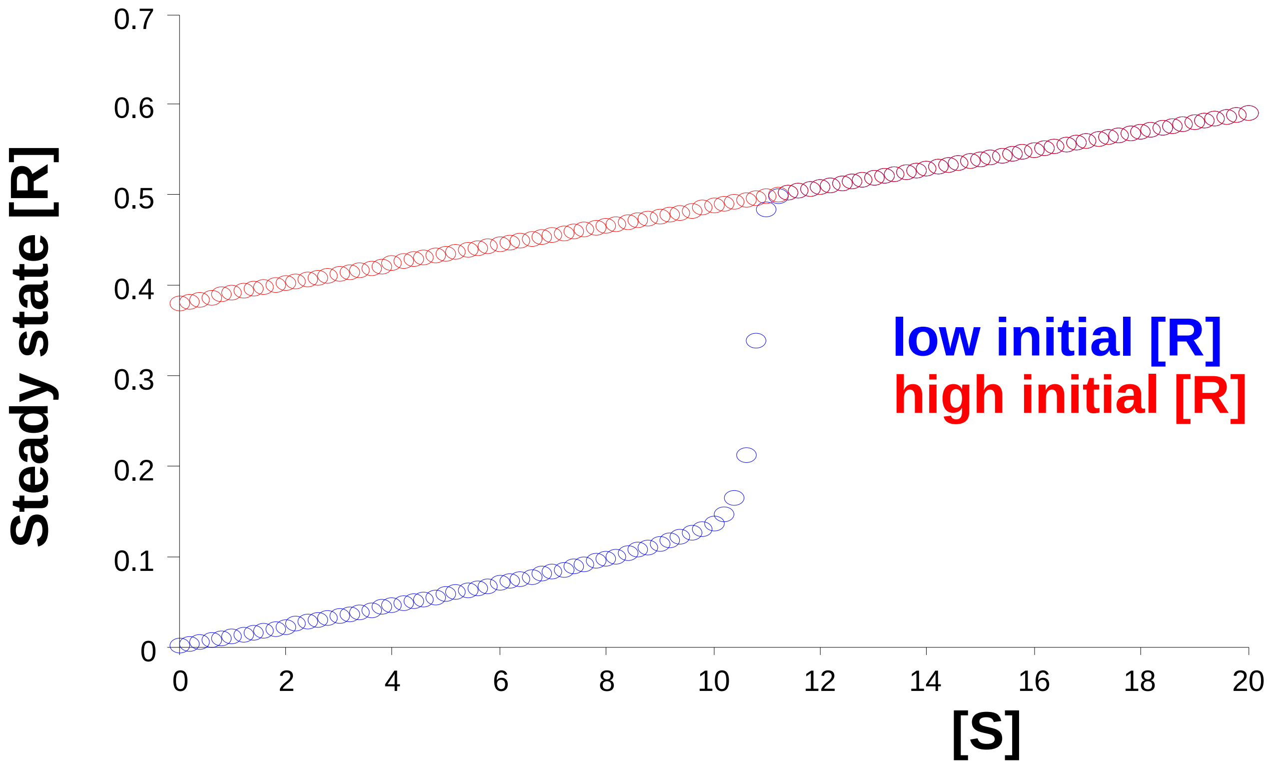
Tyson (2003) *Curr. Op. Cell Biol.* 15:221-231

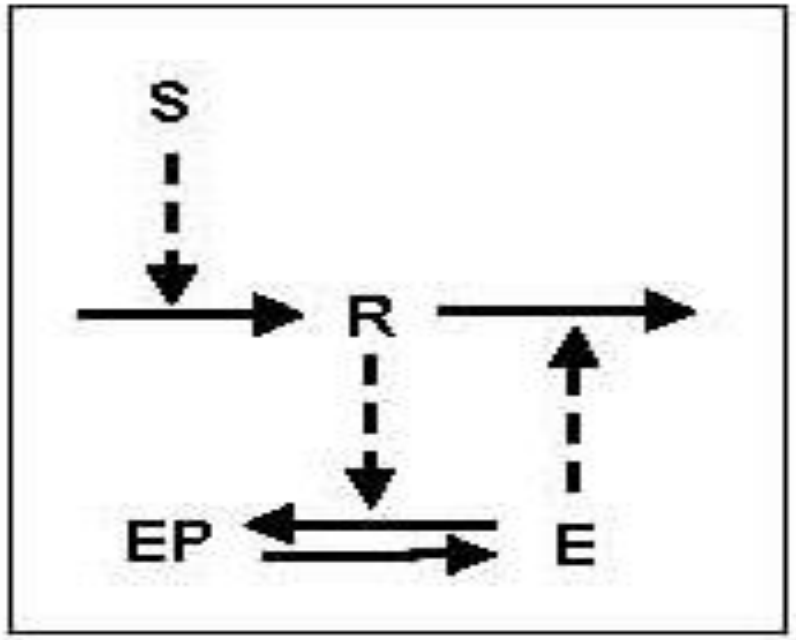
For [S] less than ~11 two steady states are possible



