

Modelling in Biology

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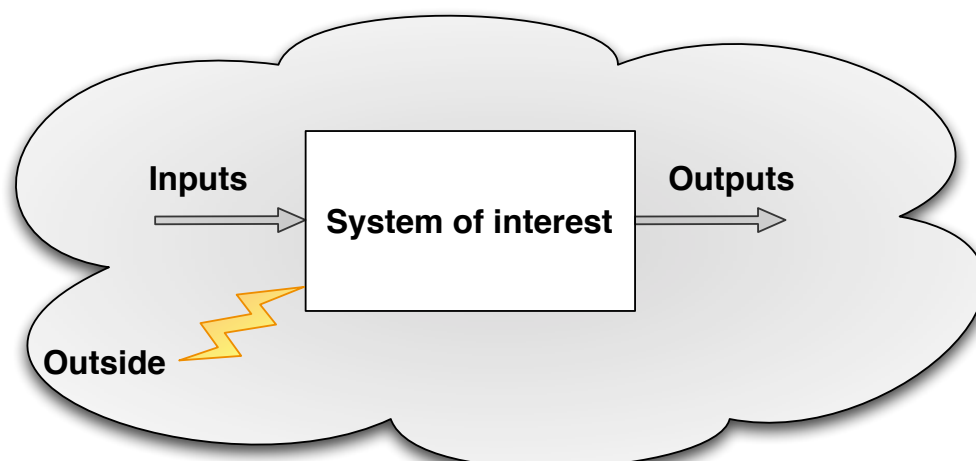
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Essential features of a modelling approach

Isolate your system of interest.

- What is important? This defines your “system of interest”
- What can be measured? What are the “observables”? This defines the “outputs” of the system.
- What can be controlled or acted upon? This defines the “inputs” of the system.



Modelling of the system of interest

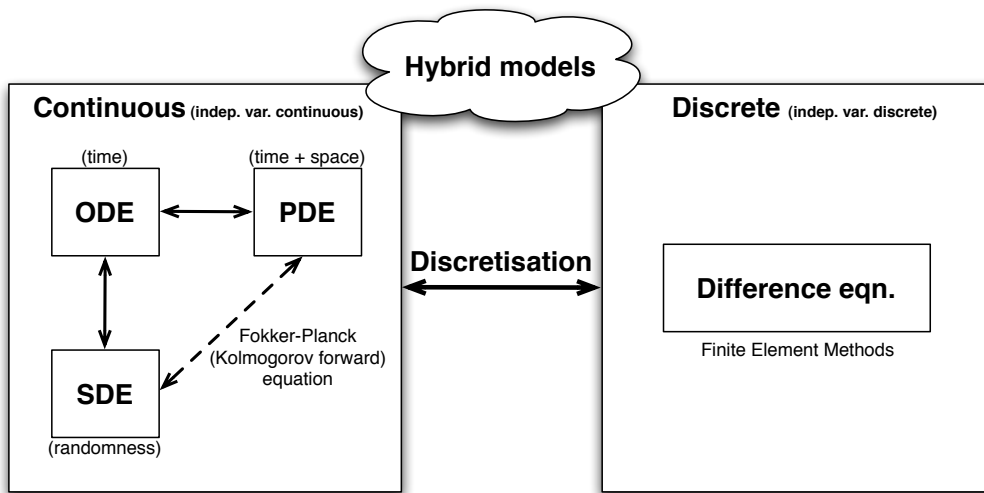
Typically, the model is composed of

- variables
 - ▶ independent, e.g., time t
 - ★ 1 indep. var.: ODEs, e.g., time t
 - ★ more than 1 indep. var.: PDEs, e.g., time t and space (x, y, z)
 - ▶ dependent
 - e.g., concentrations functions of time $\{[E](t), [S](t), [P](t)\}$
 - parameters
 - ▶ not dependent on independent variables
 - ▶ can be varied/changed under experimental conditions
 - constants
 - ▶ fixed, e.g., Avogadro constant, gravitational constant
- ⇒ Different types of models

Types of models

Continuous	Discrete
<ul style="list-style-type: none"> ● the independent variables are continuous ● ODEs, PDEs 	<ul style="list-style-type: none"> ● the independent variables are discrete ● Difference equations
Deterministic	Stochastic
<ul style="list-style-type: none"> ● var., param. and const. do not contain randomness ● they are defined by a unique function 	<ul style="list-style-type: none"> ● dynamics contain an element of randomness ● e.g., SDEs
Linear	Nonlinear
<ul style="list-style-type: none"> ● $\dot{x} = \frac{dx}{dt} = -kx$ ● Linear ODE 	<ul style="list-style-type: none"> ● $\dot{x} = \frac{dx}{dt} = -kx + x^3$ ● Nonlinear ODE
Autonomous	Non-autonomous
<ul style="list-style-type: none"> ● Without control input: $\dot{x} = -kx$ 	<ul style="list-style-type: none"> ● With control input: $\dot{x} = -kx + u$
Constructive	Data-driven
<ul style="list-style-type: none"> ● mechanistic or deductive ● also called “equation-based” or “(first) principle-based” 	<ul style="list-style-type: none"> ● phenomenological or inductive

Summary



Continuous	ODEs	PDEs	Deterministic (L or NL)
	SDEs		Stochastic (L or NL)
Discrete	Difference equations		Deterministic (L or NL)
			Stochastic (L or NL)

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A deterministic, continuous, linear model of order 1

Consider

$$\dot{x}(t) = \frac{dx(t)}{dt} = kx(t)$$

- Linear ODE.
- For $k > 0$, this is known as the *Malthusian population growth* with k denoting the growth rate *per cell*.

Analytical solution of 1st order linear ODEs

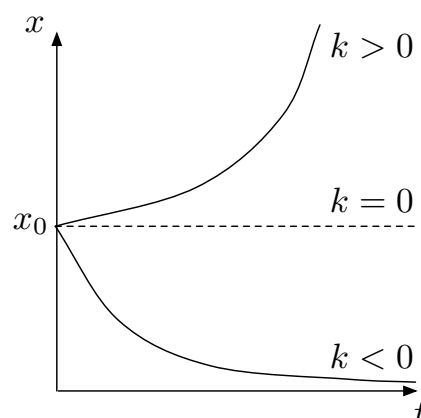
Consider the model:

$$\dot{x} = \frac{dx}{dt} = kx, \quad x(0) = x_0 \quad (1)$$

Its solution is given by

$$x(t) = x_0 e^{kt}$$

where $x_0 = x(0)$ (the initial condition).



Numerical solution of ODEs: the Euler algorithm

$$\frac{dx}{dt} = kx$$

$$\Leftrightarrow \boxed{\lim_{\Delta t \rightarrow 0} \frac{x(t + \Delta t) - x(t)}{\Delta t} = kx(t)}$$

Suppose Δt is fixed to a particular value h (doing this is called *discretising* the continuous ODE model and h is called the *discretisation step*). We then have:

$$\frac{x(t + h) - x(t)}{h} \approx kx(t)$$

$$\boxed{x(t + h) \approx x(t) + hkx(t)} \quad (2)$$

Eq. (2) is known as the “Euler algorithm”.

Linear difference equation

$$x(t + h) = x(t) + hkx(t)$$

is a discrete-time model which can also be looked at as a linear *difference equation* by taking $h = 1$, and defining for ease of notation $x_t = x(t)$:

$$\boxed{x_{t+1} = \underbrace{(1 + k)}_{\alpha} x_t = \alpha x_t} \quad (3)$$

(or equivalently $x_{t+1} - x_t = (\alpha - 1)x_t$.)

Its non-zero solution is given by

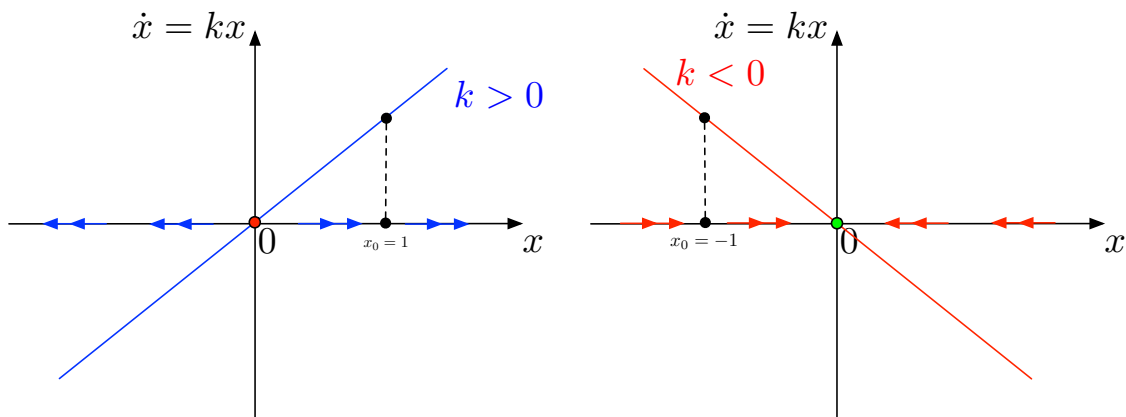
$$\boxed{x_t = x_0 \alpha^t}$$

where x_0 is the initial condition.

Phase plane

- The phase plane (a.k.a. phase space) is a representation that eliminates time as an explicit variable.
- It is very useful for obtaining a qualitative understanding of the long-term or *asymptotic* behaviour of *nonlinear* ODE models (for which, typically, analytical solutions cannot be found).

