Bistability in biochemical signaling models

Part 5

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Outline: Part 5

How to predict where bistability will be present?

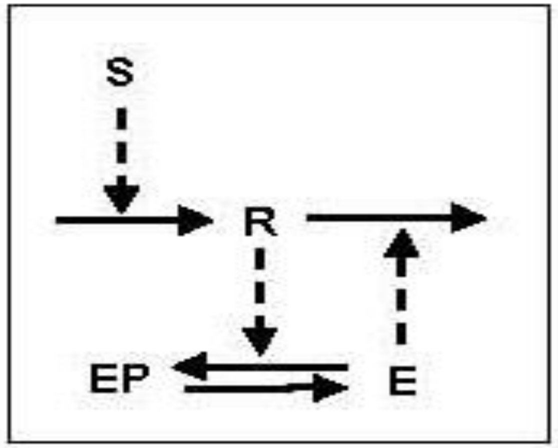
Plot nullclines in the phase plane

Mathematically rigorous: Jacobian & eigenvalues

Qualitative and graphical: direction arrows

Analysis of two variable systems

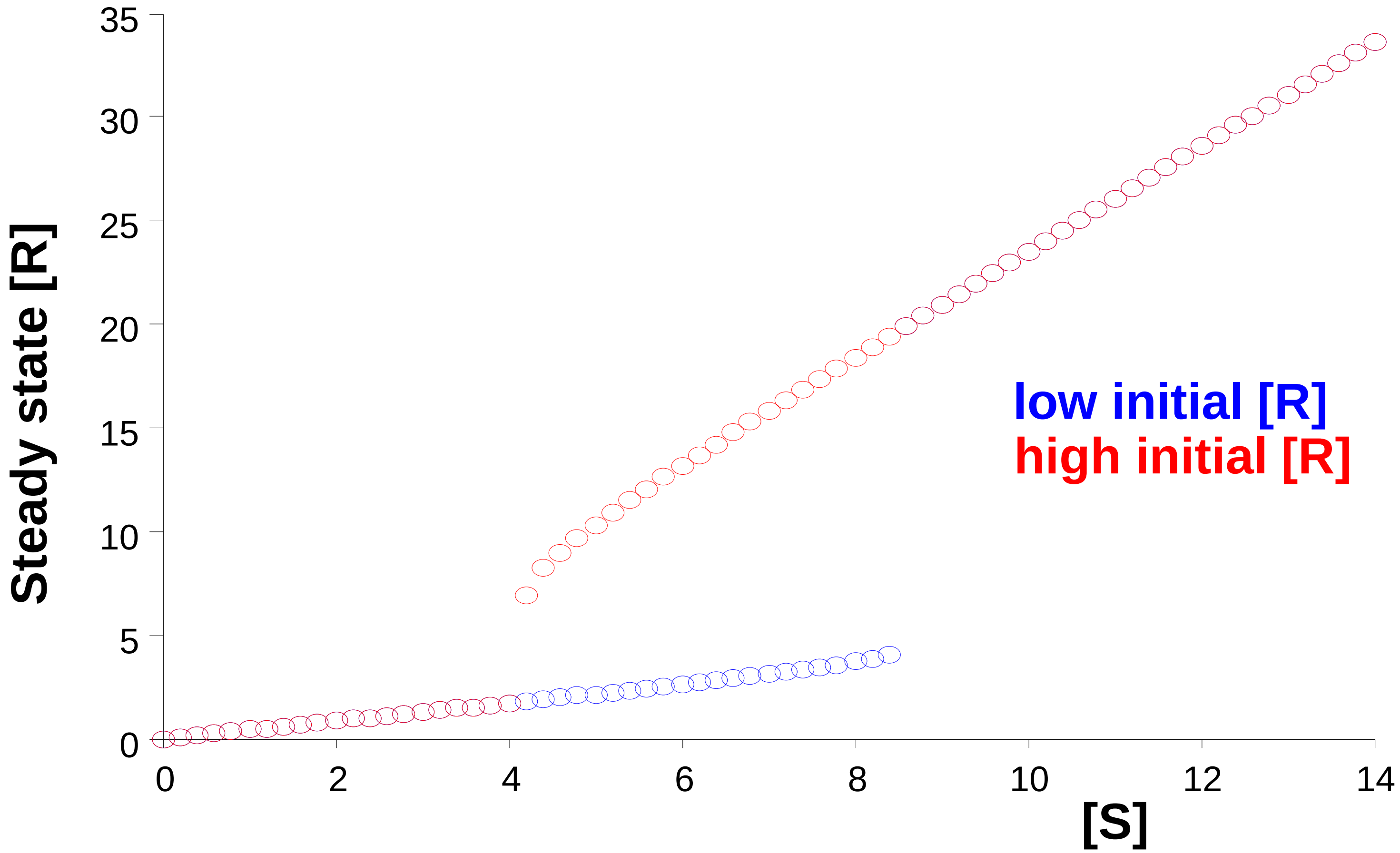