Analysis of two variable systems

2) Generic example of mutual repression

R = response
S = stimulus
E = enzyme



Tyson (2003) *Curr. Op. Cell Biol.* 15:221-231

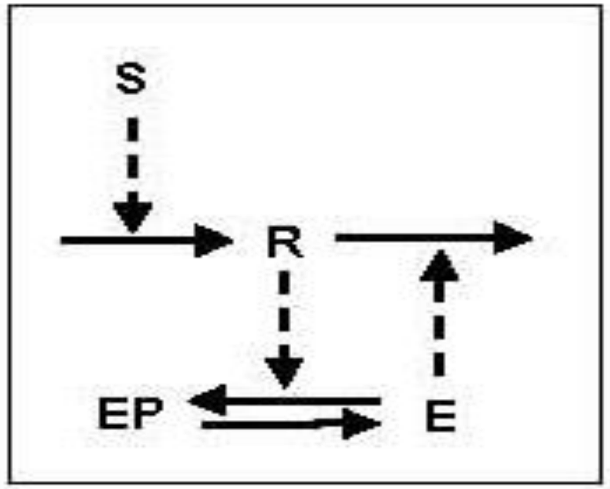
R causes phosphorylation of E, E (not EP) leads to *degradation* of R

$$\frac{d[R]}{dt} = k_0 + k_1[S] - \left(k_2 + k_2'[E]\right)[R]$$

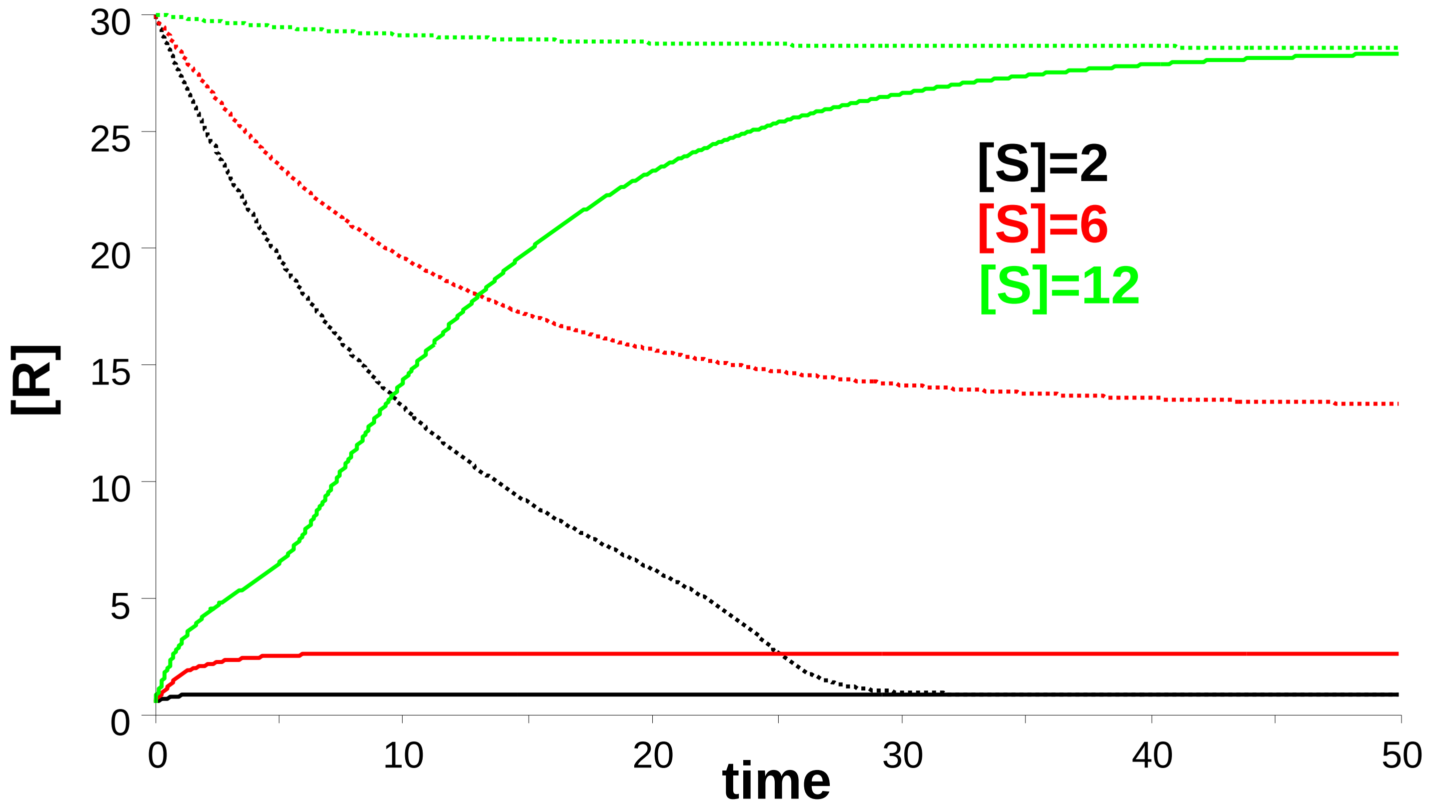
$$\frac{d[E]}{dt} = -k_{2E}[R]\frac{[E]}{[E]+K_{m2E}} + k_{1E}\frac{[E]_{TOTAL} - [E]}{[E]_{TOTAL} - [E] + K_{m1E}}$$

