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Lecture 3: Phase Plane Analysis

Dagmar Iber

Lecture 2 - Biochemical Reaction Kinetics

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Content

- Mass Balance
- Half-lives for linear decay reactions
- Michaelis-Menten
- Allosteric and competitive inhibition
- Hill equation
- MWC model
- Signaling cascades (Heinrich Model)

Technical

- Formulation of chemical reaction models
- Analytical solution of simple ODEs
- Singular perturbation methods (matching)

Typical Reactions in Biology

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Elementary Reactions

- Constant Production
- Linear Decay
- Dimer Formation
- Monomolecular Conversions
- Bimolecular Conversions

Complex Reactions

- Michaelis-Menten
- Hill-type
- MWC

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I) Simple dynamical models

- Qualitative Analysis of dynamical Models
- Define steady states
- Define stability
- Define trajectories

II) Biological Responses

- Linear, hyperbolic, sigmoidal
- Adaptation
- Oscillation
- Switches

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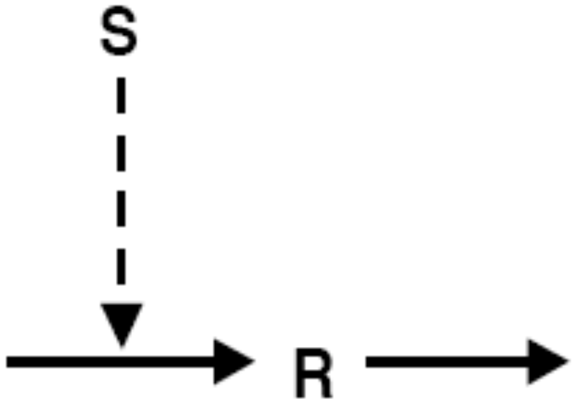
$dx/dt = f(x(t), u(t), p, t)$

- $x(t)$ – system states
- $u(t)$ – time-varying inputs
- p – parameters
- t - time

Solution Methods

- Analytical: only for very simple models
- Numerical: method of choice, but harder to gain insight into parameter dependencies of qualitative behaviours
- Graphical: qualitative analysis method for simple systems

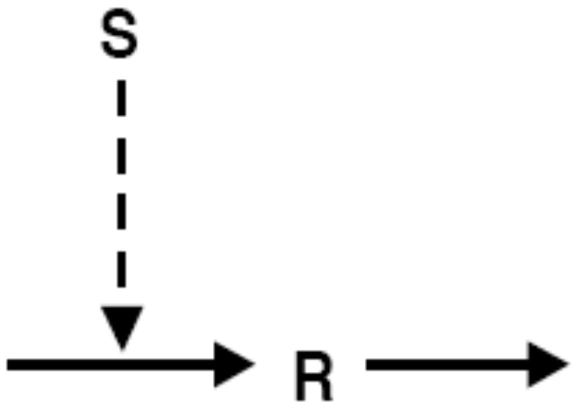
A simple example

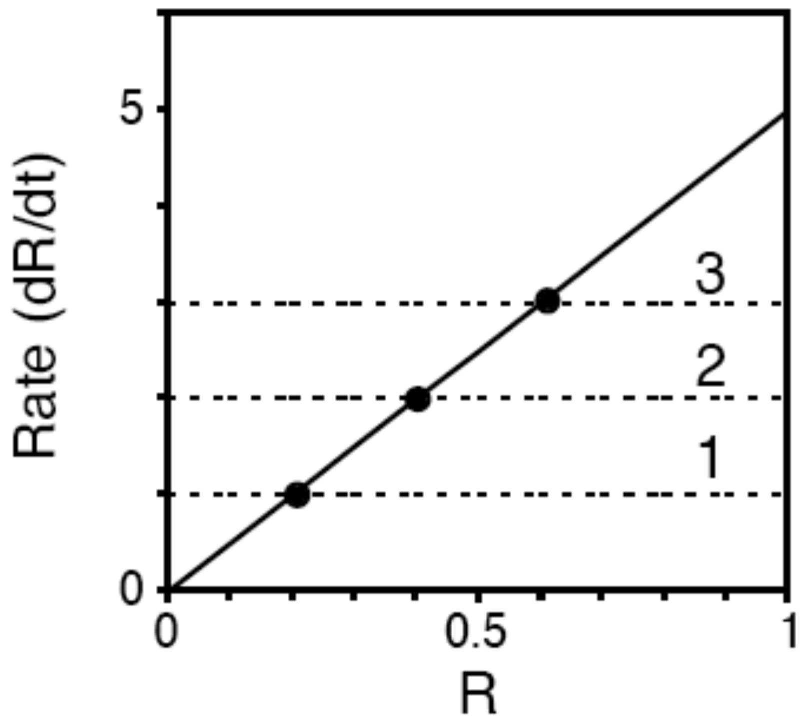


$$\frac{dR}{dt} = k_0 + k_1 S - k_2 R$$

Tyson et al (2003), Curr Opin Cell Biol, 15, 221ff

Steady State Analysis





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

$$R = \frac{k_0 + k_1 S}{k_2}$$

Stability of Steady States

Definition

A steady state is stable if the system returns to the steady state upon a perturbation.

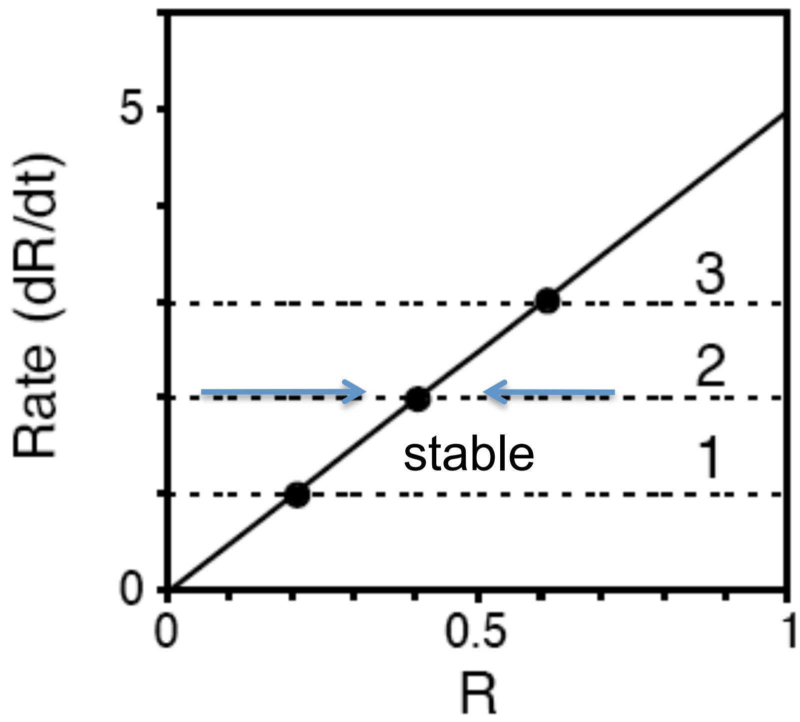
<u>Example</u>

$$\frac{dx}{dt} = f(x) \qquad \frac{dx}{dt}|_{x_s} = f(x_s) = 0$$

has a stable steady state x_s if

$$\frac{dx}{dt}|_{x_s+p} < 0 \qquad \forall p > 0$$

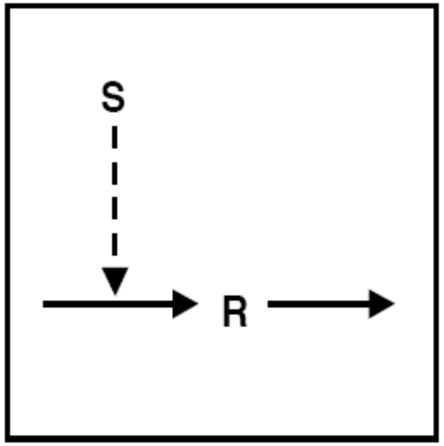
$$\frac{dx}{dt}|_{x_s+p} > 0 \qquad \forall p < 0$$