2) Generic example of mutual repression



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

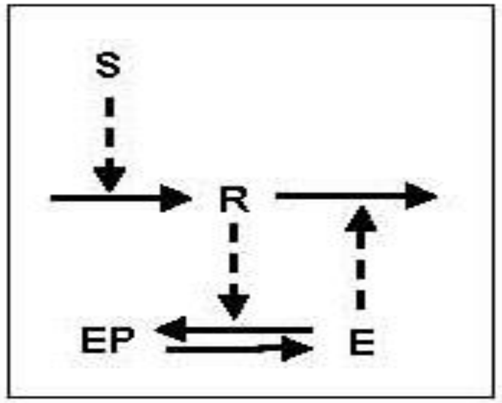
$$\frac{d[R]}{dt} = k_0 + k_1[S] - \left(k_2 + k_2'[E]\right)[R]$$

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



Analysis of two variable systems

2) Generic example of mutual repression



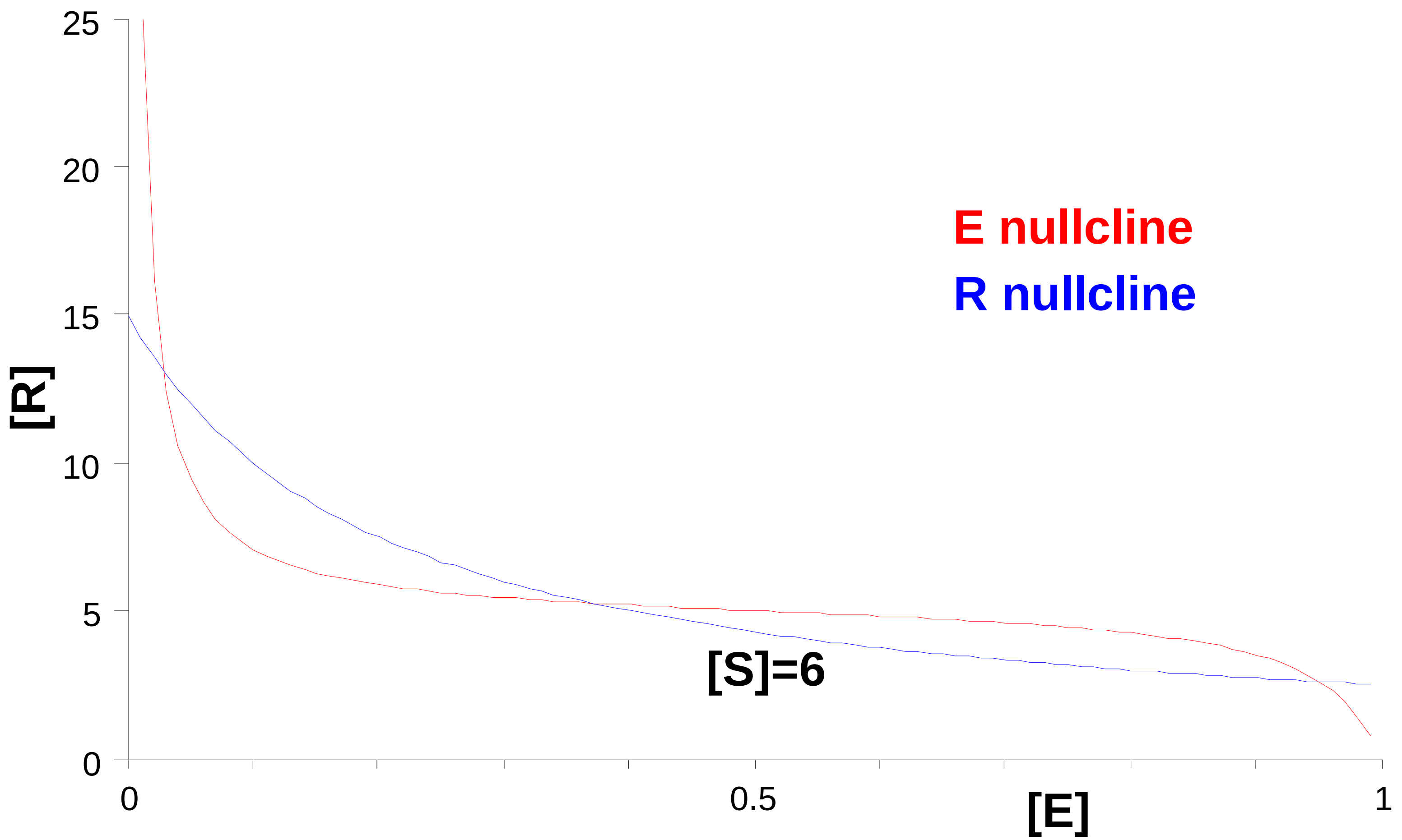
For some [S], nullclines can intersect 3 times