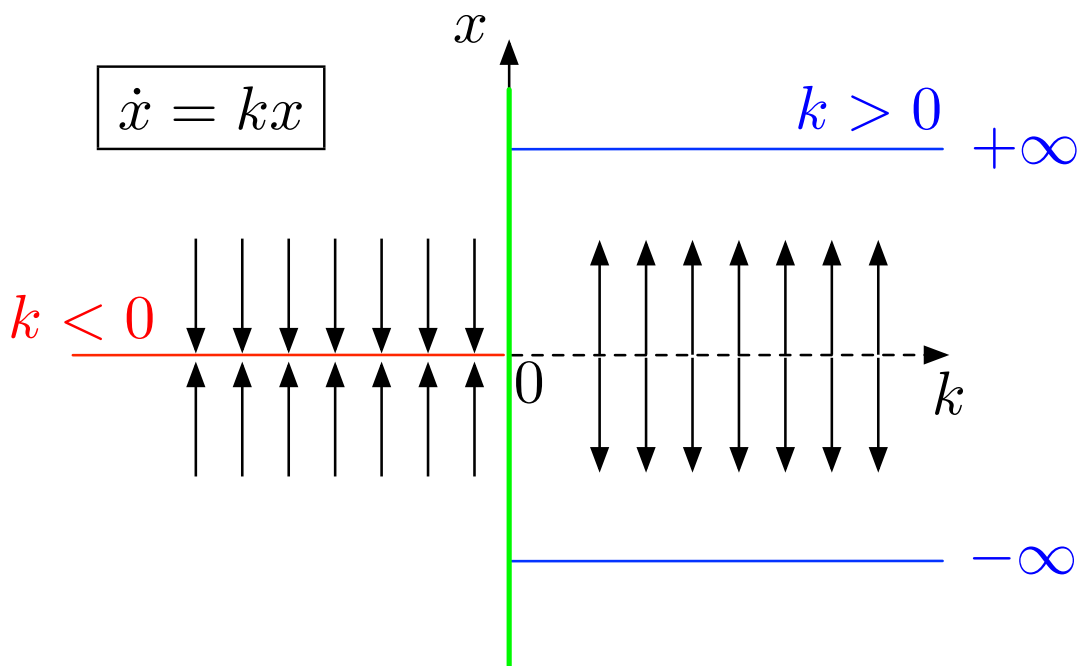
Consider $\dot{x} = kx$



$\dot{x} = kx$

Bifurcation diagram

We can summarise the information obtained through the phase plane stability analysis on a *bifurcation diagram*, i.e., a diagram giving the long-term (i.e., asymptotic) behaviour of the system when a parameter is varied. Here the parameter for the ODE model $\dot{x} = kx$ is k .



SDEs of order 1

Consider a stochastic version of the Malthusian growth model:

$$\frac{dx}{dt} = kx + \eta \quad (4)$$

where η is a random variable that represents some *uncertainties* or *stochastic effects* perturbing the system.

Eq. (4) is known as a *Langevin equation*.

Eq. (4) can also be rewritten as

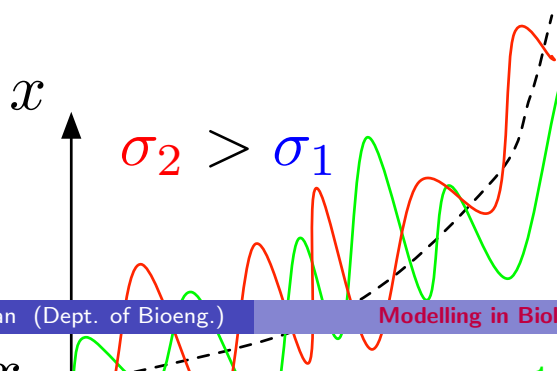
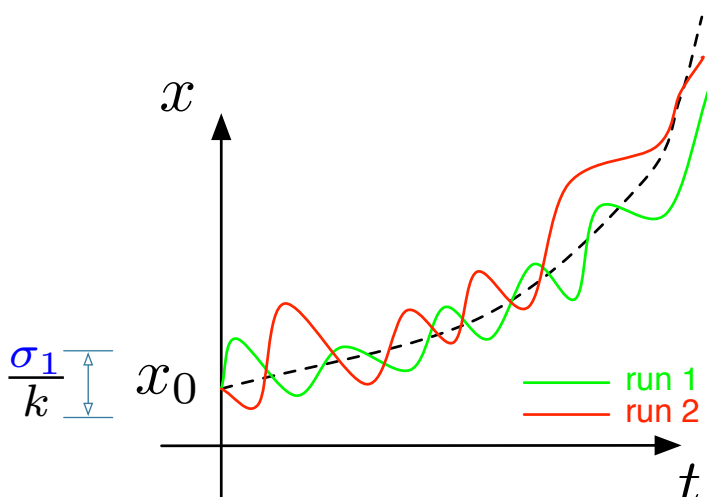
$$dx = [kx]dt + \underbrace{\eta dt}_{\approx \sigma dw} \quad (5)$$

where w represents a standard (one-dimensional) *Wiener process* (also called *Brownian motion*)

SDEs such as (5) are typically solved numerically through discretisation using the Euler algorithm:

$$x(t + \Delta t) = \underbrace{[1 + k\Delta t]x(t)}_{\text{deterministic part}} + \underbrace{(\sigma\sqrt{\Delta t}) \text{randn}}_{\text{stochastic part}}$$

SDE of order 1 (cont')



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Nonlinear ODE models of order 1

First order nonlinear ODE models are written under the generic form:

$$\dot{x} = f(x), \quad x \in \mathbb{R}, \quad f(\cdot) : \mathbb{R} \rightarrow \mathbb{R}, \quad \text{“smooth” function} \quad (6)$$

Finding the analytical solution of (6), i.e., finding $x(t, x_0)$, is, in general, no longer possible unless a closed form solution can be obtained for

$$\int \frac{1}{f(x)} dx = \int dt.$$

Non-Malthusian population growth: the logistic equation

We consider the *non-Malthusian population growth* model in which the reproduction rate takes into account the “competition for resources”. Consider that $x(t)$ represents the number of cells at time instant t .

$$\dot{x} = \overbrace{rx \left(1 - \frac{x}{k}\right)}^{=f(x)} = \left(\underbrace{r \left(1 - \frac{x}{k}\right)}_{\text{non-constant growth rate per cell}} \right) x = \underbrace{rx}_{\text{“growth rate”}} - \underbrace{\frac{rx^2}{k}}_{\text{“death rate”}} \quad (7)$$

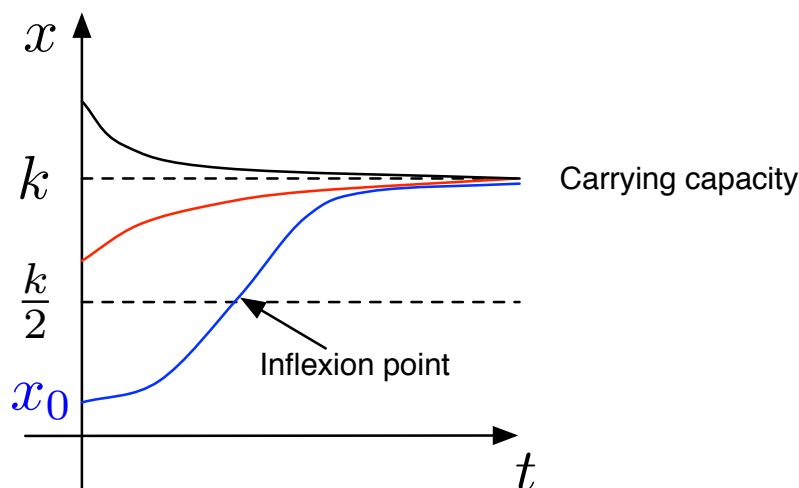
In this particular case and rather exceptionally, a closed form solution to (7) can be found:

$$x(t) = \frac{k}{1 + \frac{1}{C} e^{-rt}}, \quad C = \frac{x_0}{k - x_0}$$

This solution indicates that $x \rightarrow k$ as $t \rightarrow \infty$.

The logistic equation

Time solution: $x(t) = \frac{k}{1 + \frac{1}{C} e^{-rt}}, \quad C = \frac{x_0}{k - x_0}$



Stability analysis of the logistic equation

$$\dot{x} = rx \left(1 - \frac{x}{k}\right)$$

- Fixed points and flow:

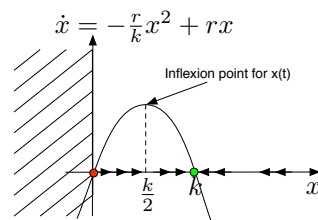
- Fixed points: $\dot{x}|_{x=x^*} = 0 \Leftrightarrow f(x^*) = 0$

- Here, $f(x^*) = rx^* \left(1 - \frac{x^*}{k}\right) = 0 \Rightarrow \begin{cases} x^* = 0 \\ x^* = k \end{cases}$

- Flow:

$$\begin{cases} 0 < x < k \Rightarrow \dot{x} > 0 \Rightarrow x \nearrow \\ x > k \Rightarrow \dot{x} < 0 \Rightarrow x \searrow \end{cases}$$

- Phase plane: \dot{x} vs x



- Asymptotic stability of fixed points: $x^* = 0$ is unstable

- $x^* = k$ is asymptotically stable, i.e.,

- stable
 - attractive

- Attractors: $x^* = k$

Stability analysis of nonlinear ODE models of order 1

Consider a nonlinear ODE model of order 1:

$$\dot{x} = f(x), \quad x \in \mathbb{R}, \quad f(\cdot) : \mathbb{R} \rightarrow \mathbb{R}, \quad \text{“smooth” function}$$

- Global stability analysis (only for models of order 1)

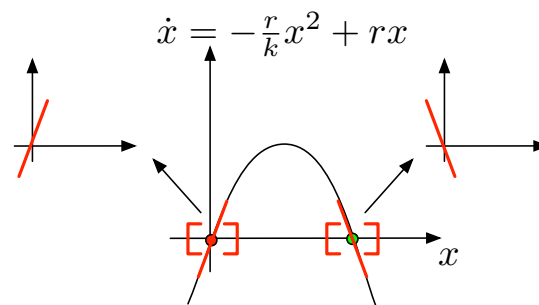
- Find all the fixed points: $\{x^* : f(x^*) = 0\}$ and put them on the phase line x of the plot \dot{x} vs x .
 - Find the flow between the fixed points and indicate them on the phase line x of the plot \dot{x} vs x .
 - Conclude what the stability of the fixed point(s) is.
 - Find the long-term behaviour of the system, i.e., its attractors.