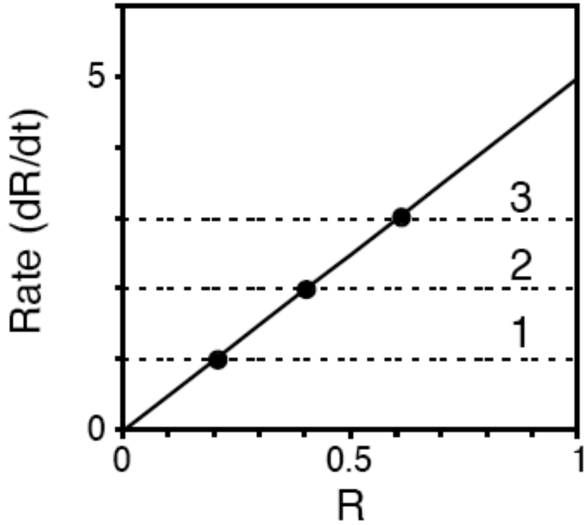


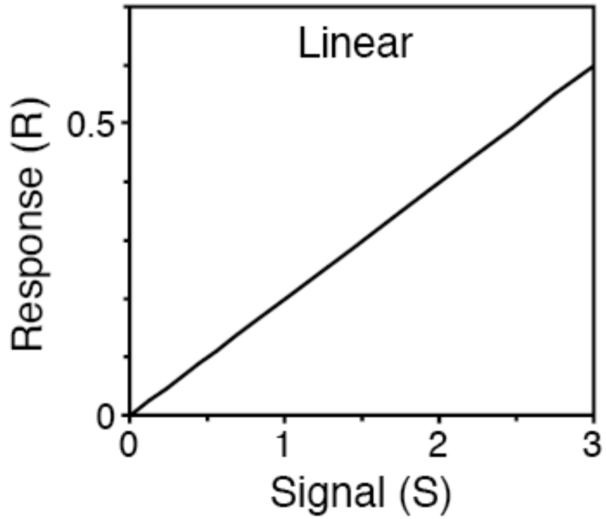
$$\frac{dR}{dt} = k_0 + k_1 S - k_2 R$$

Tyson et al (2003), Curr Opin Cell Biol, 15, 221ff

Linear Responses



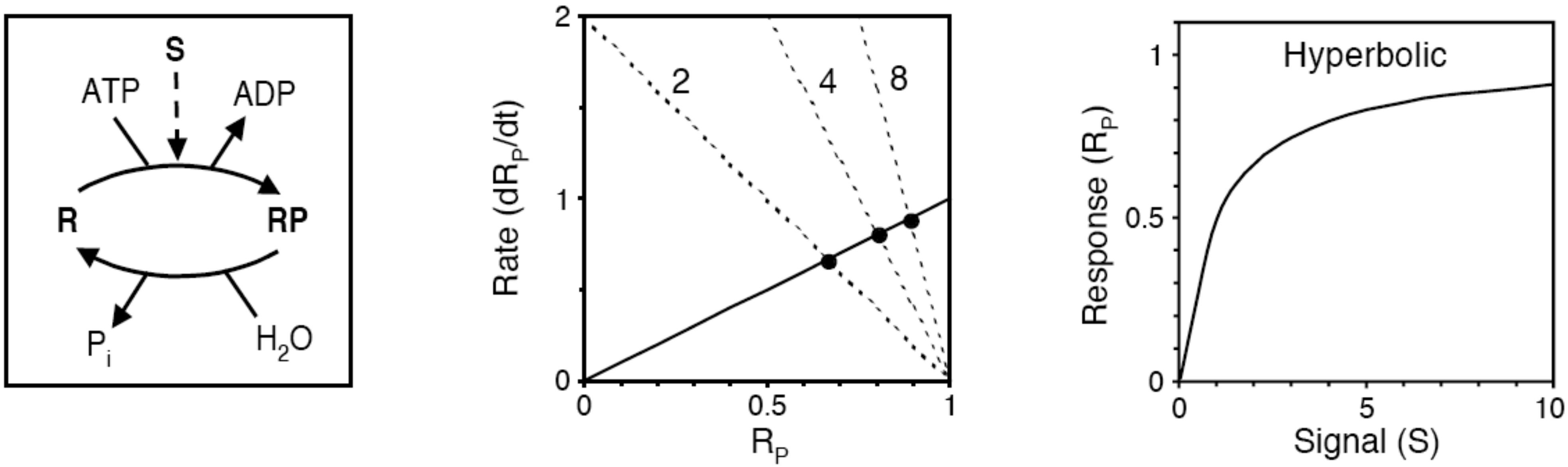




$$\frac{dR}{dt} = k_0 + k_1 S - k_2 R$$

Tyson et al (2003), Curr Opin Cell Biol, 15, 221ff

Hyperbolic Responses



$$\frac{dR_P}{dt} = k_1 S (R_T - R_P) - k_2 R_P$$

with steady state

$$R_{P,ss} = \frac{R_T S}{(k_2/k_1) + S}$$

<u>Michaelis-Menten Type</u>

Tyson et al (2003), Curr Opin Cell Biol, 15, 221ff

Sigmoidal Responses

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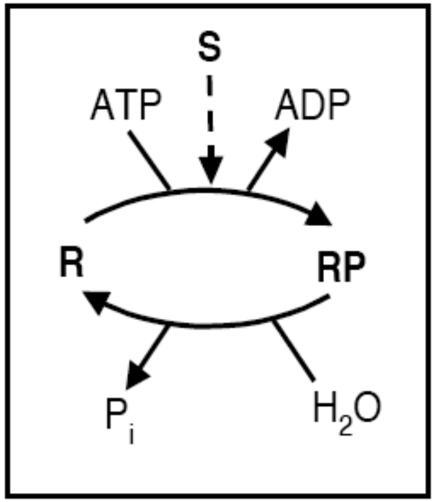
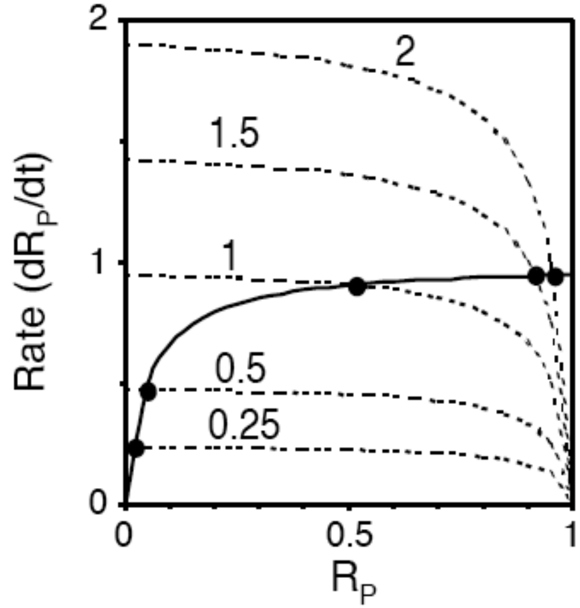




$$\frac{dR_P}{dt} = \frac{k_1 S(R_T - R_P)}{K_{m1} + R_T - R_P} - \frac{k_2 R_P}{k_{m2} + R_P}$$