R nullcline

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

E nullcline

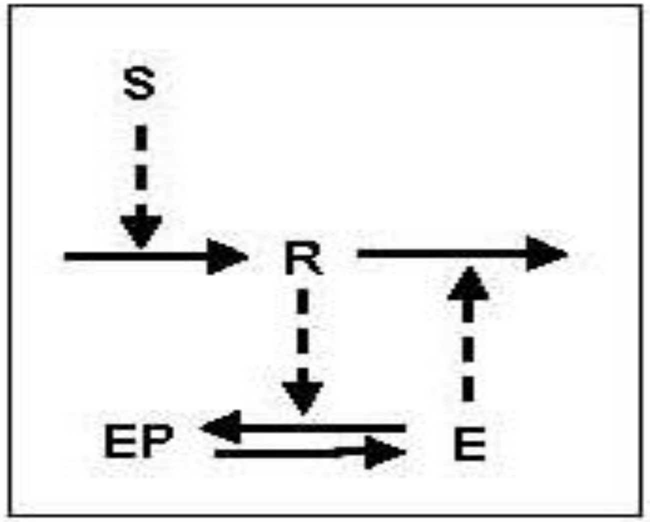
$$[R] = \frac{k_{1E}\dfrac{[E]_{TOTAL} - [E]}{[E]_{TOTAL} - [E] + K_{m1e}}}{k_{2E}\dfrac{[E]}{[E] + K_{m2e}}}$$



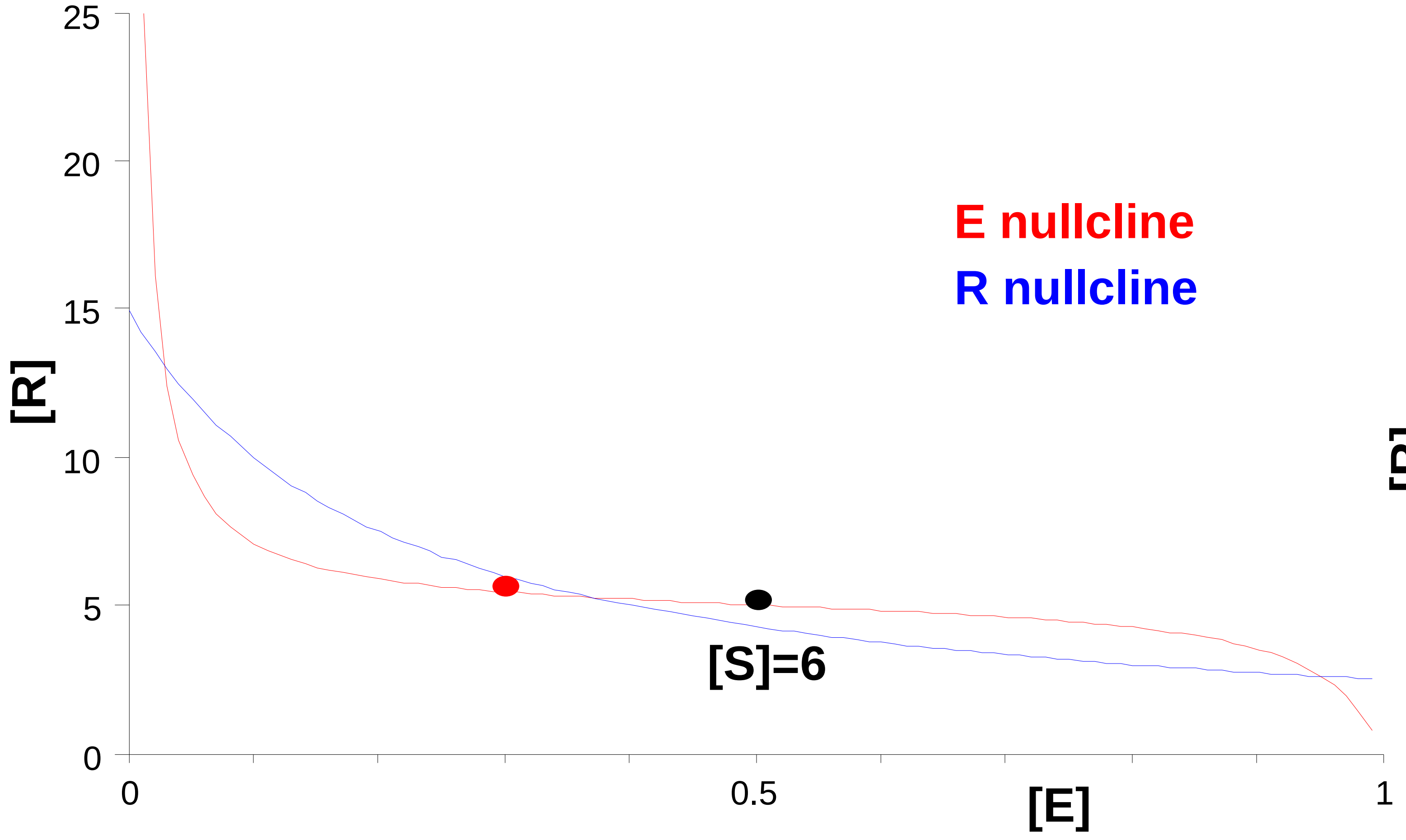
How do we tell if the fixed points are stable or unstable?