- Local/linear stability analysis (possible for all orders)

- Find the fixed points.
 - Linearise the dynamics around *each* fixed point.
 - Study the stability of the corresponding linear systems ($\text{eig}(A)$).
 - Link together the local stability information around each fixed point to establish a complete picture of the attractors.

Linear stability analysis of ODE models of order 1

- Find the fixed points of the system: $f(x^*) = 0$.
- Examine the close neighbourhood of the fixed points, i.e., analyse the local stability of the fixed points by considering *small perturbations* around them.



Linear stability analysis of ODE models of order 1

Consider the dynamics of the system when x is “close to” the fixed point x^* , i.e., consider $\dot{x} = f(x)$ when $x = x^* + \xi$ with $\xi = (x - x^*)$ “small”, i.e., $|\xi| \ll 1$:

$$\begin{aligned} \frac{dx}{dt} &= \frac{d\xi}{dt} \\ &= f(x^* + \xi) \\ &= \underbrace{f(x^*)}_{=0} + \left. \frac{df}{dx} \right|_{x=x^*} \underbrace{\xi}_{\text{“small”}} + \underbrace{O(\xi^2)}_{\text{H.O.T. (“very small”)}} \quad (\text{Taylor series expansion}) \end{aligned}$$

So, we have:

$$\frac{d\xi}{dt} \approx \left. \frac{df}{dx} \right|_{x=x^*} \xi \quad (\text{linear system})$$

$$\Rightarrow \xi(t) \approx \xi_0 e^{\left. \frac{df}{dx} \right|_{x=x^*} t}$$

Local stability analysis (only two possibilities):

- $\left. \frac{df}{dx} \right|_{x=x^*} > 0 \Rightarrow \dot{\xi}\xi > 0 \Rightarrow |\xi| \nearrow \Rightarrow x = x^*$ is unstable
- $\left. \frac{df}{dx} \right|_{x=x^*} < 0 \Rightarrow \dot{\xi}\xi < 0 \Rightarrow |\xi| \searrow \Rightarrow x = x^*$ is locally asymptotically stable, i.e., locally stable and attractive

Linear stability analysis of the logistic equation

For $\dot{x} = rx \left(1 - \frac{x}{k}\right)$, we have $\frac{df}{dx} = r - \frac{2xr}{k}$

- $\frac{df}{dx} \Big|_{x=0} = r > 0 \Rightarrow \dot{\xi} \xi > 0 \Rightarrow |\xi| \nearrow \Rightarrow x = 0$ is unstable
- $\frac{df}{dx} \Big|_{x=k} = -r < 0 \Rightarrow \dot{\xi} \xi < 0 \Rightarrow |\xi| \searrow \Rightarrow x = k$ is locally asymptotically stable, i.e., locally stable and attractive

Bifurcations for nonlinear ODE models of order 1

Consider:

$$\dot{x} = f(x, r)$$

where r is a parameter and $f(\cdot) : \mathbb{R} \times \mathbb{R} \rightarrow \mathbb{R}$ is a “smooth” *function*.

Bifurcation

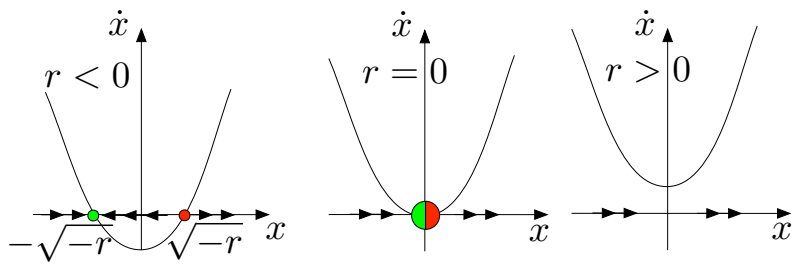
A bifurcation occurs when a change in the parameter(s) of the model produces a qualitative (or “large”) change in the long-term behaviour (of the attractors) of the system, e.g., :

- the number of attractors (e.g., fixed points) changes,
- the type of attractors changes (e.g., from fixed point to limit cycle),
- the stability of attractors (e.g., fixed points or limit cycles) changes.

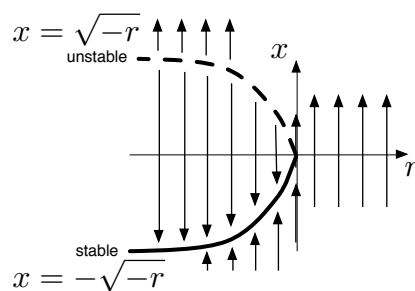
Saddle-node Bifurcation

$$\dot{x} = r + x^2, \quad x \in \mathbb{R}$$

Consider different values for the parameter r :



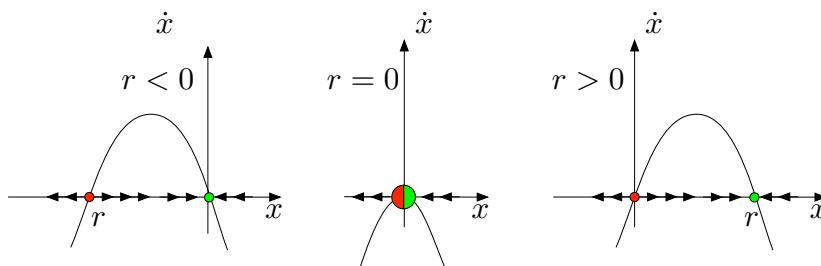
Saddle-node *bifurcation diagram*:



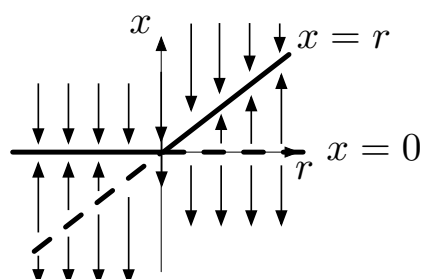
Transcritical Bifurcation

$$\dot{x} = rx - x^2 = x(r - x), \quad x \in \mathbb{R}$$

Consider different values for the parameter r :



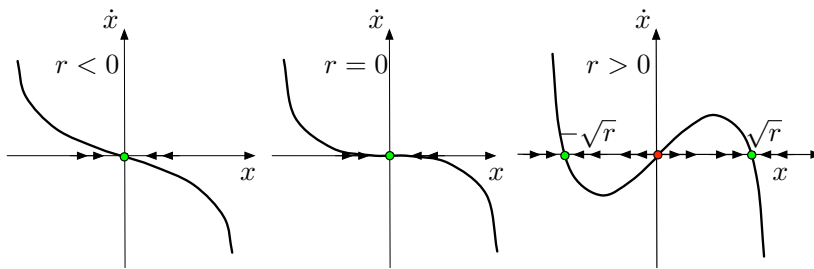
Transcritical bifurcation diagram:



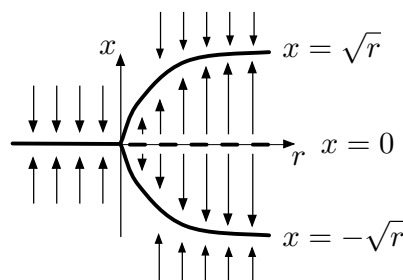
Pitchfork Bifurcation

$$\dot{x} = rx - x^3 = x(r - x^2), \quad x \in \mathbb{R}$$

Consider different values for the parameter r :



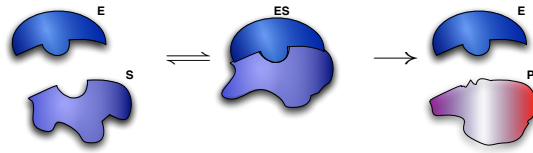
Pitchfork bifurcation diagram (supercritical):



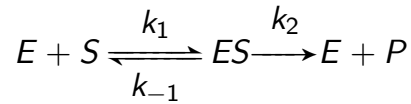
Summary of behaviours for NL ODE models of order 1

- Motions (solutions) are on the real line, i.e., $x \in \mathbb{R}$
- Attractors are either the fixed points or $\pm\infty$ (no oscillatory or other types of behaviour)
- Three types of bifurcation can occur:
 - ▶ Saddle node
 - ▶ Transcritical
 - ▶ Pitchfork (subcritical or supercritical)

Enzymatic reactions and the law of mass action



Enzymatic reaction:



Law of mass action: For a simple enzymatic reaction we have 4 species \Rightarrow 4 ODEs

$$\frac{d[ES]}{dt} = k_1[E][S] - k_{-1}[ES] - k_2[ES] \quad (8)$$

$$\frac{d[E]}{dt} = -k_1[E][S] + k_{-1}[ES] + k_2[ES] \quad (9)$$

$$\frac{d[S]}{dt} = -k_1[E][S] + k_{-1}[ES] \quad (10)$$

$$\frac{d[P]}{dt} = k_2[ES] \quad (11)$$

Elimination of variables – model reduction through time scale separation

1 Conservation laws

$$\blacktriangleright (8) + (9) \Rightarrow \frac{d[ES]}{dt} + \frac{d[E]}{dt} = 0$$

$$\Rightarrow [ES] + [E] = [E]_0 \quad (12)$$

$$\blacktriangleright (9) - (10) - (11) \Rightarrow \frac{d[E]}{dt} - \frac{d[S]}{dt} - \frac{d[P]}{dt} = 0$$

$$\Rightarrow [E] = [S] + [P] + \kappa \quad (13)$$

2 Quasi-stationary approximation (time scale separation)

$$\blacktriangleright \frac{d[ES]}{dt} \approx 0$$

$$\Rightarrow \boxed{\frac{d[S]}{dt} \approx -\frac{d[P]}{dt} \approx -V_{\max} \frac{[S]}{K_M + [S]}} \quad (\text{the Michaelis-Menten equation})$$

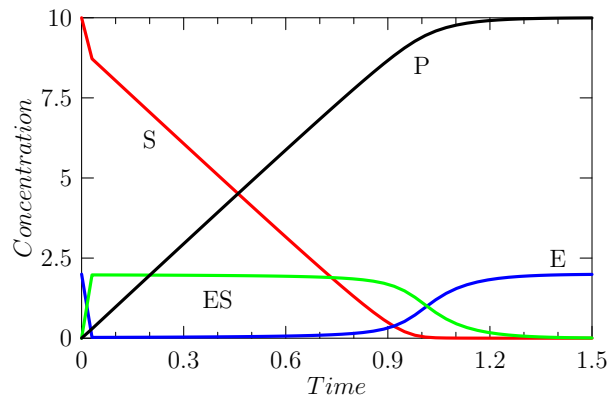
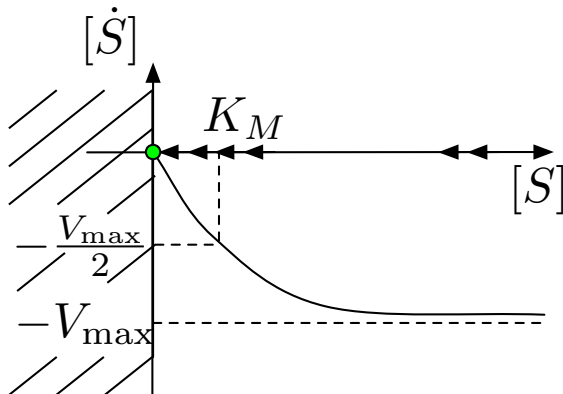
with

$$V_{\max} = k_2[E]_0, \quad K_M = \frac{k_{-1} + k_2}{k_1}$$

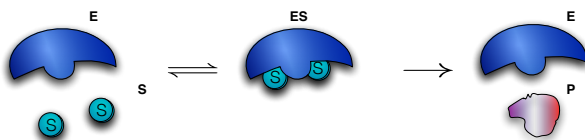
The Michaelis-Menten equation

$$\frac{d[S]}{dt} \approx -\frac{d[P]}{dt} \approx -V_{\max} \frac{[S]}{K_M + [S]}$$

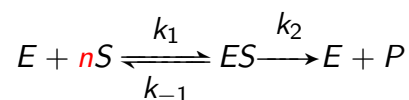
(the *Michaelis-Menten* equation)



Enzymatic cooperative reactions – The Hill equation



A model for the enzymatic reaction with cooperativity is:



where ES represents the enzyme- n -substrates complex and n is called the *cooperativity coefficient*.

Law of mass action: 4 species \Rightarrow 4 ODEs

$$\frac{d[ES]}{dt} = k_1[E][S]^n - k_{-1}[ES] - k_2[ES] \quad (14)$$

$$\frac{d[E]}{dt} = -k_1[E][S]^n + k_{-1}[ES] + k_2[ES] \quad (15)$$

$$\frac{d[S]}{dt} = n(-k_1[E][S]^n + k_{-1}[ES]) \quad (16)$$

$$\frac{d[P]}{dt} = k_2[ES] \quad (17)$$

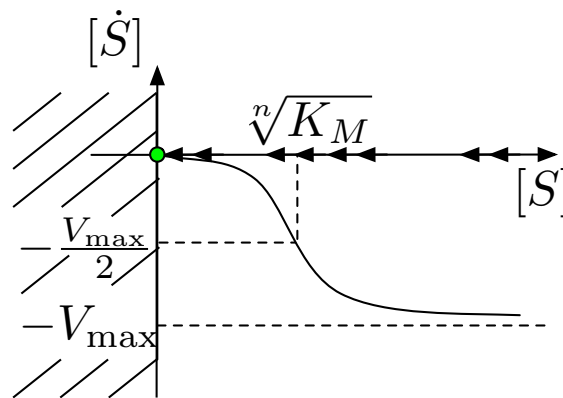
The Hill equation

Using a similar model reduction approach as for the non-cooperative enzymatic reactions we saw before (Michaelis-Menten), it is easy to see that the following 1st order nonlinear ODE model is obtained:

$$\frac{d[S]}{dt} \approx -\frac{d[P]}{dt} \approx -V_{\max} \frac{[S]^n}{K_M + [S]^n} \quad (\text{the Hill equation})$$

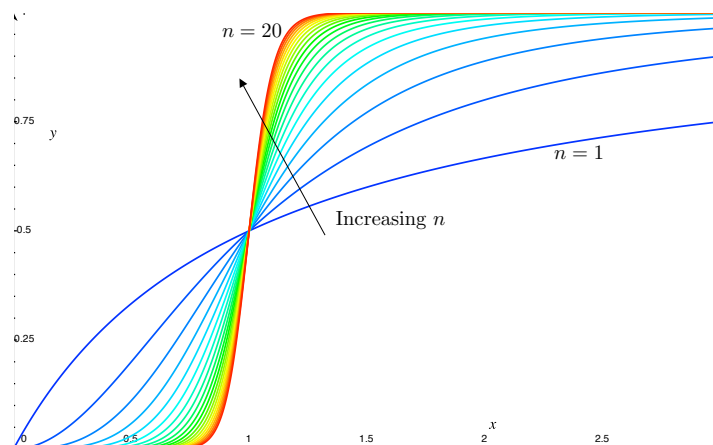
with

$$V_{\max} = nk_2[E]_0, \quad K_M = \frac{k_{-1} + k_2}{k_1}$$



The Hill equation: effect of the cooperativity coefficient n

The Hill function is defined as $h(x) = V_{\max} \frac{x^n}{K_M + x^n}$. The effect of the Hill coefficient n is illustrated hereafter for $V_{\max} = 1$ and $K_M = 1$:

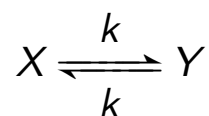


This is very useful for a cell which can then use this type of “step-regulated” reaction as a switch since for low concentrations (i.e., $x \leq \sqrt[n]{K_M}$) nothing happens, while for high concentrations (i.e., $x > \sqrt[n]{K_M}$) the enzymatic reaction happens at its maximal rate V_{\max} .

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A chemical example of a linear ODE model of order 2

Consider the chemical reaction:



Using the law of mass action, the corresponding ODEs write:

$$[\dot{X}] = -k[X] + k[Y] \quad (18)$$

$$[\dot{Y}] = k[X] - k[Y], \quad k > 0 \quad (19)$$

To solve (18)-(19) analytically, we define the vector $\mathbf{x} = \begin{pmatrix} x_1 \\ x_2 \end{pmatrix} = \begin{pmatrix} [X] \\ [Y] \end{pmatrix}$ and rewrite the equation under the form $\dot{\mathbf{x}} = A\mathbf{x}$. We then use a change of variables in order to *diagonalise* the matrix A .

Diagonalisation, eigenvalues and eigenvectors

The system of equations (18)-(19) can be rewritten as:

$$\begin{pmatrix} \dot{x}_1 \\ \dot{x}_2 \end{pmatrix} = k \underbrace{\begin{pmatrix} -1 & 1 \\ 1 & -1 \end{pmatrix}}_{=A} \begin{pmatrix} x_1 \\ x_2 \end{pmatrix} \Leftrightarrow \dot{\mathbf{x}} = kA\mathbf{x} \quad (20)$$

To solve (20), we diagonalise A , i.e., we find its *eigenvalues* and *eigenvectors*.

- 1 **Eigenvalues:** Solutions of $\det(A - \lambda I) = 0$. Here, we have: $\lambda_1 = 0$ and $\lambda_2 = -2$.
- 2 **Eigenvectors (normalised):** Solutions of $A\mathbf{v} = \lambda\mathbf{v}$, for each eigenvalue λ . Here, we have: $\mathbf{v}_1 = \frac{1}{\sqrt{2}} \begin{pmatrix} 1 \\ 1 \end{pmatrix}$ corresponding to $\lambda_1 = 0$ and $\mathbf{v}_2 = \frac{1}{\sqrt{2}} \begin{pmatrix} 1 \\ -1 \end{pmatrix}$ corresponding to $\lambda_2 = -2$.