Tyson et al (2003), Curr Opin Cell Biol, 15, 221ff

Sigmoidal Responses - 'Goldbeter-Koshland' function

$$\frac{dR_P}{dt} = \frac{k_1 S(R_T - R_P)}{K_{m1} + R_T - R_P} - \frac{k_2 R_P}{k_{m2} + R_P}$$

Steady-state condition:

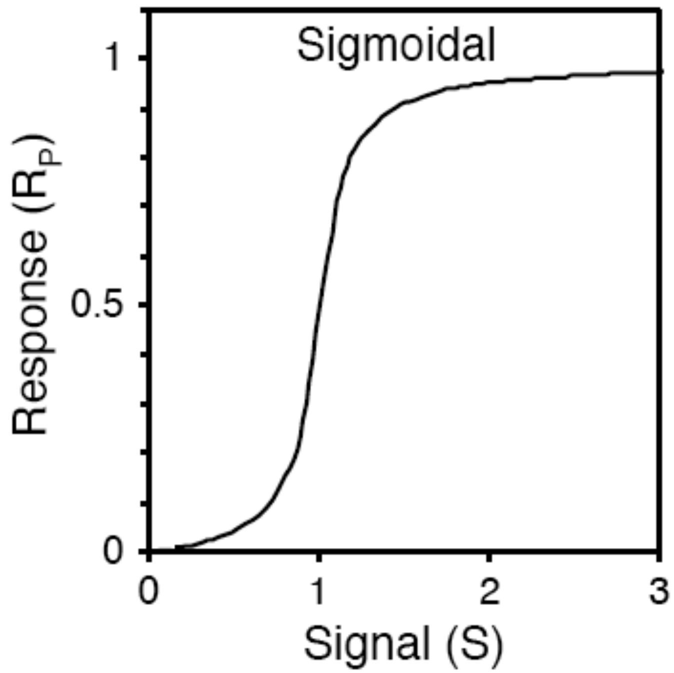
$$k_1 S(R_T - R_P)(K_{m2} + R_P) = k_2 R_P(K_{m1} + R_T - R_P)$$

Biophysically acceptable solution :

$$\frac{R_{P_{ss}}}{R_T} = G(k_1, k_2 S, \frac{K_{m1}}{R_T}, \frac{K_{m2}}{R_T})$$

with

$$G(u,v,J,K) = \frac{2uK}{v - u + vJ + uK + \sqrt{(v - u + vJ + uK)^2 - 4(v-u)uK}}$$



Hill Type (cooperative, allosteric regulation)

Tyson et al (2003), Curr Opin Cell Biol, 15, 221ff

COUPLED SYSTEMS

Example: Protein Expression

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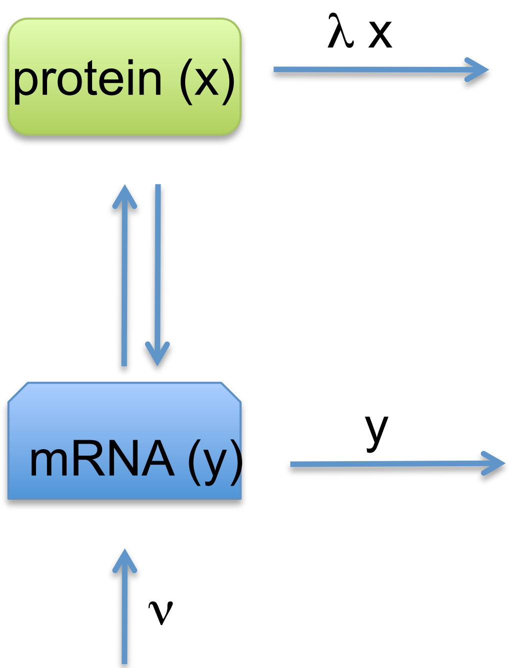
Reaction scheme



Equations

$$\frac{dx}{dt} = y - \lambda x$$

$$\frac{dy}{dt} = \nu + x - y$$

Nullclines

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Equations

$$\frac{dx}{dt} = y - \lambda x$$

$$\frac{dy}{dt} = \nu + x - y$$

Nullclines

$$y = \lambda x$$

$$y = \nu + x$$

Steady States

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Nullclines

$$y = \lambda x$$

$$y = \nu + x$$

Steady states are given by the intersection of the nullclines

$$x = \frac{\nu}{\lambda - 1}$$

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Equations

$$\frac{dx}{dt} = y - \lambda x$$

$$\frac{dy}{dt} = \nu + x - y$$

Nullclines

$$y = \lambda x$$

$$y = \nu + x$$

Steady State

$$x = \frac{\nu}{\lambda - 1}$$

Stability of Steady States - graphical

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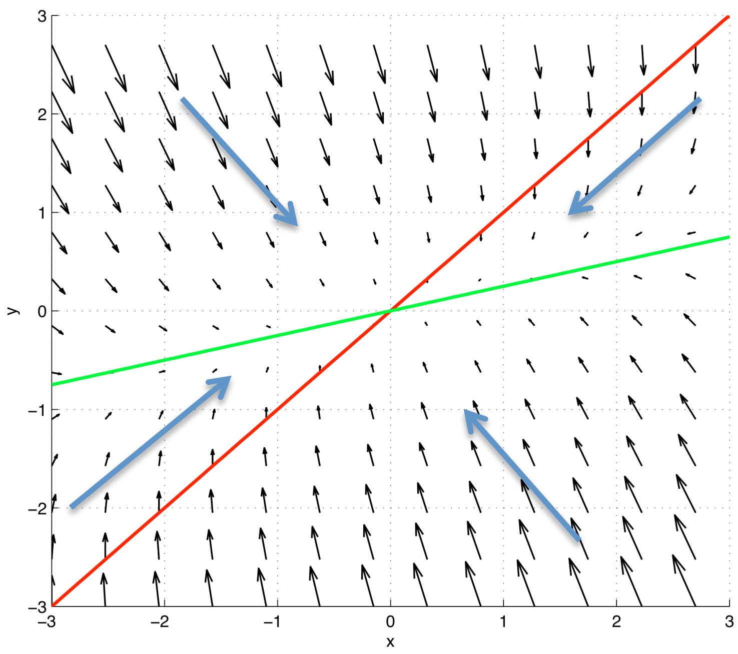
Equations

$$\frac{dx}{dt} = y - \lambda x$$

$$\frac{dy}{dt} = \nu + x - y$$



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Quiver plot

- shows tangent vectors to the trajectories
- Length denotes speed

$$\frac{dx}{dt} = y - \lambda x$$

$$\frac{dy}{dt} = \nu + x - y$$

Matlab Code

```
[x,y]=meshgrid(-3:0.475: 3, -3:0.475:3);
z1=-x+y;
z2= x-0.25*y;
quiver(x,y,z1,z2, 'k')
grid

Nullclines
x1 = linspace(-3, 3)
x2 = linspace(-1, 1)
plot(x1,x1, 'r')   %nullcline for x1
plot(x2, 4*x2, 'g') %nullcline for x2
```

Stability of Steady States - algebraic

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1. Rewrite set of ODE as

$$\dot{x} = \begin{bmatrix} a_{11} & a12 \\ a_{21} & a22 \end{bmatrix} x + \begin{pmatrix} b_1 \\ b_2 \end{pmatrix} = Ax + b$$

2. Determine steady states

$$\dot{x} = Ax + b = 0 \qquad Ax = -b$$

3. Determine eigenvalues

$$|Ax - \lambda I| = 0$$

For details see script!