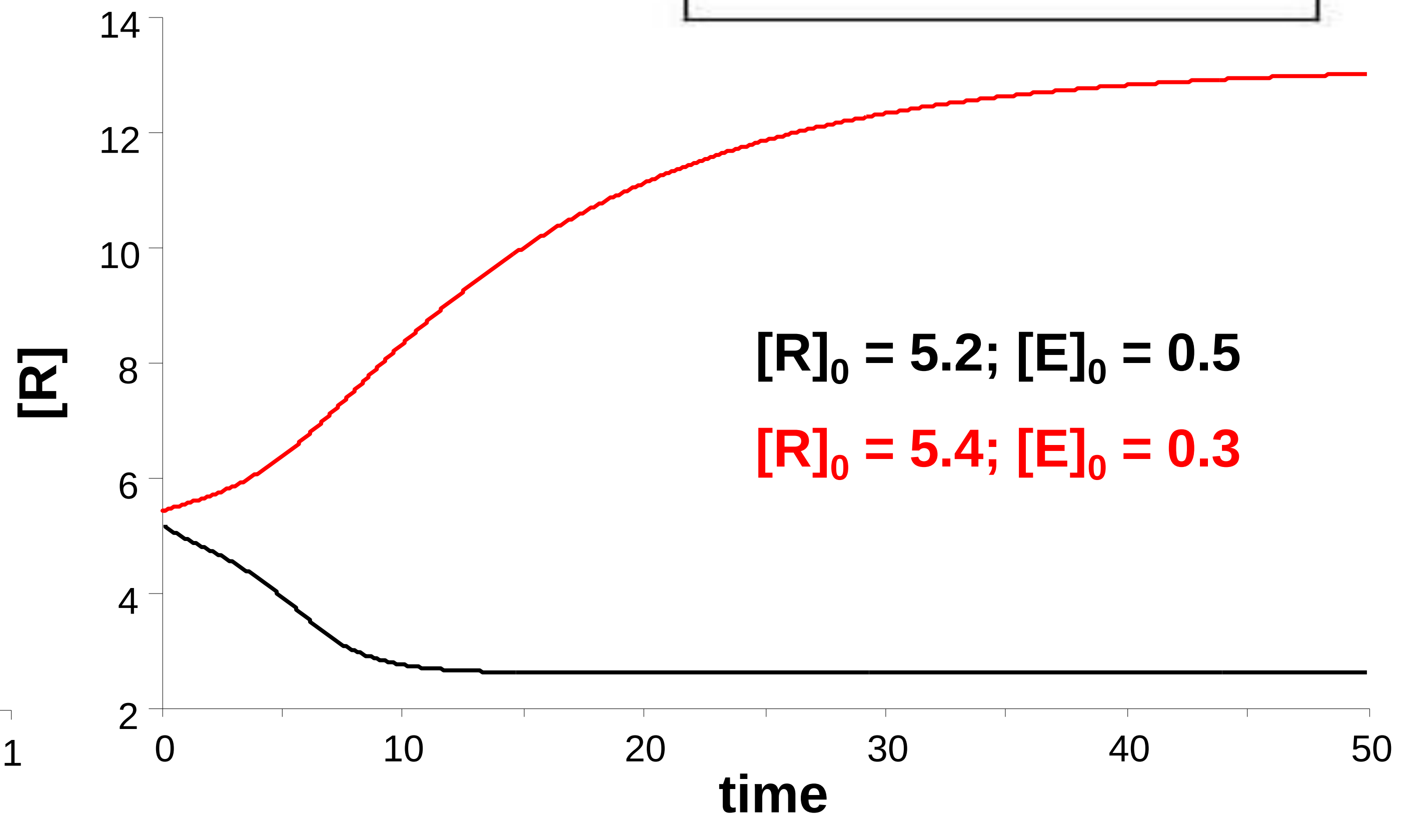
Analysis of two variable systems

2) Generic example of mutual repression



[R] vs. time at [S] = 6





This suggests (but does not prove) the middle fixed point is unstable

Stability analysis of ODE systems

How can we understand stable and unstable fixed points mathematically?

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

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

Compute the "Jacobian" matrix:

$$J = \begin{bmatrix} \dfrac{\partial f}{\partial [E]} & \dfrac{\partial f}{\partial [R]} \\ \dfrac{\partial g}{\partial [E]} & \dfrac{\partial g}{\partial [R]} \end{bmatrix} = \begin{bmatrix} \dfrac{-k_{2e}[R]K_{m2e}}{\left([E]+K_{m2e}\right)^2} - \dfrac{k_{1e}K_{m1e}}{\left([E]_{TOTAL} - [E] + K_{m1e}\right)^2} & \dfrac{-k_{2e}[E]}{[E]+K_{m2e}} \\ -k_{3r}[R] & -(k_{2r} + k_{3r}[E]) \end{bmatrix}$$

Evaluate this at the fixed points defined by [E*], [R*]

(This is where analytical computations become difficult)

Stability analysis of ODE systems

Evaluate Jacobian matrix at the fixed points defined by [E*], [R*]

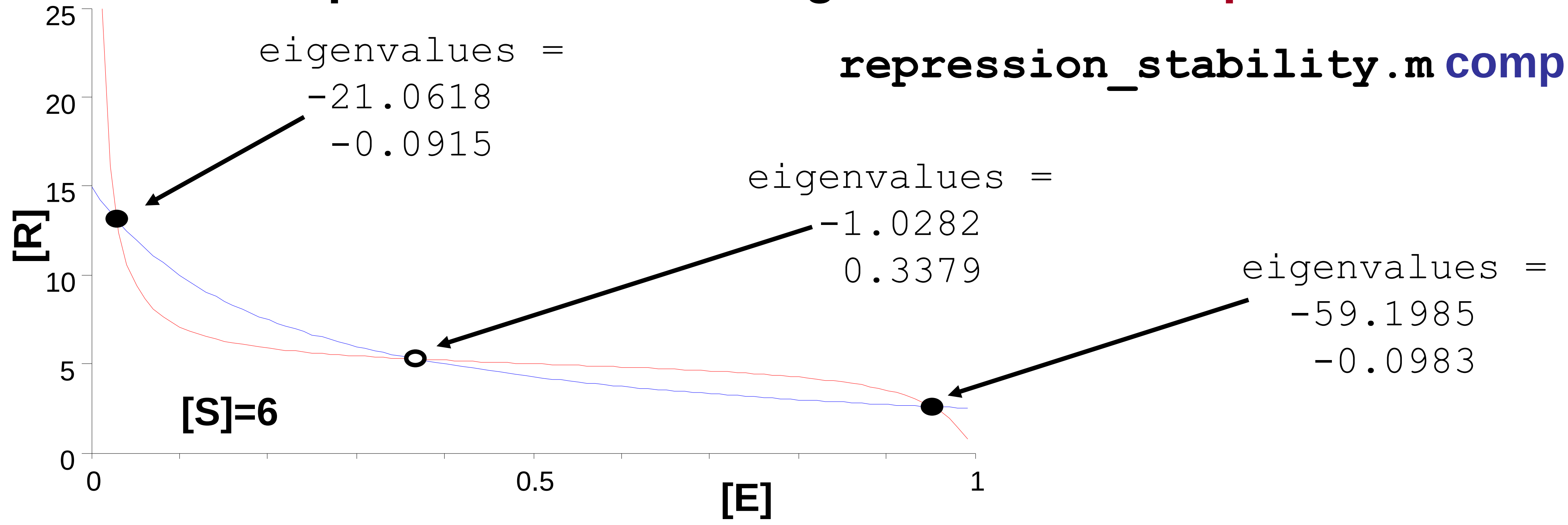
$$J = \begin{bmatrix} \dfrac{-k_{2e}[R*]K_{m2e}}{([E*]+K_{m2e})^2} - \dfrac{k_{1e}K_{m1e}}{([E]_{TOTAL} - [E*] + K_{m1e})^2} & \dfrac{-k_{2e}[E*]}{[E*]+K_{m2e}} \\ -k_{3r}[R*] & -(k_{2r} + k_{3r}[E*]) \end{bmatrix}$$