Diagonalisation, eigenvalues and eigenvectors (cont')

From the eigenvectors of A , we construct a new matrix V having the eigenvectors of A as columns:

$$V = \begin{pmatrix} | & | \\ \mathbf{v}_1 & \mathbf{v}_2 \\ | & | \end{pmatrix} = \frac{1}{\sqrt{2}} \begin{pmatrix} 1 & 1 \\ 1 & -1 \end{pmatrix}$$

We then have (theorem on diagonalisation of matrices):

$$V^{-1}AV = \Lambda = \begin{pmatrix} \lambda_1 & 0 \\ 0 & \lambda_2 \end{pmatrix} = \begin{pmatrix} 0 & 0 \\ 0 & -2 \end{pmatrix} \quad (21)$$

Now, recall the initial model was $\dot{\mathbf{x}} = kA\mathbf{x}$. Multiplying this latter equation by V^{-1} on the left gives:

$$\begin{aligned} V^{-1} \frac{d}{dt} \mathbf{x} &= \frac{d}{dt} \underbrace{(V^{-1}\mathbf{x})}_{=\mathbf{X}} = k \underbrace{V^{-1}AV}_{=\Lambda} \underbrace{(V^{-1}\mathbf{x})}_{=\mathbf{X}} = k\Lambda\mathbf{X} \\ \Rightarrow \boxed{\frac{d\mathbf{X}}{dt} = k\Lambda\mathbf{X}}, & \quad \mathbf{X} = V^{-1}\mathbf{x} \end{aligned} \quad (22)$$

Diagonalisation, eigenvalues and eigenvectors (cont')

$$\begin{pmatrix} \dot{X}_1 \\ \dot{X}_2 \end{pmatrix} = k \begin{pmatrix} 0 & 0 \\ 0 & -2 \end{pmatrix} \begin{pmatrix} X_1 \\ X_2 \end{pmatrix} = k \begin{pmatrix} \lambda_1 & 0 \\ 0 & \lambda_2 \end{pmatrix} \begin{pmatrix} X_1 \\ X_2 \end{pmatrix} \quad (23)$$

$$\Leftrightarrow \begin{cases} \dot{X}_1 = k\lambda_1 X_1 \\ \dot{X}_2 = k\lambda_2 X_2 \end{cases}$$

$$\Rightarrow \begin{cases} X_1(t) = X_1(0)e^{k\lambda_1 t} \\ X_2(t) = X_2(0)e^{k\lambda_2 t} \end{cases}$$

The last step is to transform back into the original coordinates using $\mathbf{X} = V^{-1}\mathbf{x}$ which implies $\mathbf{x} = V\mathbf{X}$. Using $\mathbf{x} = V\mathbf{X}$, i.e.,

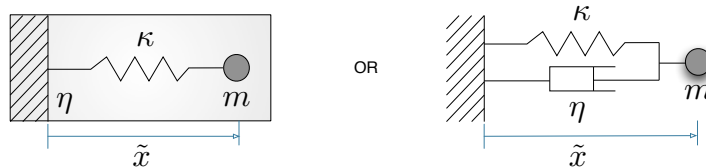
$$\mathbf{x} = \begin{pmatrix} | & | \\ \mathbf{v}_1 & \mathbf{v}_2 \\ | & | \end{pmatrix} \begin{pmatrix} X_1 \\ X_2 \end{pmatrix} = \mathbf{v}_1 X_1 + \mathbf{v}_2 X_2, \text{ we obtain}$$

$$\mathbf{x}(t) = \mathbf{v}_1 X_1(t) + \mathbf{v}_2 X_2(t) \Leftrightarrow \boxed{\mathbf{x}(t) = \mathbf{v}_1 X_1(0)e^{k\lambda_1 t} + \mathbf{v}_2 X_2(0)e^{k\lambda_2 t}}$$

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The mass-spring-damper system

Let us consider the mass-spring-damper system:



for which the equation of motion is

$$m\ddot{x} + \eta\dot{x} + \kappa x = 0 \quad (24)$$

To solve (24), we put the model in the form $\dot{\mathbf{x}} = A\mathbf{x}$ and diagonalise A :

$$\begin{cases} \dot{x} = y \\ \dot{y} = -\frac{\kappa}{m}x - \frac{\eta}{m}y \end{cases} \Rightarrow \begin{pmatrix} \dot{x} \\ \dot{y} \end{pmatrix} = \underbrace{\begin{pmatrix} 0 & 1 \\ -\frac{\kappa}{m} & -\frac{\eta}{m} \end{pmatrix}}_{=A} \begin{pmatrix} x \\ y \end{pmatrix}$$

The eigenvalues of A are $\lambda_{\pm} = \frac{-\eta \pm \sqrt{\eta^2 - 4\frac{\kappa}{m}}}{2}$. The general solution is thus

$\boxed{\mathbf{x}(t) = \mathbf{c}_+ e^{\lambda_+ t} + \mathbf{c}_- e^{\lambda_- t}}$ where \mathbf{c}_{\pm} are proportional to the eigenvectors associated with λ_{\pm} .

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- 2 Linear models of order 1
- 3 Nonlinear ODE models of order 1
- 4 Linear ODE models of order 2 and higher
- 5 Nonlinear ODE models of order 2
- 6 Nonlinear ODE models of order 3 and higher
- 7 Modelling gene regulation networks

Stability analysis of nonlinear ODE models of order 2

Consider a nonlinear ODE model of order 2:

$$\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}), \quad \mathbf{x} \in \mathbb{R}^2 \Leftrightarrow \begin{pmatrix} \dot{x}_1 \\ \dot{x}_2 \end{pmatrix} = \begin{pmatrix} f_1(x_1, x_2) \\ f_2(x_1, x_2) \end{pmatrix}, \quad f(\cdot) : \mathbb{R}^2 \rightarrow \mathbb{R}^2, \text{ "smooth" function}$$

- 1 Global stability analysis (difficult for models of order ≥ 2)
- 2 Local stability analysis (possible for all orders)
 - ▶ Find the fixed points: $\{\mathbf{x}^* : \mathbf{f}(\mathbf{x}^*) = \mathbf{0}\}$.
 - ▶ Linearise the dynamics around *each* fixed point.
 - ▶ Study the stability of the corresponding linear systems.
 - ▶ Draw the local flows around each fixed point:
 - ▶ Try to link together the local stability information around each fixed point to establish a global picture of the attractors in the state space.
 - ★ *Nullclines*: the curves in the phase plane corresponding to *individual* first derivatives being zero ($\dot{x}_1 = 0$ or $\dot{x}_2 = 0$), i.e., the curves $f_1(x_1, x_2) = 0$ and $f_2(x_1, x_2) = 0$.
 - ★ *Trajectories in the phase plane (phase space for models of order 3 or higher) cannot cross, except at the fixed points.*

Linearisation of ODE models of order 2

- Find the fixed points, i.e., the points \mathbf{x}^* s.t.

$$\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}^*) = \mathbf{0} \Leftrightarrow \begin{cases} f_1(x_1^*, x_2^*) = 0 \\ f_2(x_1^*, x_2^*) = 0 \end{cases}$$

- Linearise the dynamics around *each* fixed point (using Taylor):
Consider $\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x})$ with $\mathbf{x} = \mathbf{x}^* + \boldsymbol{\xi}$ where $\boldsymbol{\xi} \in \mathbb{R}^2$ s.t. $\|\boldsymbol{\xi}\| \ll 1$:

$$\dot{\boldsymbol{\xi}} = \dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}^* + \boldsymbol{\xi}) = \underbrace{\mathbf{f}(\mathbf{x}^*)}_{=0} + \underbrace{\begin{pmatrix} \left. \frac{\partial f_1(x_1, x_2)}{\partial x_1} \right|_{\mathbf{x}=\mathbf{x}^*} & \left. \frac{\partial f_1(x_1, x_2)}{\partial x_2} \right|_{\mathbf{x}=\mathbf{x}^*} \\ \left. \frac{\partial f_2(x_1, x_2)}{\partial x_1} \right|_{\mathbf{x}=\mathbf{x}^*} & \left. \frac{\partial f_2(x_1, x_2)}{\partial x_2} \right|_{\mathbf{x}=\mathbf{x}^*} \end{pmatrix}}_{\triangleq J(\mathbf{x}^*)} \boldsymbol{\xi} + \underbrace{\mathcal{O}(\|\boldsymbol{\xi}\|^2)}_{H.O.T.}$$

We thus obtain:

$$\dot{\boldsymbol{\xi}} = J(\mathbf{x}^*) \boldsymbol{\xi} \quad (25)$$

where $J(\mathbf{x}^*)$ is the *Jacobian* matrix evaluated at the fixed point \mathbf{x}^* , i.e., a constant matrix whose (i, j) element is $J_{ij}(\mathbf{x}^*) = \left. \frac{\partial f_i(\mathbf{x})}{\partial x_j} \right|_{\mathbf{x}=\mathbf{x}^*}$.