Characteristic polynomial

$$P(\lambda) = \lambda^2 + a_1\lambda + a_0$$

Steady State Classification

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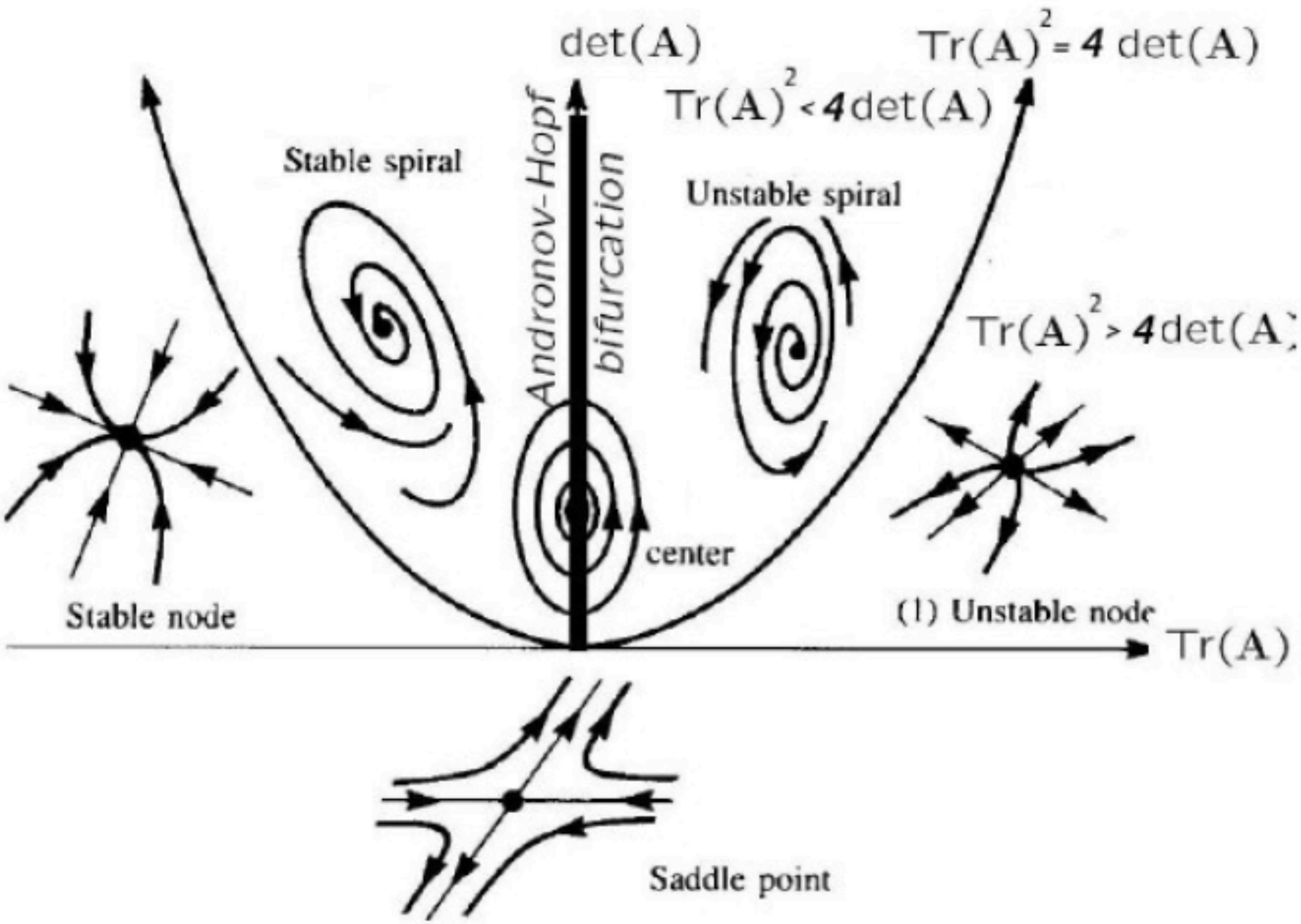

Higher dimensional systems

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$$\dot{x} = \begin{bmatrix} a_{11} & \cdots & a_{1n} \\ \vdots & \ddots & \vdots \\ a_{n1} & \cdots & a_{nn} \end{bmatrix} x + \begin{pmatrix} b_1 \\ \vdots \\ b_n \end{pmatrix} = Ax + b$$

1. Determine steady states

$$\dot{x} = Ax + b = 0 \qquad Ax = -b$$

2. Determine eigenvalues

$$|Ax - \lambda I| = 0$$

Characteristic polynomial

$$P(\lambda) = \lambda^n + a_1 \lambda^{n-1} + \ldots + a_n$$

Descartes' Rule of Signs

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Consider the polynomial $P(\lambda) = \lambda^n + a_1\lambda^{n-1} + ... + a_n = 0$

Let N be the number of sign changes in the sequence of coefficients $\{a_n, a_{n-1},...,a_o\}$, ignoring any that are zero.

Then there are at most N roots of P(λ) which are real and positive, and further, there are N, N-2 or N-4, ... real positive roots.

By setting $\omega=-\lambda$ and again applying this rule, information is obtained about possible negative roots.

Ruth-Hurwitz condition

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- Provides necessary and sufficient condition that the real parts of all eigenvalues are negative
- Derived using complex variable methods

The real parts of all zeros of P(λ)

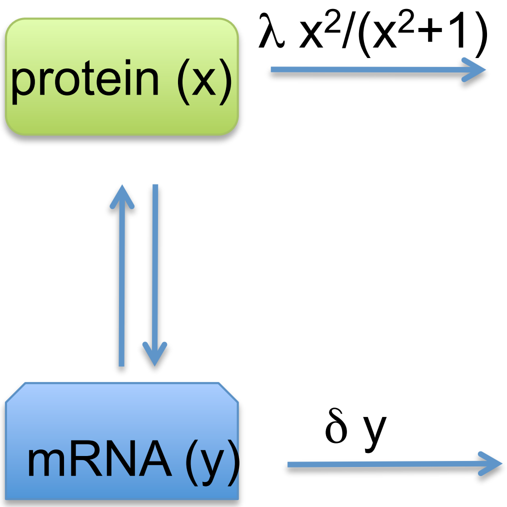
$$P(\lambda) = \lambda^n + a_1\lambda^{n-1} + ... + a_n = 0$$

are negative as long as the following condition is met for all i = 0, 1,…, n

$$D_k = \begin{vmatrix} a_1 & a_3 & \cdot & \cdot & \cdot & \cdot \\ 1 & a_2 & a_4 & \cdot & \cdot & \cdot \\ 0 & a_1 & a_3 & \cdot & \cdot & \cdot \\ 0 & 1 & a_2 & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ 0 & 0 & \cdot & \cdot & \cdot & a_k \end{vmatrix} > 0, k = 1, 2, ..., n$$