The eigenvalues of the Jacobian (at the fixed points) determine stability

The real part of either is positive: the fixed point is unstable

Real parts of both are negative: the fixed point is stable

`repression_stability.m` computes these



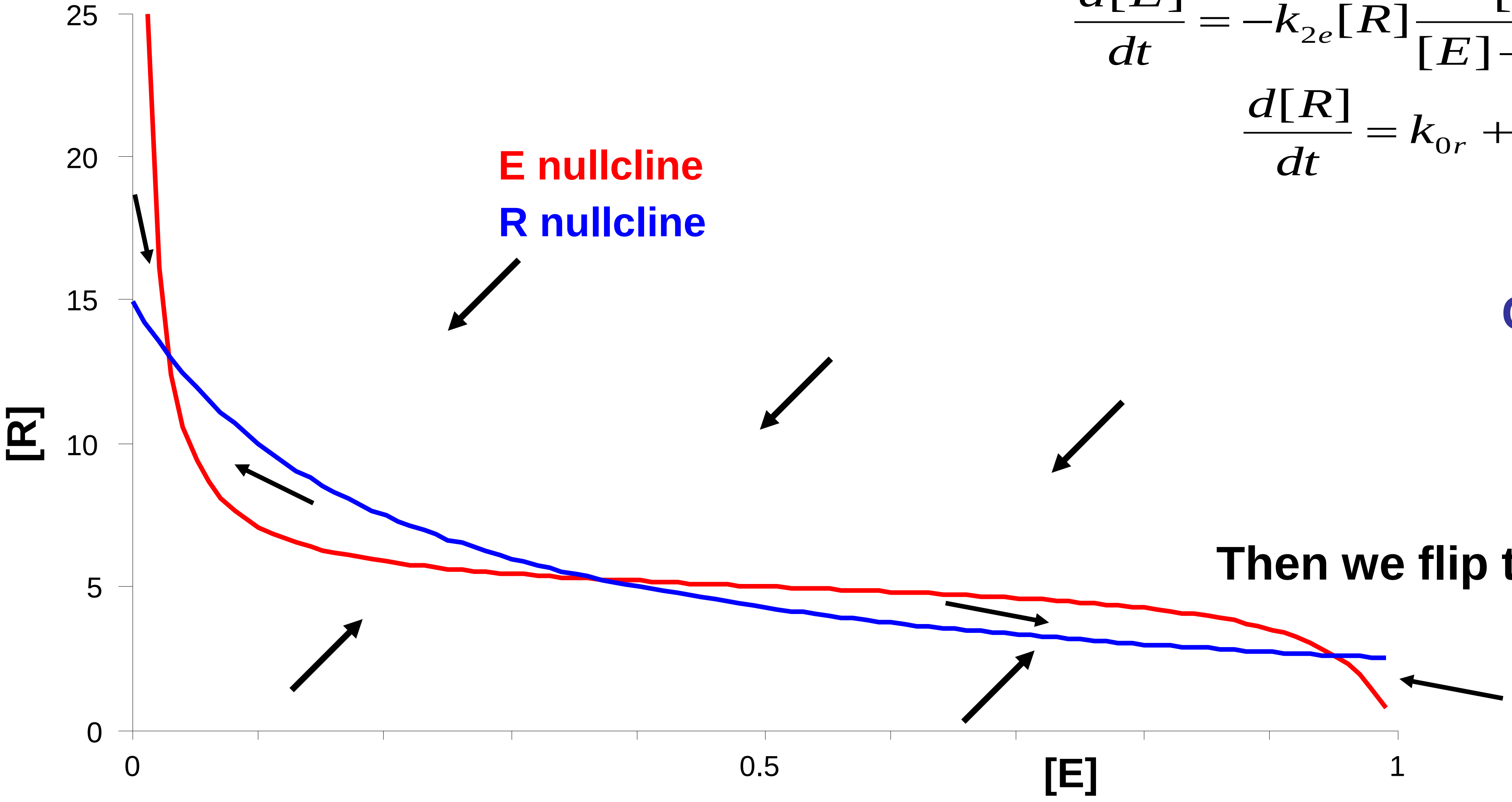
Qualitative, graphical stability analysis