- Study the stability of (25) at each fixed point \mathbf{x}^*
 \Rightarrow Diagonalise $J(\mathbf{x}^*)$ (i.e., $\tilde{\boldsymbol{\xi}} = V^{-1}\boldsymbol{\xi}$)

Diagonalisation of the Jacobian for models of order 2

Consider

$$J(\mathbf{x}^*) = \begin{pmatrix} a & b \\ c & d \end{pmatrix}$$

The eigenvalues of $J(\mathbf{x}^*)$ are given by solving

$$\det(J(\mathbf{x}^*) - \lambda I) = 0$$

which gives the algebraic equation

$$\lambda^2 - \underbrace{(a + d)}_{=\tau} \lambda + \underbrace{(ad - bc)}_{=\Delta} = 0$$

where

- τ is the *trace* of $J(\mathbf{x}^*)$, i.e., the sum of the diagonal elements of $J(\mathbf{x}^*)$ ($= \lambda_+ + \lambda_-$)
- Δ is the *determinant* of $J(\mathbf{x}^*)$ ($= \lambda_+ \lambda_-$)

Diagonalisation of the Jacobian for models of order 2 (cont')

Eigenvalues:

$$\lambda^2 - \tau\lambda + \Delta = 0$$

$$\Rightarrow \lambda_{\pm} = \frac{\tau \pm \sqrt{\tau^2 - 4\Delta}}{2}$$

Therefore, diagonalising $J(\mathbf{x}^*)$, we can see that the general solution is of the form:

$$\xi(t) = \mathbf{c}_+ e^{\lambda_+ t} + \mathbf{c}_- e^{\lambda_- t}, \quad \xi(t) \in \mathbb{R}^2, \mathbf{c}_+, \mathbf{c}_- \in \mathbb{C}^2, \lambda_+, \lambda_- \in \mathbb{C} \quad (26)$$

where λ_{\pm} are the eigenvalues of $J(\mathbf{x}^*)$ and \mathbf{c}_{\pm} are proportional to the corresponding eigenvectors.

Local stability analysis for models of order 2

The general solution for a linear ODE of order 2 is:

$$\xi(t) = \mathbf{c}_+ e^{\lambda_+ t} + \mathbf{c}_- e^{\lambda_- t}, \quad \lambda_{\pm} = \frac{\tau \pm \sqrt{\tau^2 - 4\Delta}}{2}, \quad \mathbf{c}_{\pm} \propto \text{eigenvec. assoc. with } \lambda_{\pm} \quad (27)$$

The local behaviours are dictated by the signs of $\tau (= \lambda_+ + \lambda_-)$, $\Delta (= \lambda_+ \lambda_-)$, and $\tau^2 - 4\Delta (= (\lambda_+ - \lambda_-)^2)$.

- ① $\Delta > 0$: $\sqrt{\tau^2 - 4\Delta} < |\tau|$
 - ▶ $\tau > 0$:
 - ① $\tau^2 - 4\Delta > 0$: $\lambda_+ > \lambda_- > 0$ (A)
 - ② $\tau^2 - 4\Delta < 0$: λ_{\pm} complex conjugate with pos. real part (B)
 - ▶ $\tau < 0$:
 - ① $\tau^2 - 4\Delta > 0$: $\lambda_- < \lambda_+ < 0$ (C)
 - ② $\tau^2 - 4\Delta < 0$: λ_{\pm} complex conjugate with neg. real part (D)
 - ▶ $\tau = 0$: λ_{\pm} purely imaginary (E)
- ② $\Delta < 0$: $\lambda_- < 0 < \lambda_+$ (F)

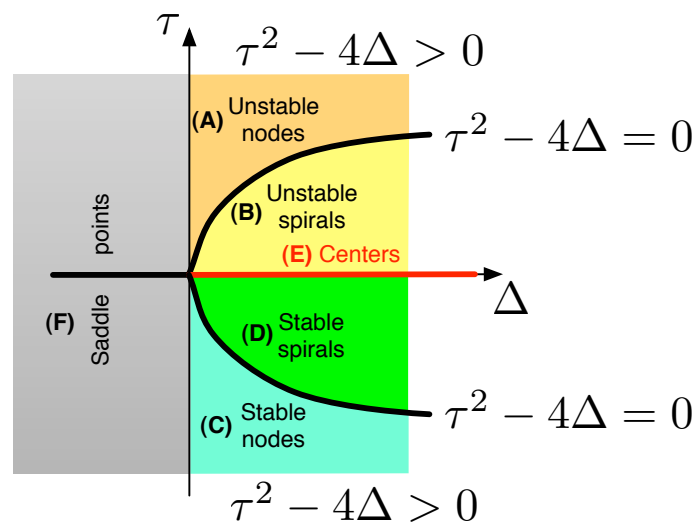
Local stability analysis for models of order 2 (cont')

In the diagonalised coordinates, i.e., for $\tilde{\xi} = V^{-1}\xi$:

$$\tilde{\xi}_1(t) = \tilde{\xi}_1(0)e^{\lambda_+ t}, \quad \tilde{\xi}_2 = \tilde{\xi}_2(0)e^{\lambda_- t}, \quad \lambda_{\pm} = \frac{\tau \pm \sqrt{\tau^2 - 4\Delta}}{2}$$

- (A) $\lambda_+ > \lambda_- > 0$: Exponential growth in both directions: **Repelling or unstable node**
- (B) λ_{\pm} complex conjugate with pos. real part: $\tilde{\xi}_{1,2}(t) = \tilde{\xi}_{1,2}(0)e^{\frac{\tau}{2}t}e^{\pm i\omega t}$ with $\tau > 0, \omega = \frac{\sqrt{|\tau^2 - 4\Delta|}}{2}$: **Unstable spiral**
- (C) $\lambda_- < \lambda_+ < 0$: Exponential decay in both directions: **Attracting or stable node**
- (D) λ_{\pm} complex conjugate with neg. real part: $\tilde{\xi}_{1,2}(t) = \tilde{\xi}_{1,2}(0)e^{\frac{\tau}{2}t}e^{\pm i\omega t}$ with $\tau < 0, \omega = \frac{\sqrt{|\tau^2 - 4\Delta|}}{2}$: **Stable spiral**
- (E) λ_{\pm} purely imaginary: $\tilde{\xi}_{1,2}(t) = \tilde{\xi}_{1,2}(0)e^{\pm i\omega t}$ with $\omega = \sqrt{\Delta}$: periodic oscillations: **Center**
- (F) $\lambda_- < 0 < \lambda_+$: exp. decay in one dir. and exp. growth in the other: **Saddle point**

Summary of the possible local behaviours for models of order 2

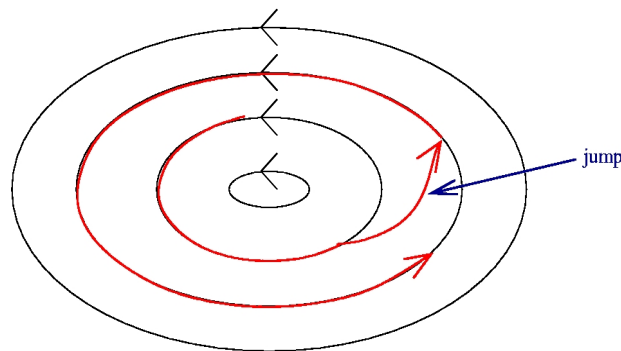


Linear (or harmonic) oscillations (centers)

$$\begin{cases} \dot{x} = y \\ \dot{y} = -x \end{cases}$$

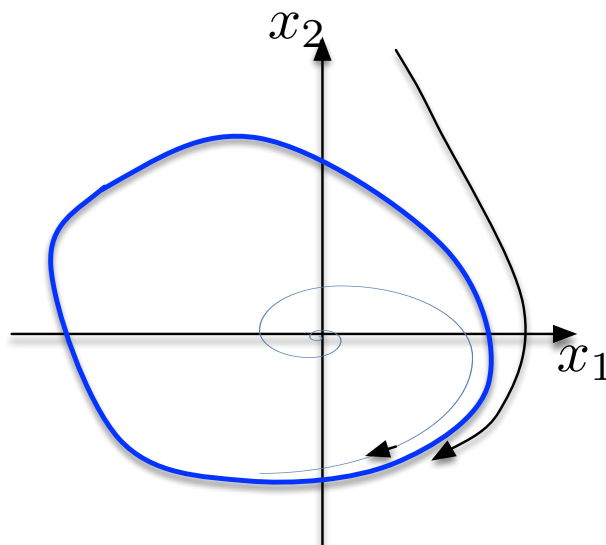
Linear (or “harmonic”) oscillations have 2 serious limitations:

- 1 They are “fragile” or non-robust to small perturbations in the model
- 2 The oscillation characteristics (amplitude and phase) depend on the initial condition



Limit cycles

A stable *limit cycle* is a periodic trajectory which attracts other solutions to it (at least those starting “close to” the limit cycle).



Limit cycles: an example

$$\dot{x} = -\omega y + x(\mu - x^2 - y^2) \quad (28)$$

$$\dot{y} = \omega x + y(\mu - x^2 - y^2) \quad (29)$$

where μ is a parameter while $\omega \neq 0$ is a constant.