NONLINEAR DYNAMICS

Reaction scheme



Equations

$$\frac{dx}{dt} = y - \lambda \frac{x^2}{x^2+1}$$

$$\frac{dy}{dt} = x - y$$

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Equations

$$\frac{dx}{dt} = y - \lambda \frac{x^2}{x^2 + 1}$$

$$\frac{dy}{dt} = x - y$$

Nullclines

$$y = \lambda \frac{x^2}{x^2 + 1}$$

$$y = x$$

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Nullclines

$$y = \lambda \frac{x^2}{x^2 + 1}$$

$$y = x$$

Steady states are given by the intersection of the nullclines

$$x = \lambda \frac{x^2}{x^2 + 1}$$

Solve the cubic polynomial…
… or take a graphical approach

Phase Plane Analysis

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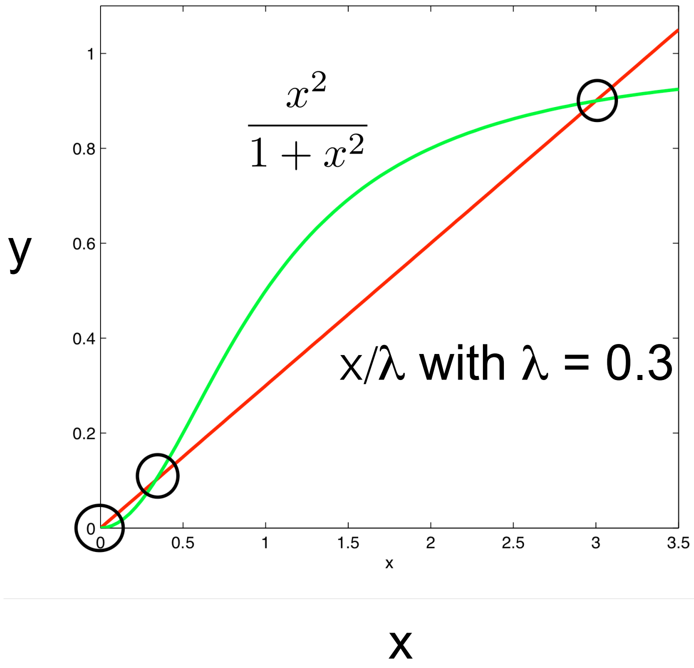
Equations

$$\frac{dx}{dt} = y - \lambda \frac{x^2}{x^2 + 1}$$

$$\frac{dy}{dt} = x - y$$



Stability of Steady States - graphical

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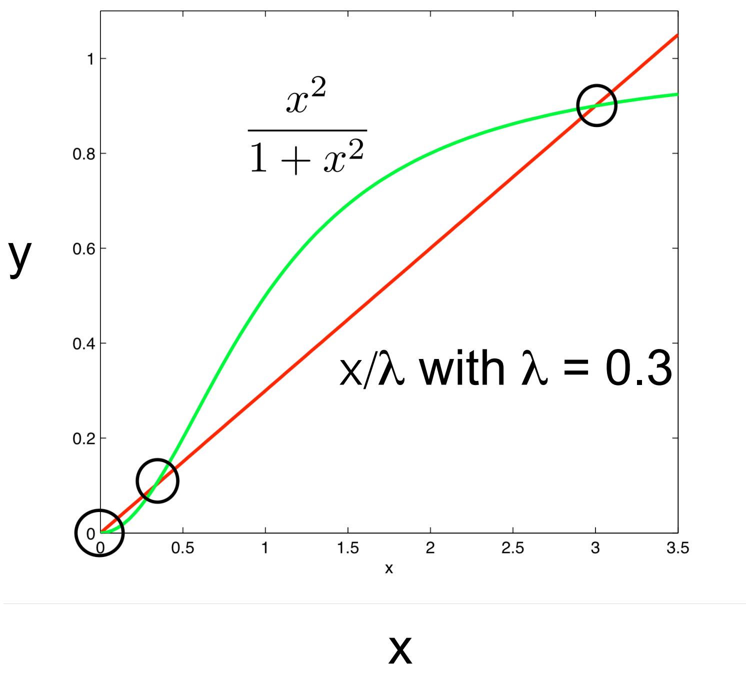
Equations

$$\frac{dx}{dt} = y - \lambda \frac{x^2}{x^2+1}$$

$$\frac{dy}{dt} = x - y$$



Stability of Steady States - algebraic

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Linear Stability Analysis

- Linearize system at ODEs at all steady states
- Proceed as before with linear system
- For details see script

Eigenvalues

Symbolic Toolbox in Matlab

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Definitions

- Define symbolic matrices and vectors `A = sym([8/9 1/2 1/3; 1/2 1/3 1/4; 1/3 1/4 1/5])`
- Convert a matrix to symbolic format by writing `A = sym(A)`
- Define symbolic variables as `syms x`

Linear Algebra

- Determine eigenvectors and eigenvalues with `[T, E]=eig(A)`
- Determine determinant with `det(A)`
- Solve linear system of equation `Ax = b` by writing `x = A\b`

BIFURCATION

Multiple steady states

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Reaction Scheme

$$\frac{dx}{dt} = \nu + \frac{x^2}{1+x^2} - \delta x$$

Steady States

$$\frac{dx}{dt} = 0 \qquad \nu + \frac{x^2}{1+x^2} - \delta x = 0$$

Would need to solve cubic polynomial to determine steady states.

It is easier to use a graphical approach.

Graphical Analysis

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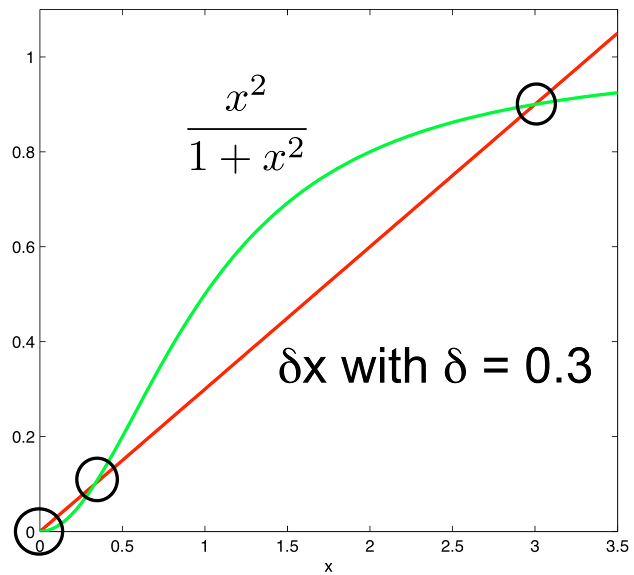
Reaction scheme

$$\frac{dx}{dt} = \nu + \frac{x^2}{1+x^2} - \delta x$$

Graphical Representation



3 steady states

Stability of Steady States

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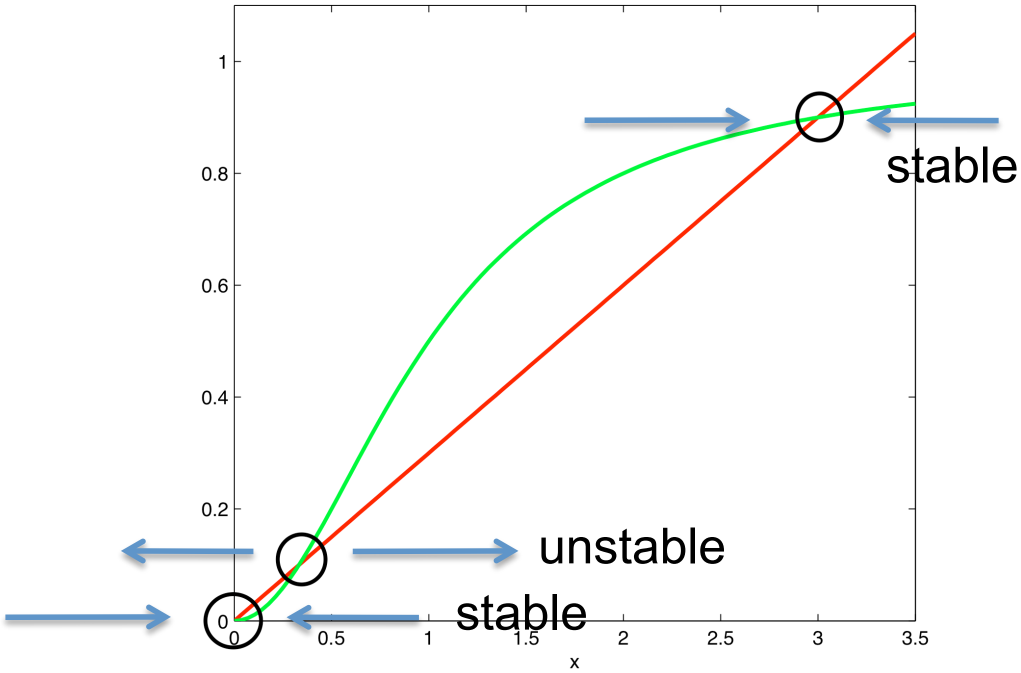
Definition