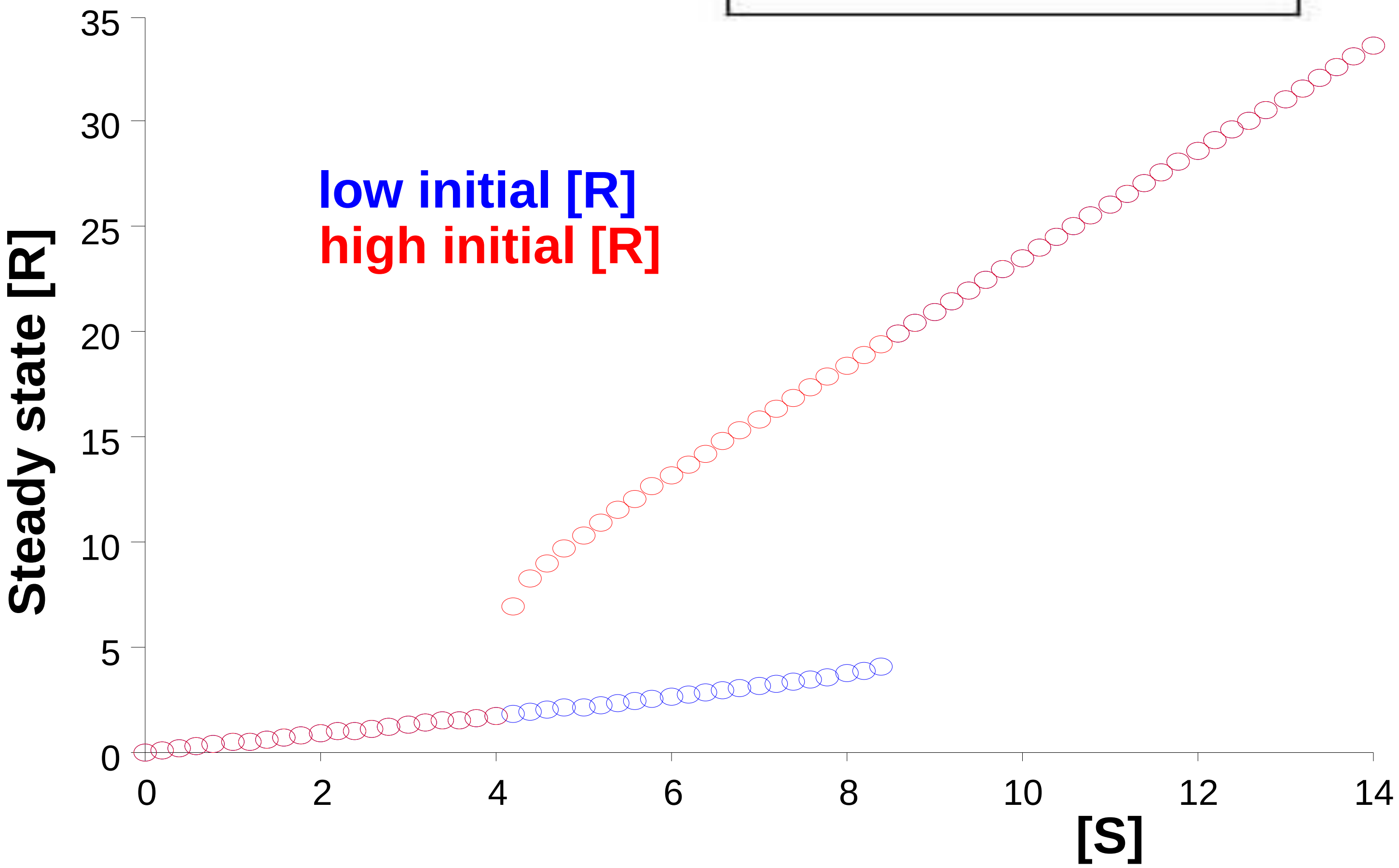
Analysis of two variable systems

2) Generic example of mutual repression



Time course of [R] at different values of [S]





Initial conditions determine which steady-state is reached