- Fixed points:

$$\begin{cases} -\omega y^* + x^*(\mu - x^{*2} - y^{*2}) = 0 \\ \omega x^* + y^*(\mu - x^{*2} - y^{*2}) = 0 \end{cases}$$

$$\Rightarrow -\omega \frac{y^*}{x^*} = \omega \frac{x^*}{y^*} \Leftrightarrow y^{*2} + x^{*2} = 0 \Rightarrow \boxed{(x^*, y^*) = (0, 0)}$$

- Linearisation around $(0, 0)$:

$$J(x, y) = \begin{pmatrix} (\mu - x^2 - y^2) + x(-2x) & -\omega - 2xy \\ \omega - 2xy & (\mu - x^2 - y^2) + y(-2y) \end{pmatrix}$$

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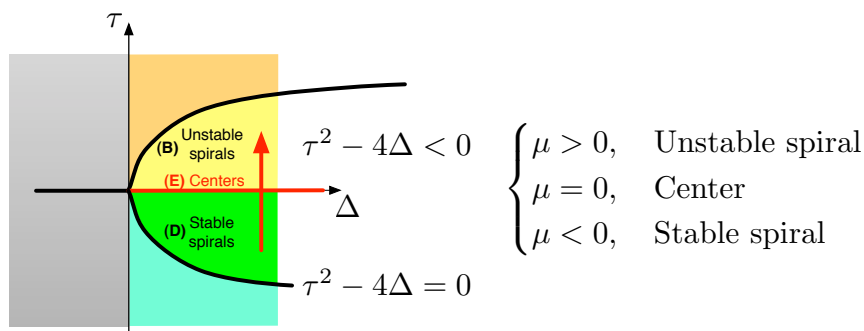
Limit cycles: an example (cont')

Local stability analysis of $(0, 0)$:

$$J(0, 0) = \begin{pmatrix} \mu & -\omega \\ \omega & \mu \end{pmatrix}$$

$$\Rightarrow \boxed{\lambda_{\pm} = \mu \pm i\omega}$$

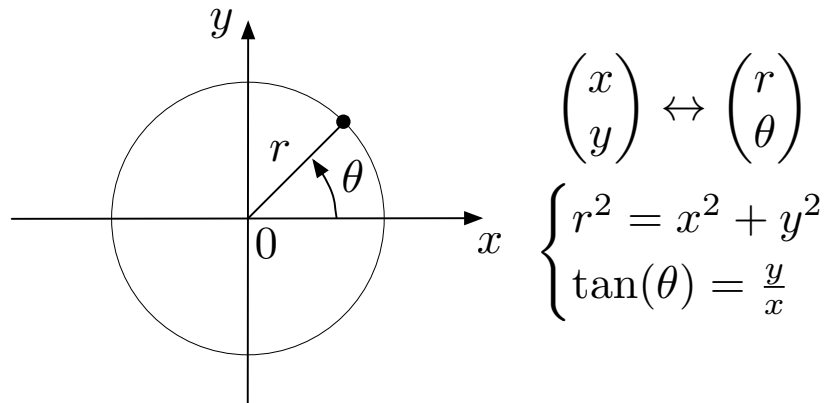
$$\begin{cases} \tau = 2\mu \\ \Delta = \mu^2 + \omega^2 > 0 \\ \tau^2 - 4\Delta = 4\mu^2 - 4\mu^2 - 4\omega^2 < 0 \end{cases}$$



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Global stability analysis for the limit cycle example (rare)

To perform the global analysis explicitly (which typically is very hard to do; the example we have chosen here is an exception in that respect), we rewrite (28)-(29) in polar coordinates:



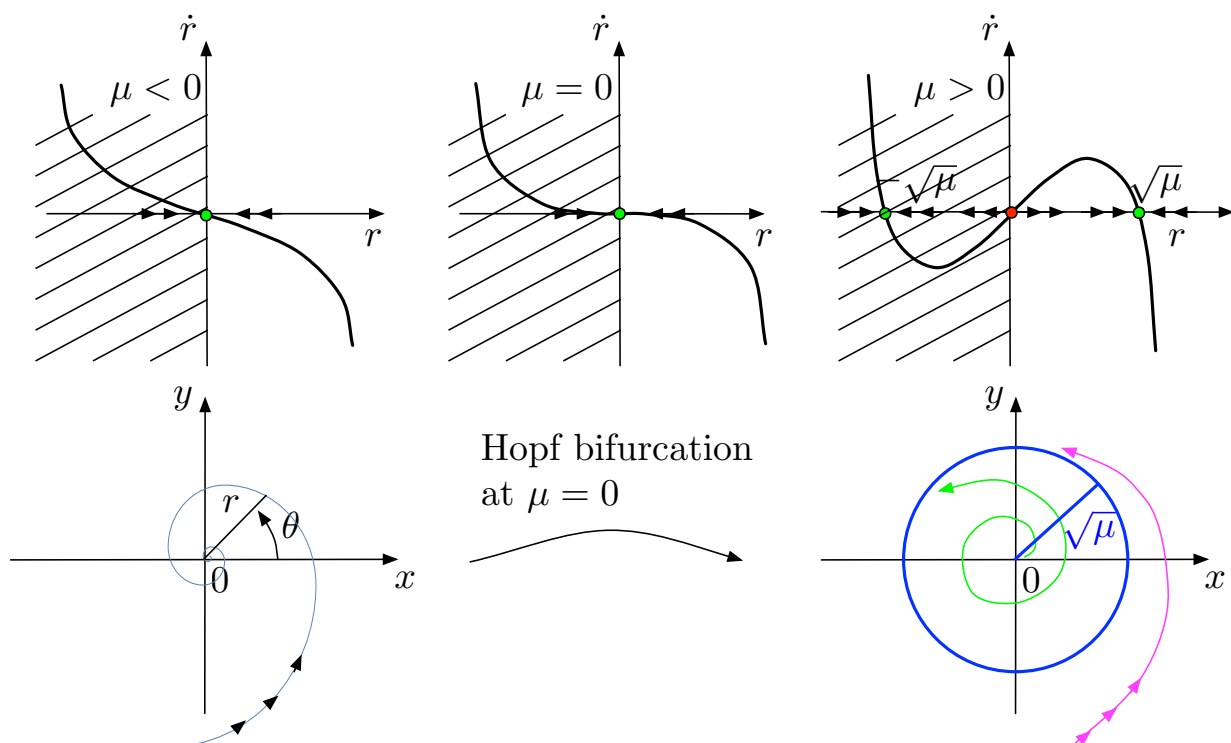
i.e., transform $\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x})$ with $\mathbf{x} = \begin{pmatrix} x \\ y \end{pmatrix}$ into $\dot{\mathbf{p}} = \mathbf{F}(\mathbf{p})$ with $\mathbf{p} = \begin{pmatrix} r \\ \theta \end{pmatrix}$.

This gives:

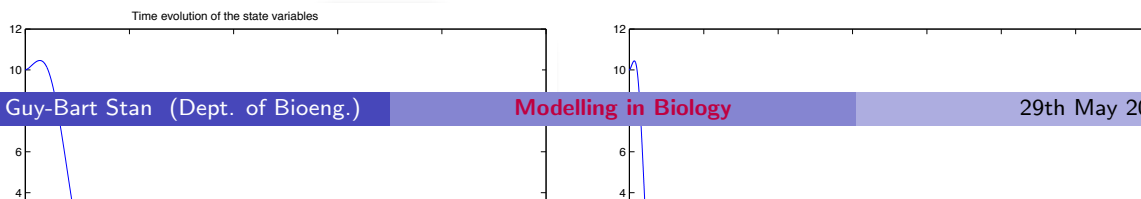
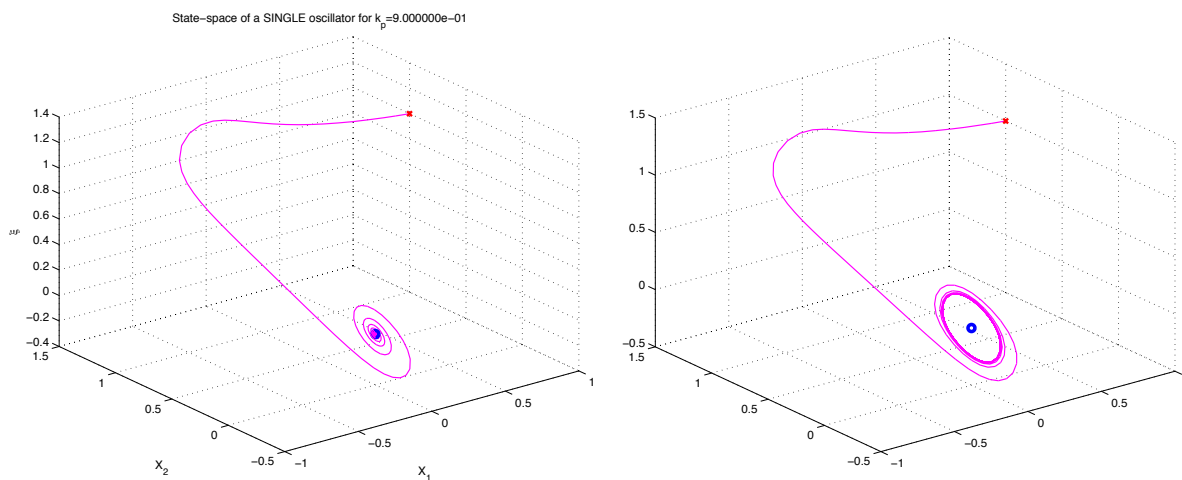
$$\dot{r} = r(\mu - r^2) \tag{30}$$

$$\dot{\theta} = \omega \tag{31}$$

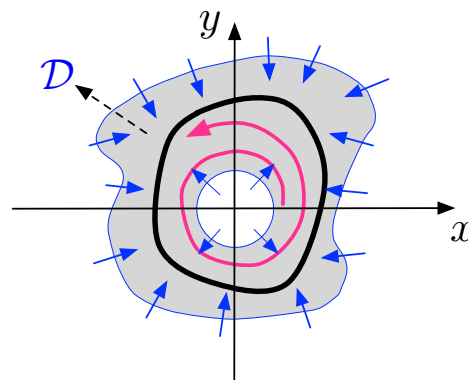
Global stability analysis for the limit cycle example (cont')



Example of a limit cycle in a model of order 3



The Poincaré-Bendixson Theorem



A loose statement of the Poincaré-Bendixson Theorem

Suppose $\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x})$, $\mathbf{x} \in \mathbb{R}^2$, is a continuously differentiable vector field and there exists a bounded subset \mathcal{D} of the phase plane such that

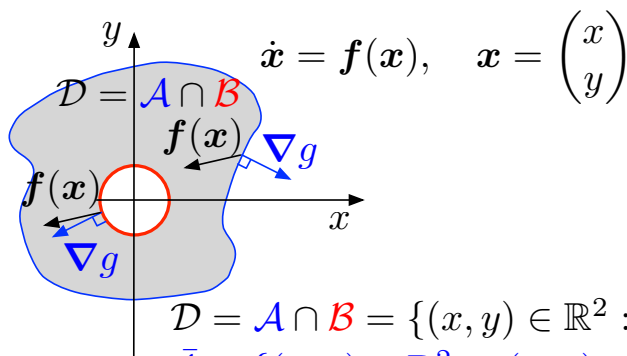
- no trajectory can exit \mathcal{D} ,
- and there are no fixed points inside \mathcal{D} .