In 2D phase plane, direction determined by:

$$\begin{bmatrix} d[E]/dt \\ d[R]/dt \end{bmatrix}$$

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

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



Consider [E] big; [R] big:

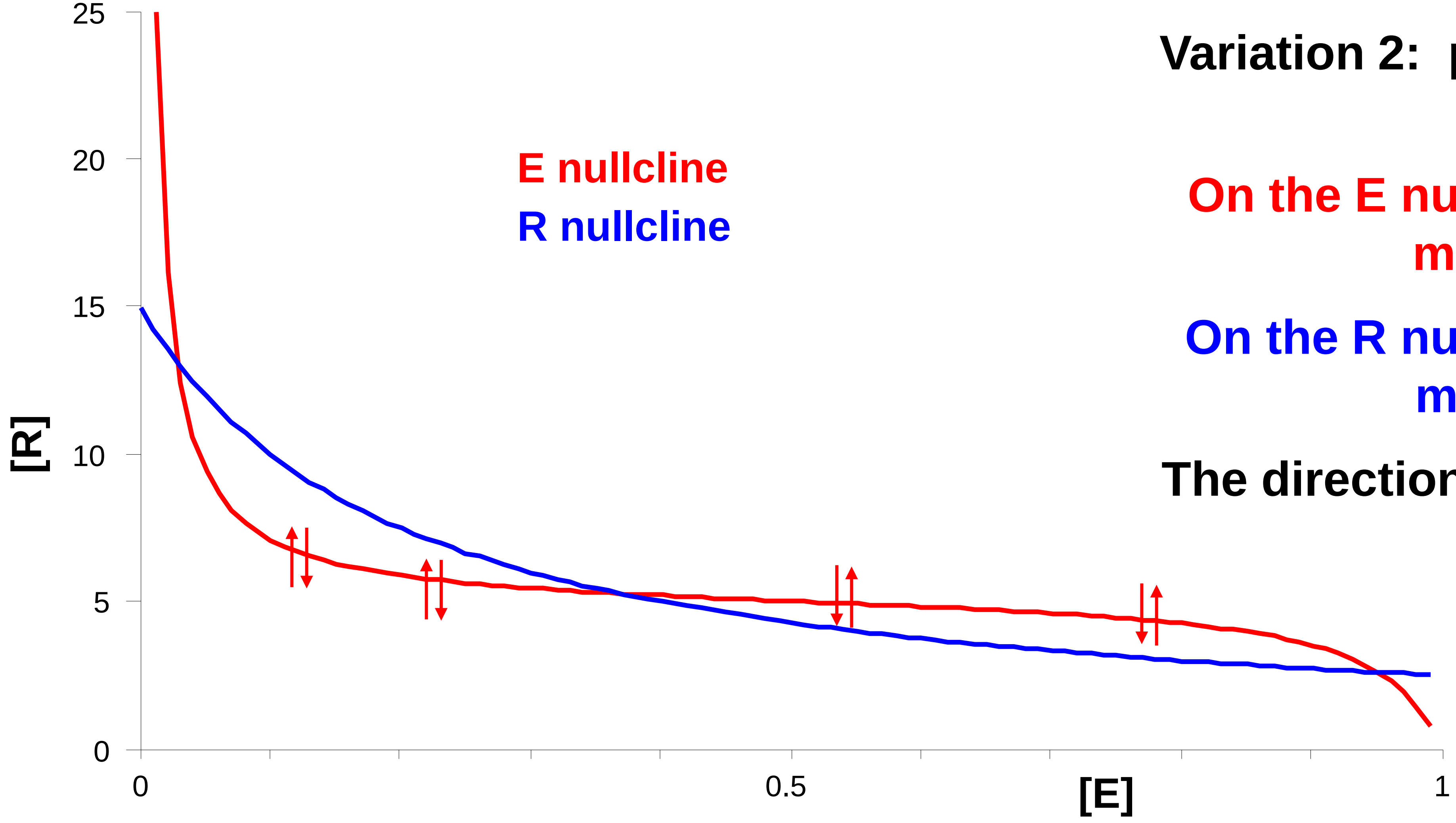
$$\frac{d[E]}{dt} < 0; \frac{d[R]}{dt} < 0$$