Analysis of two variable systems

2) Generic example of mutual repression

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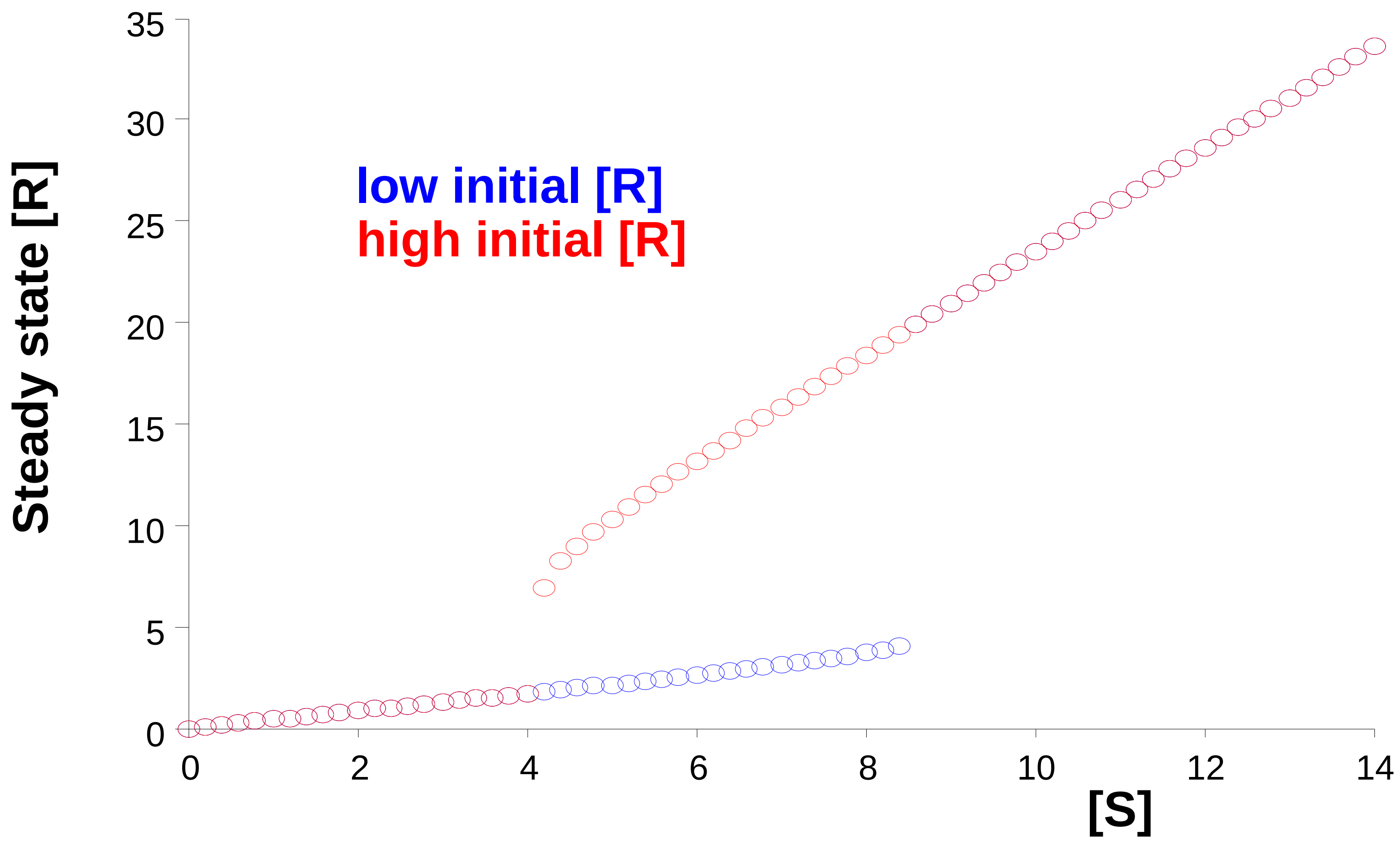