A steady state is stable if the system returns to the steady state upon a perturbation.

$$\frac{dx}{dt} = \nu + \frac{x^2}{1+x^2} - \delta x$$

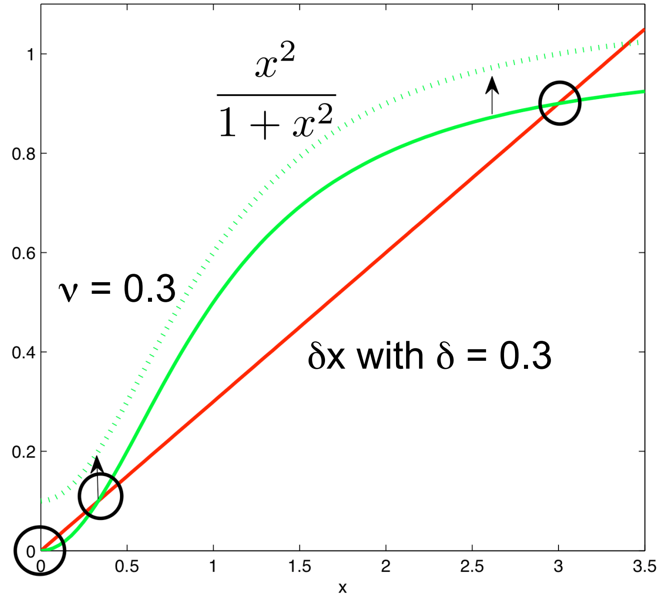


Impact of perturbations

Reaction scheme

$$\frac{dx}{dt} = \nu + \frac{x^2}{1+x^2} - \delta x$$

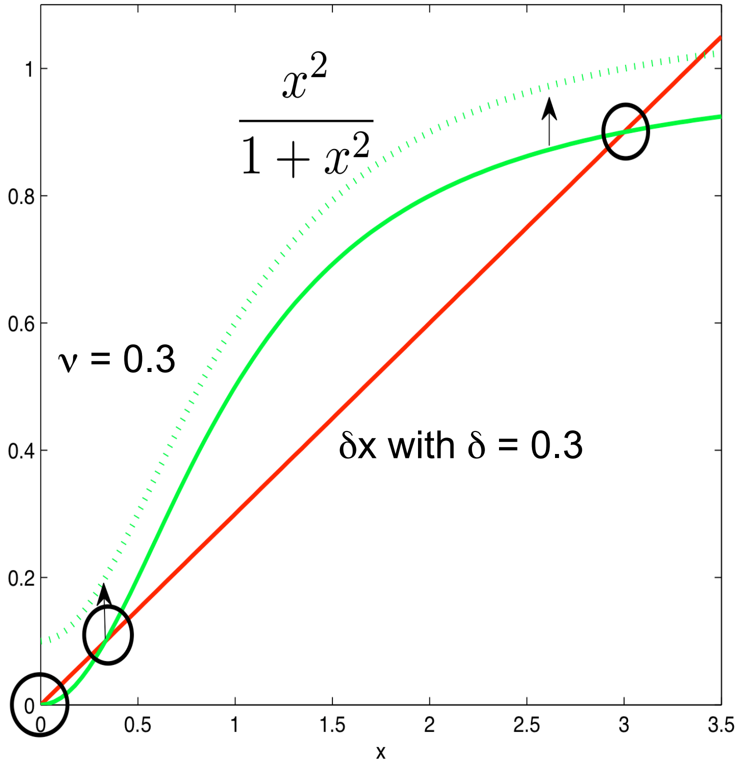
Graphical Representation



2 steady states disappear as
ν increases from 0 to 0.1

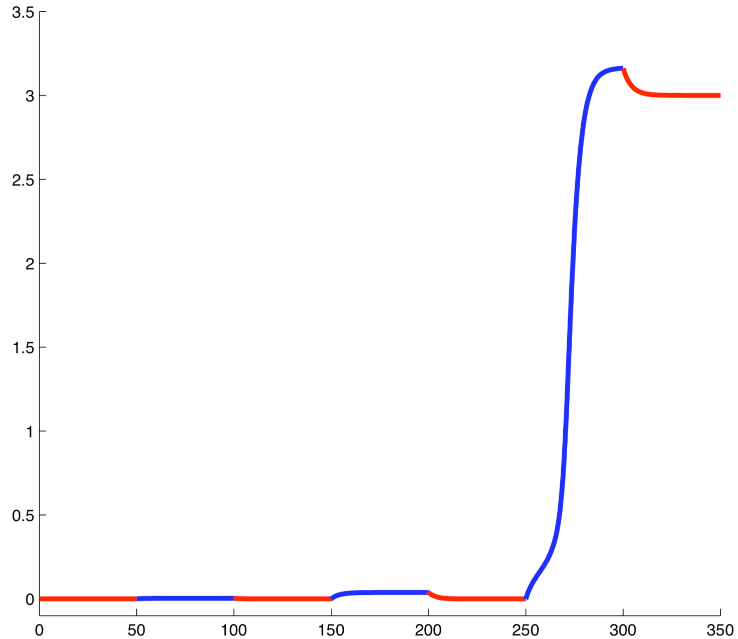
Impact of perturbations

Graphical Analysis



$$\frac{dx}{dt} = \nu + \frac{x^2}{1+x^2} - \delta x$$

Impact of perturbation ν



$\nu = 0,\ 10^{-3},\ 0\ ,\ 10^{-2},\ 0,\ 0.04,\ 0$

Example: Control of Xenopus oocyte maturation

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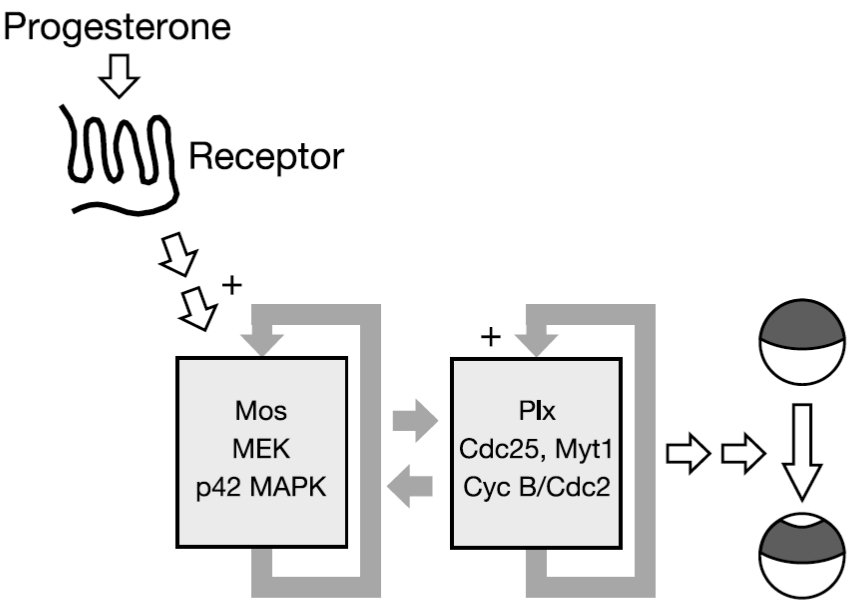
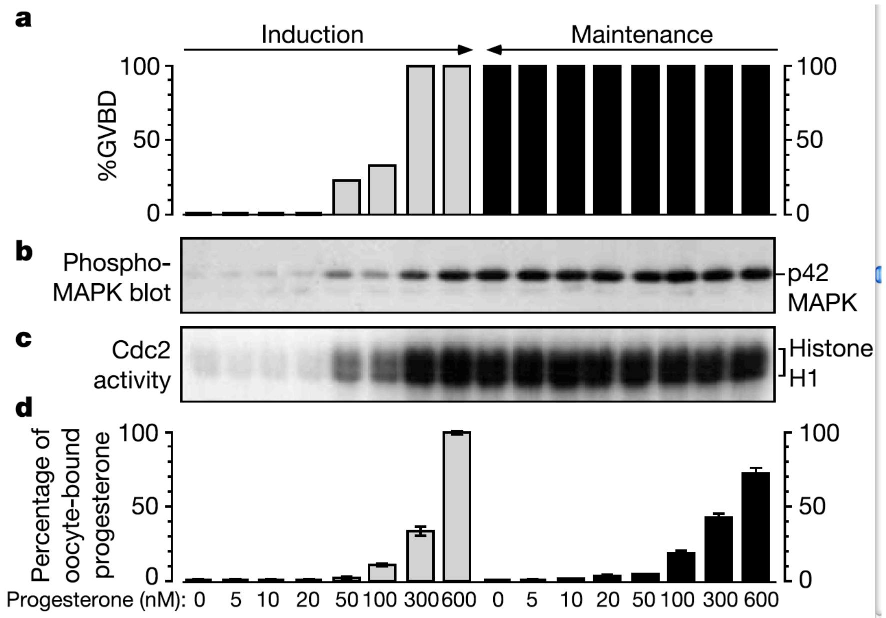
Network



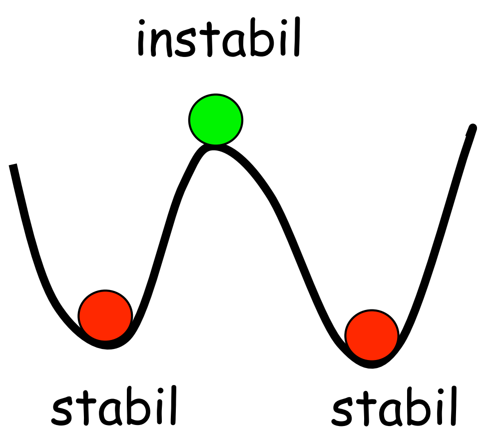
Wash-out experiments