Then we flip the arrow each time we cross a nullcline

With these simple rules, we can (often) determine stability

Analysis of two variable systems

A qualitative, graphical analysis of stability



Variation 2: plot arrows ON the nullclines

On the E nullcline, dE/dt=0, direction of movement is up/down

On the R nullcline, dR/dt=0, direction of movement is left/right

The direction changes when a nullcline is crossed

With these simple rules, we can (often) determine stability

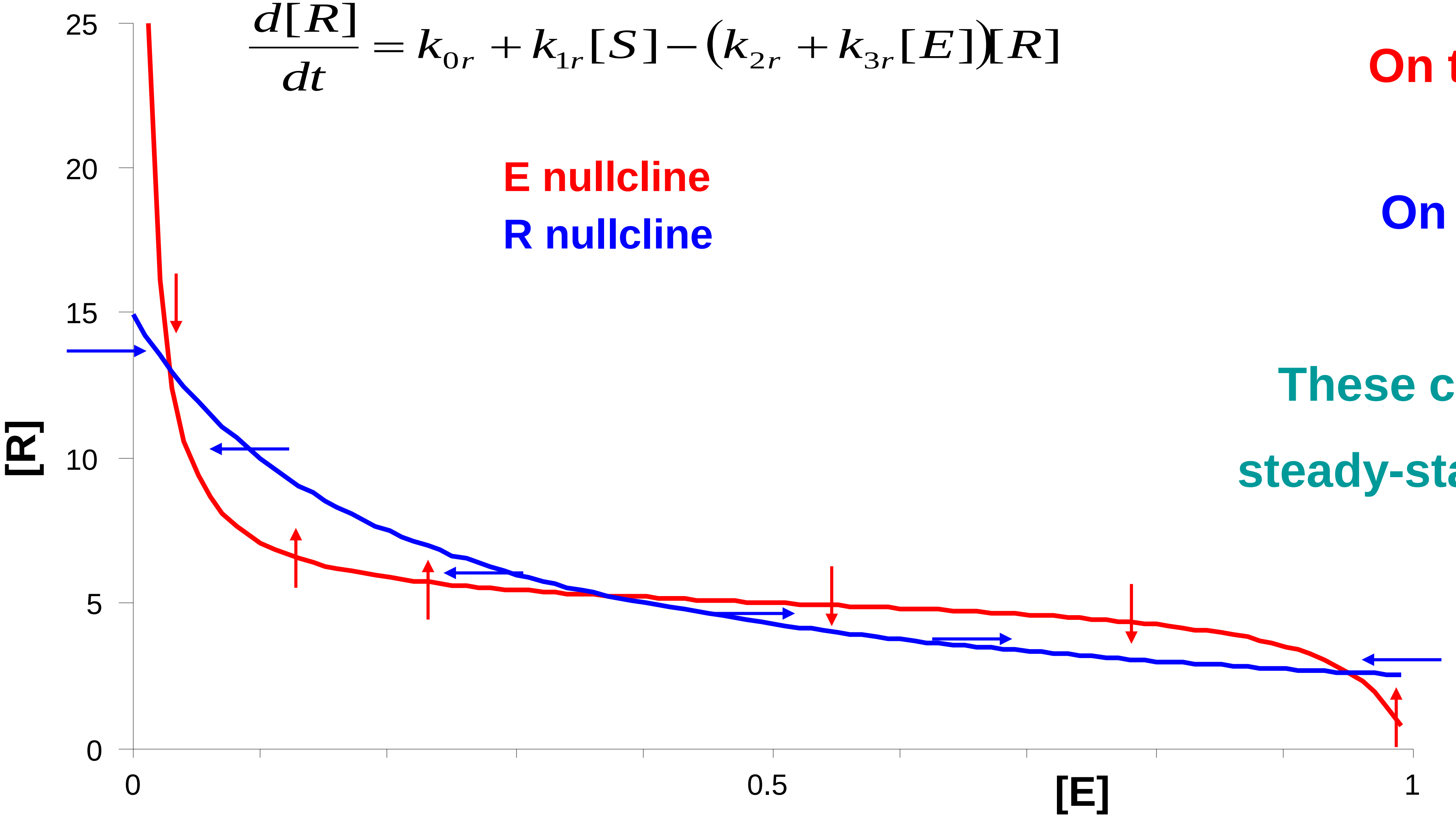
Graphical analysis of stability

Examine equations to determine directions

(Remember that R is the ordinate)

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

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



We plot dR/dt on E nullcline
We plot dE/dt on R nullcline

On the E nullcline, and above the R nullcline, dR/dt < 0

On the R nullcline, and above the E nullcline, dE/dt < 0

These considerations suggest that middle steady-state is unstable, left and right steady-states are stable

Summary

In a two-variable system mutual activation or mutual repression can produce bistability.

When nullclines intersect 3 times, bistability may be present.

Stability of fixed points can be determined graphically by:

- plotting direction arrows for extreme values of the two variables
- flipping arrows in one direction each time a nullcline is crossed