How can we determine that bistability will occur at only some values of [S]?

Analysis of two variable systems

2) Generic example of mutual repression

We are going to plot nullclines, i.e. points where either $\frac{d[R]}{dt} = 0$ **or** $\frac{d[E]}{dt} = 0$

$$\frac{d[R]}{dt} = k_0 + k_1[S] - \left(k_2 + k_2^{'}[E]\right)[R] = 0$$

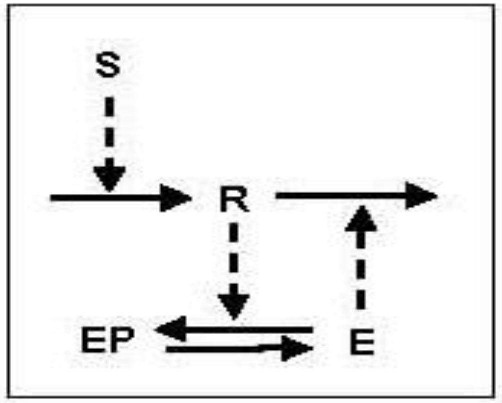
$$\frac{d[E]}{dt} = -k_{2E}[R]\frac{[E]}{[E] + K_{m2E}} + k_{1E}\frac{[E]_{TOTAL} - [E]}{[E]_{TOTAL} - [E] + K_{m1E}} = 0$$

First equation: equally easy to solve for [E] in terms of [R] or vice-versa

Second equation: MUCH easier to solve for [R] as function of [E]