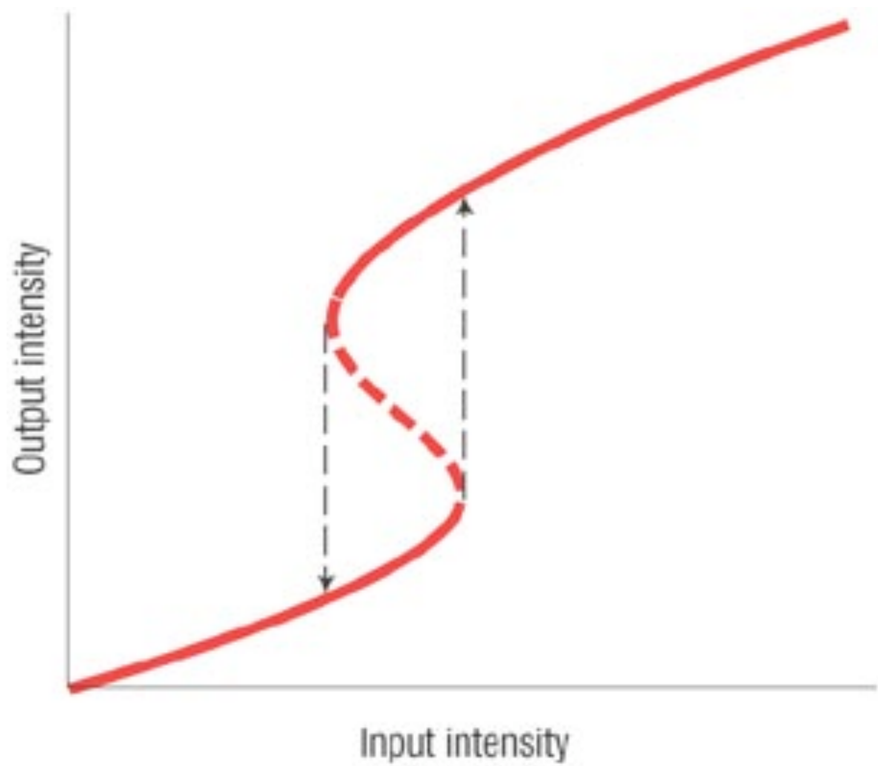
Wen Xiong & James E. Ferrell Jr (2003) Nature

Hysteresis – a bistable switch

A bistable switch



Bifurcation Diagram



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Bifurcation Parameter

As the value of a bifurcation parameter is changed the stability of at least one equilibrium point changes

Bifurcation Diagram

- Determine the stability of each steady state over a range of the bifurcation parameter
- Plot the values of the steady states and indicate the stability of the steady states

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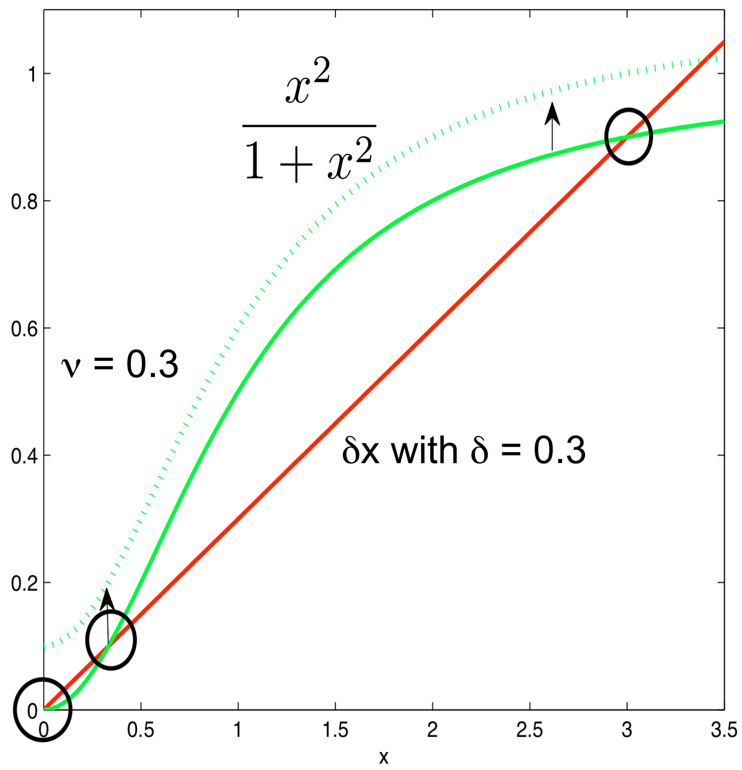
Saddle-Node

- Occurs when two fixed points collide and annihilate each other



Bifurcation Types II

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Transcritical Bifurcation

- At least one steady state changes its stability
- In the example, this is the case for r = 0