Analysis of two variable systems

2) Generic example of mutual repression



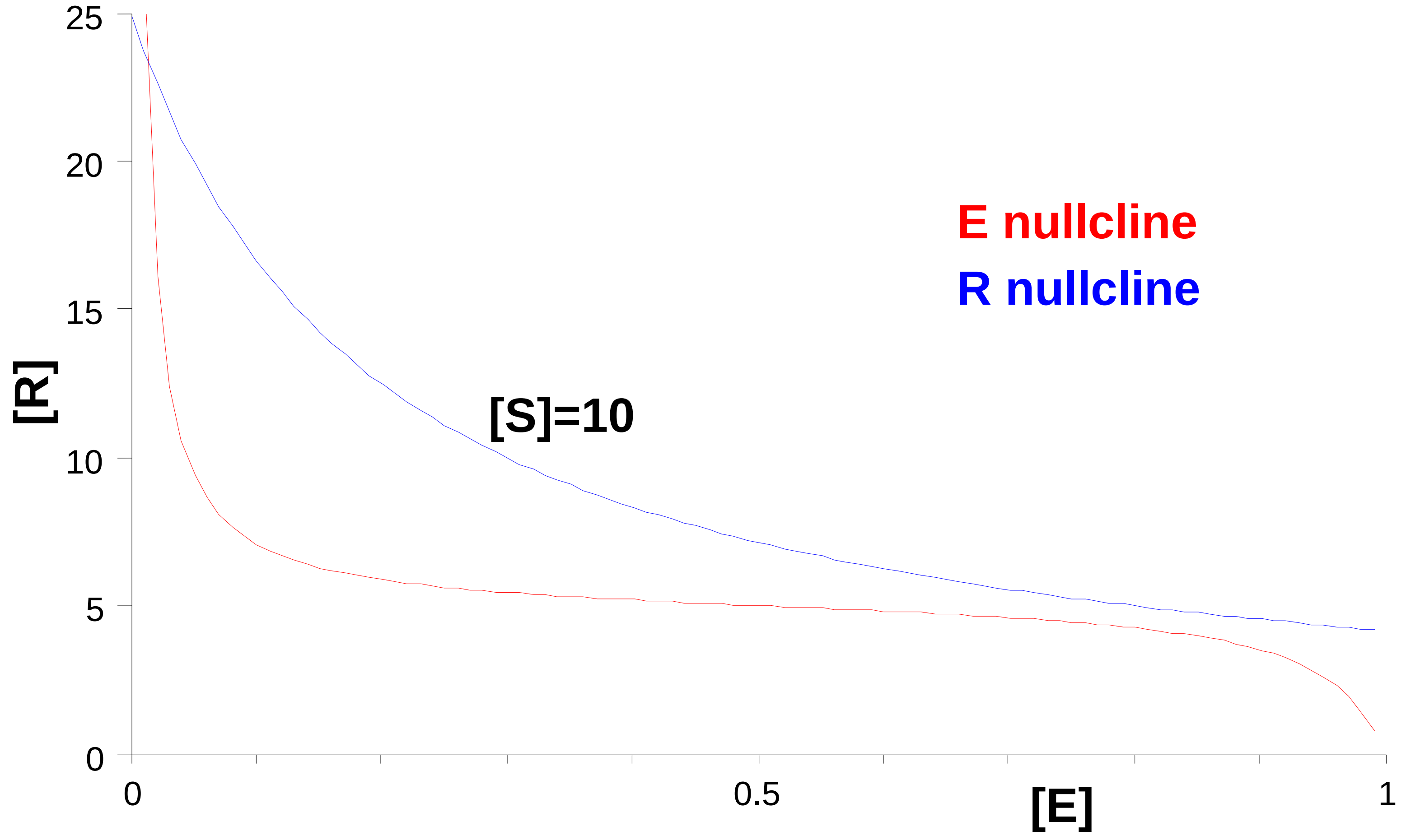
What do the nullclines look like?

R nullcline

$$[R] = \frac{k_{0r} + k_{1r}[S]}{\left(k_{2r} + k_{3r}[E]\right)}$$

E nullcline

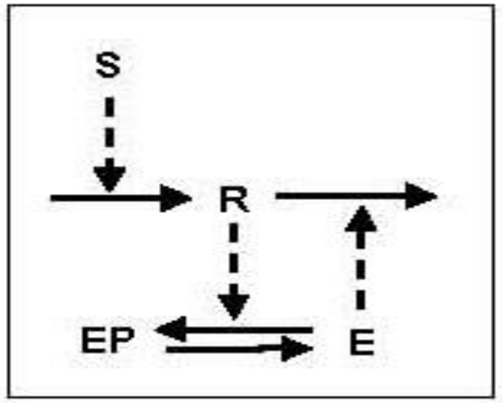
$$[R] = \frac{k_{1E}\dfrac{[E]_{TOTAL} - [E]}{[E]_{TOTAL} - [E] + K_{m1e}}}{k_{2E}\dfrac{[E]}{[E] + K_{m2e}}}$$