Example

$$\frac{dx}{dt} = rx - x^2.$$

Bifurcation Types III

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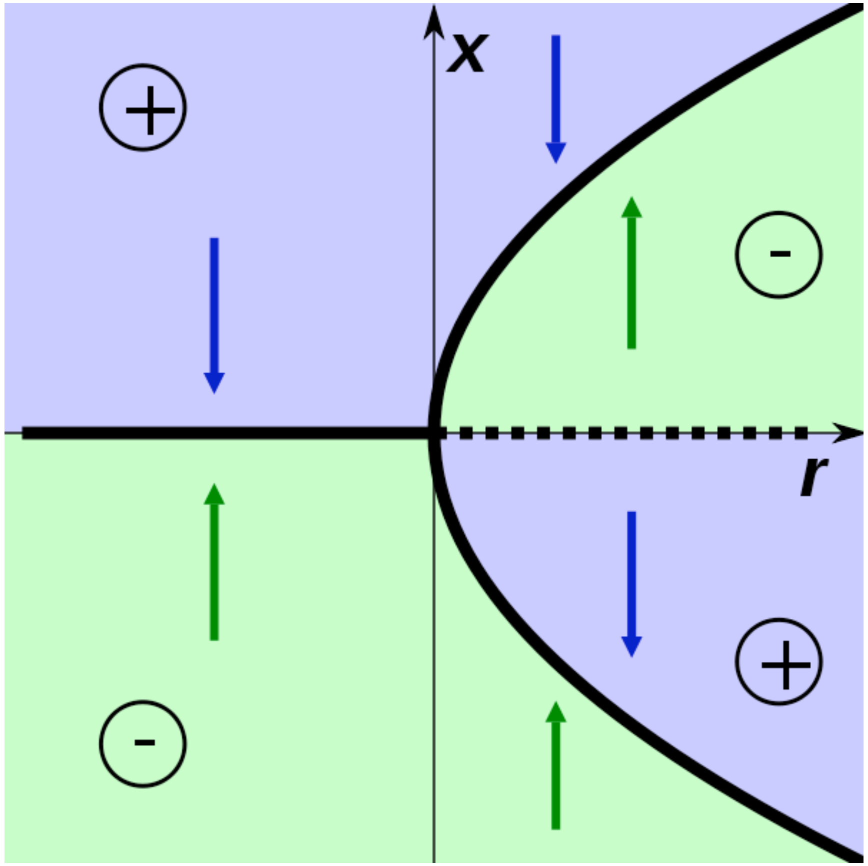
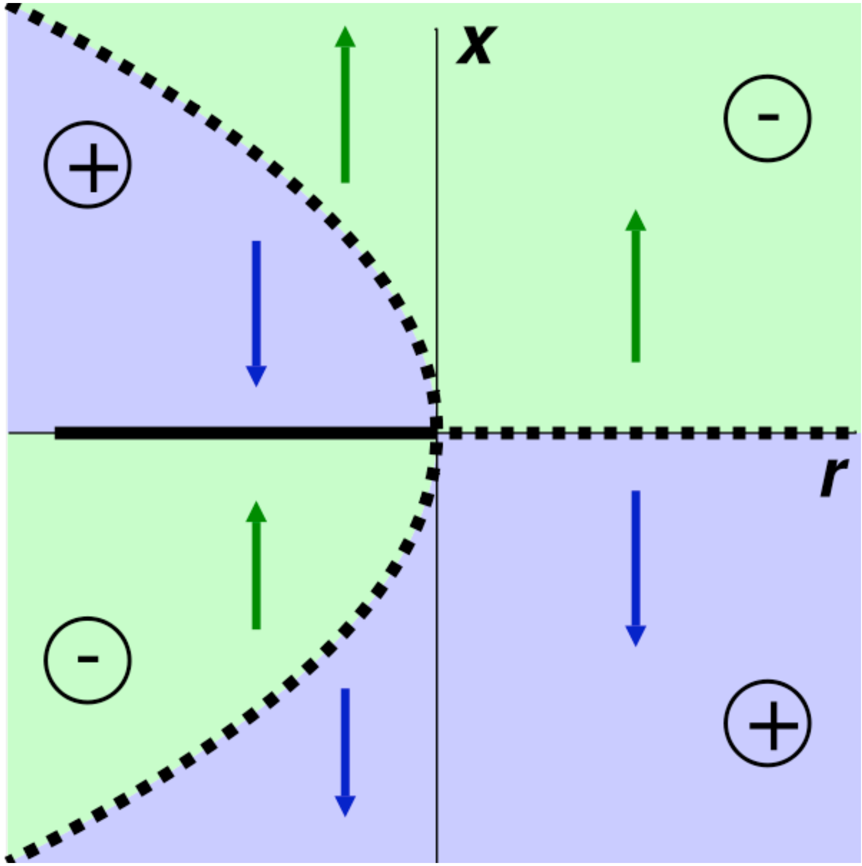
Pitchfork (supercritical)



Pitchfork (subcritical)

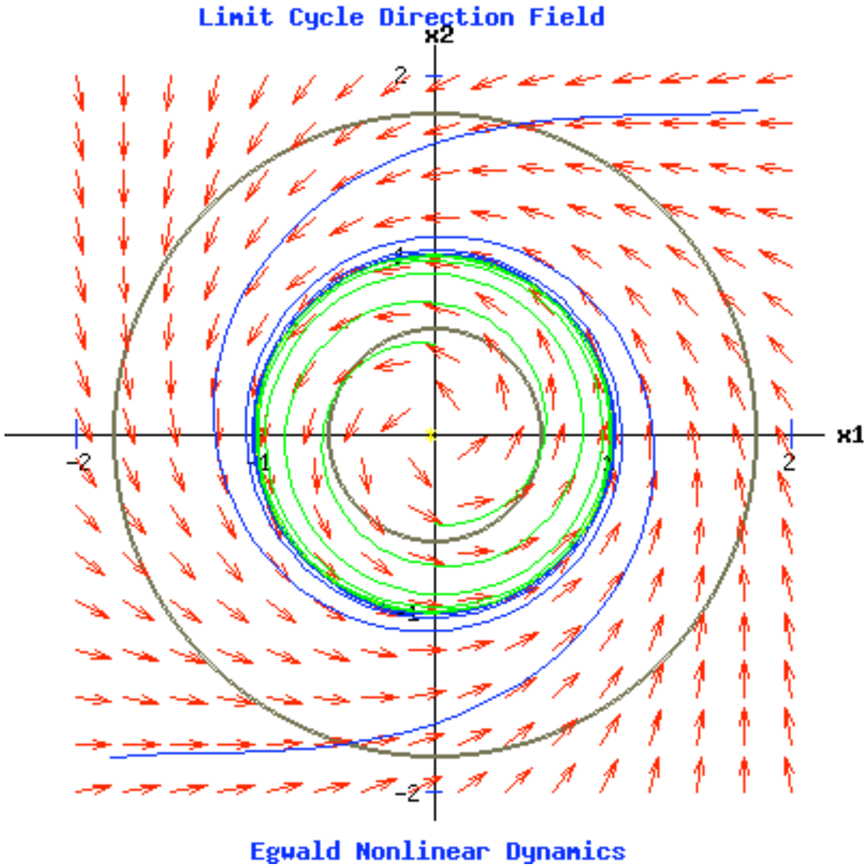


Bifurcation Type IV

Hopf Bifurcation

- Imaginary part of eigenvalues becomes non-zero
- Limit cycles (oscillations)

Phase Plane



Summary

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- Steady states (graphical)
- Phase Plane Analysis
  - Steady states
  - Nullclines
  - Phase vector diagram
- Stability of steady states
  - Characteristic polynomial
  - Stable & unstable node
  - Saddle point
  - Spiral
  - center
- Linearization of non-linear systems
  - Jacobian
- Bifurcations
  - Saddle node
  - Transcritical
  - Pitchfork
  - Hopf