One intersection: monotstable

Analysis of two variable systems

2) Generic example of mutual repression



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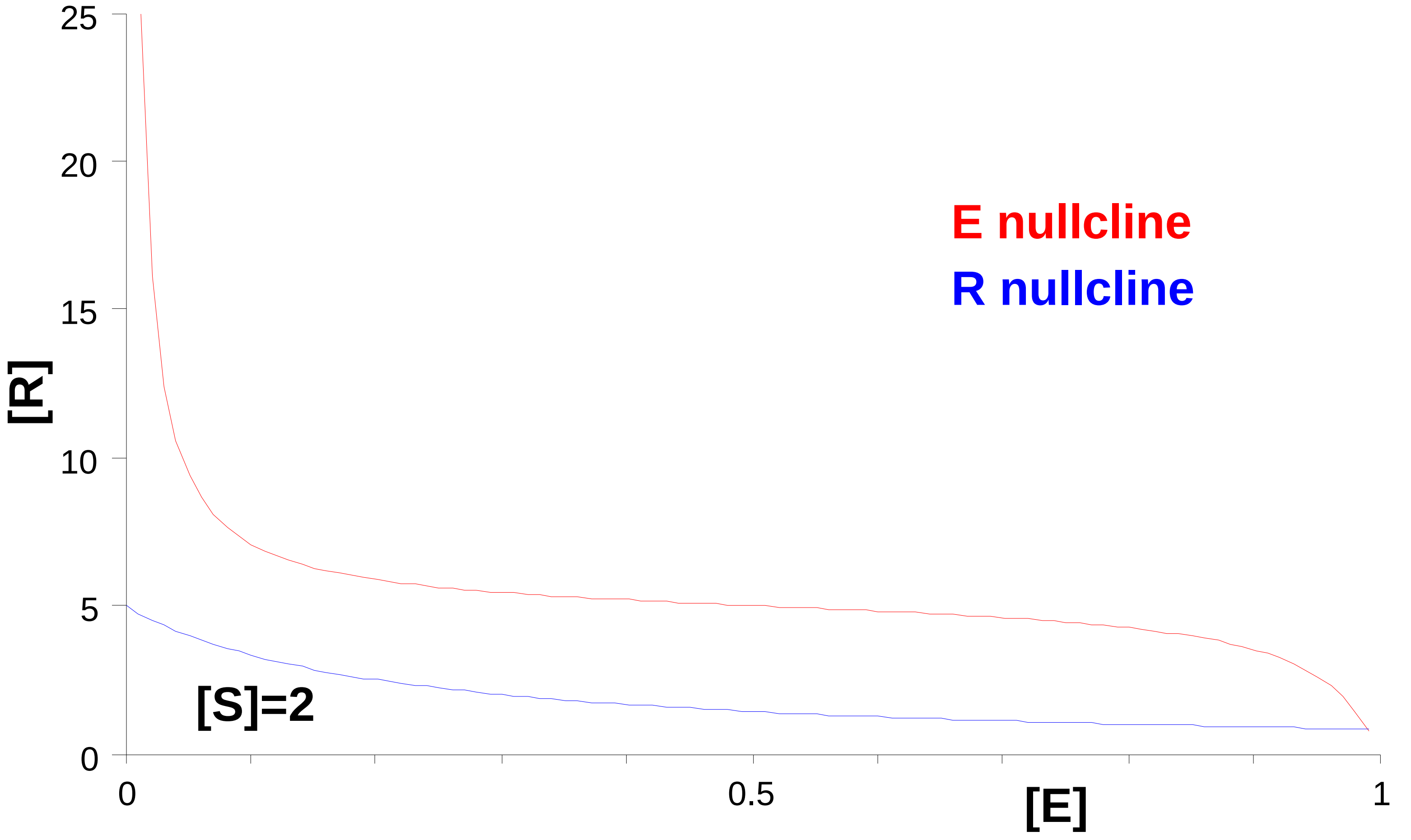

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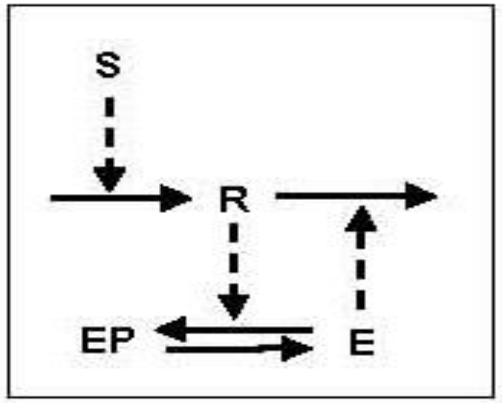

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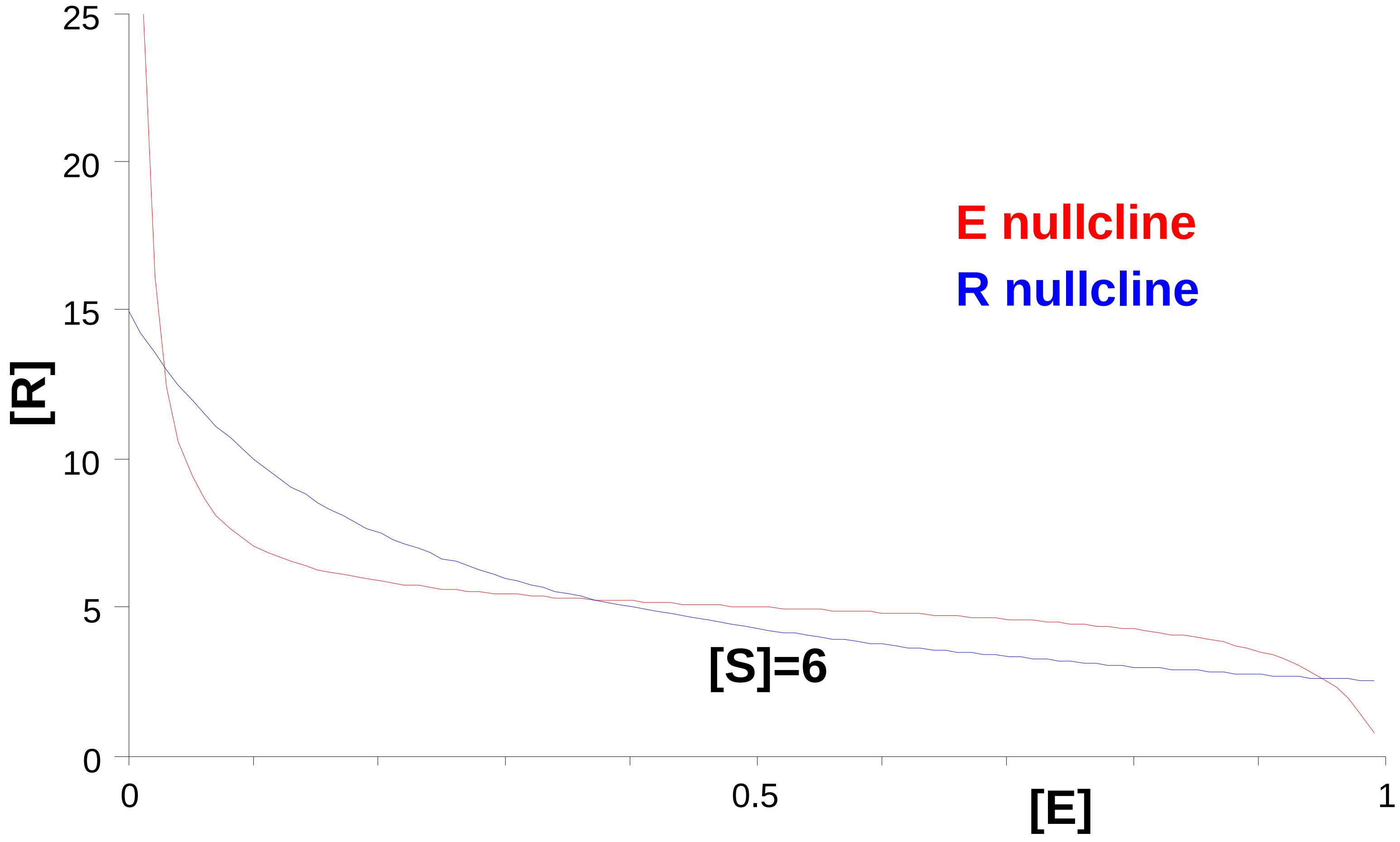

Next lecture: how can we assess stability of fixed points?

Summary

In a two-variable system, bistability can be produced by:

- mutual activation
- mutual repression

Bifurcation diagrams summarize which regions of particular parameters are associated with bistability.

Plotting nullclines in the phase plane is the first step towards predicting whether bistability is present.