Then, there exists at least one limit cycle in \mathcal{D} and any trajectory that enters \mathcal{D} converges to a limit cycle.

The Poincaré-Bendixson Theorem: How can we find \mathcal{D} ?

We need to show that:

$$\boxed{\nabla^T g(x, y) \mathbf{f}(x, y) < 0, \forall \mathbf{x} \in \bar{\mathcal{A}}} \quad \text{and} \quad \boxed{\nabla^T b(x, y) \mathbf{f}(x, y) > 0, \forall \mathbf{x} \in \bar{\mathcal{B}}}$$



$$\begin{aligned} \mathcal{D} &= \mathcal{A} \cap \mathcal{B} = \{(x, y) \in \mathbb{R}^2 : g(x, y) \leq 0, b(x, y) \geq 0\} \\ \bar{\mathcal{A}} &= \{(x, y) \in \mathbb{R}^2 : g(x, y) \equiv 0\} \\ \bar{\mathcal{B}} &= \{(x, y) \in \mathbb{R}^2 : b(x, y) \equiv 0\} \end{aligned}$$

The Poincaré-Bendixson Theorem: an example

Consider the second order model in example in (28)-(29) for $\mu > 0$:

$$\begin{aligned} \dot{x} &= -\omega y + x(\mu - x^2 - y^2) \\ \dot{y} &= \omega x + y(\mu - x^2 - y^2) \end{aligned}$$

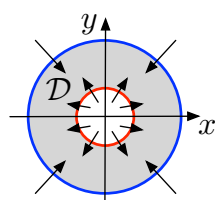
We thus have: $\mathbf{f}(x, y) = \begin{pmatrix} -\omega y + x(\mu - x^2 - y^2) \\ \omega x + y(\mu - x^2 - y^2) \end{pmatrix}$.

Consider the function $G(x, y) = x^2 + y^2 - R^2$. Therefore, $\nabla G = \begin{pmatrix} 2x \\ 2y \end{pmatrix}$.

Now, define $\bar{\mathcal{D}} = \{(x, y) : g(x, y) = x^2 + y^2 - R^2 = 0\}$.

For any point $(x, y) \in \bar{\mathcal{D}}$, we thus have:

$$\nabla^T G(x, y) \mathbf{f}(x, y) = 2R^2 (\mu - R^2) \begin{cases} < 0 & \text{if } R > \sqrt{\mu} \\ > 0 & \text{if } R < \sqrt{\mu}, \end{cases}$$



Summary of behaviours for ODE models of order 1 and 2

- Models of order 1
 - ▶ Attractors: fixed points, or ∞
 - ▶ Local (linear) and global stability analysis are equivalent
 - ▶ Bifurcations: Saddle node, Transcritical, or Pitchfork
- Models of order 2
 - ▶ Attractors: fixed points, limit cycles, or ∞
 - ▶ Local stability analysis (linearisation) around fixed points \neq global stability analysis
 - ▶ Bifurcation: all those of order 1 + Hopf + others

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Behaviours for ODE models of order 3 and higher

$$\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}), \quad \mathbf{x} \in \mathbb{R}^d, \quad d \geq 3, \quad \mathbf{f}(\cdot) : \mathbb{R}^d \rightarrow \mathbb{R}^d, \quad \text{“smooth” function} \quad (32)$$

Behaviours for ODE models of order 3 and higher

In one sentence: everything that happens in lower order models + 2 other phenomena:

- quasi-periodicity
- deterministic chaos

Summary for systems of order 1, 2, and 3 and higher

	1D	2D	3D and higher
Attractors	Only F.P. or $\pm\infty$	Same as 1D + limit cycles	Same as 2D + quasi-periodic attractor + chaotic attractor
Behaviours	Decay or explosion	Same as 1D + robust periodic oscillations	Same as 2D + quasi-periodicity + chaos
Bifurcations	Saddle-Node Transcritical Pitchfork	Same as 1D + Hopf + others	Same as 2D + many more

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The central dogma

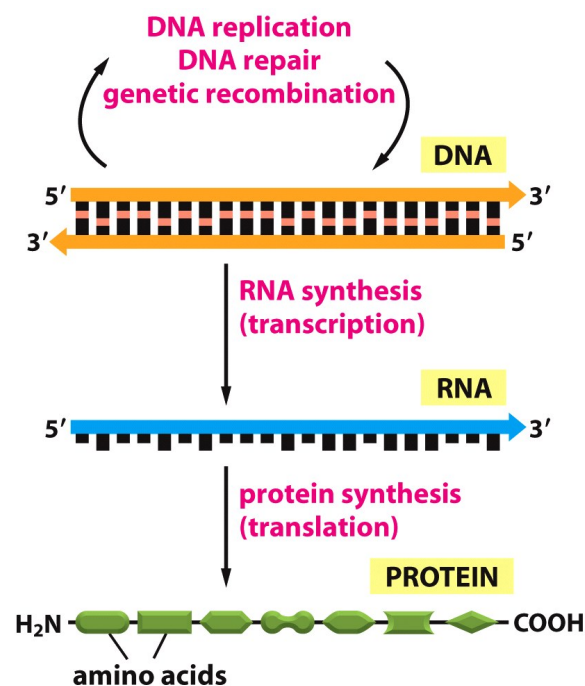
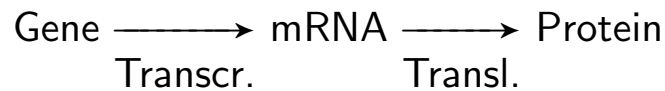


Figure 7-1 Essential Cell Biology 3/e (© Garland Science 2010)

Transcription and mRNA polymerase
 Translation and Ribosome
 Translation and Proteins

Constitutive gene expression

As we have seen, the central dogma can be summarized as:



When gene expression is unregulated, it is said to be *constitutive*, and the gene is always on.

Using the law of mass action¹, a model for constitutive expression is given as:

$$\dot{m} = k_1 - d_1 m \tag{33}$$

$$\dot{p} = k_2 m - d_2 p \tag{34}$$

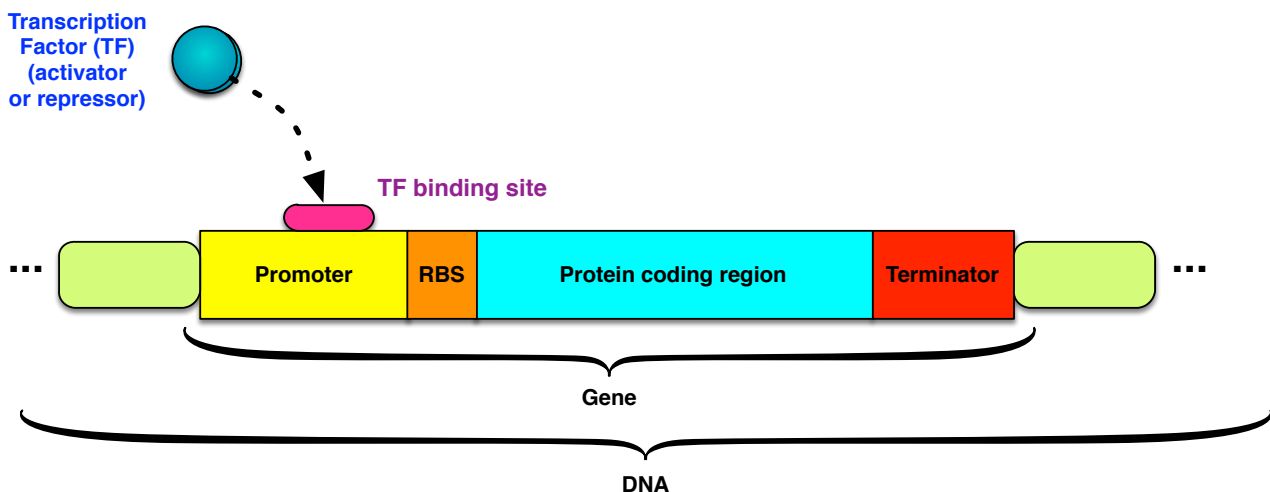
where $m = [mRNA]$ and $p = [Protein]$

- k_1 is the constitutive transcription rate.
- d_1 is the mRNA degradation rate.
- k_2 is the translation rate.
- d_2 is the protein degradation rate.

¹This is based on empirical studies since strictly speaking it does not really make sense to use the law of mass action for gene expression.

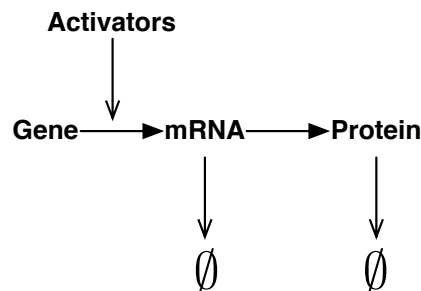
Gene transcription regulation

At the transcription level, gene expression can be controlled by certain proteins called *transcription factors*:



Gene transcription regulation by activators

Consider the case of a gene whose transcription is **activated** by the cooperative binding of activators to the transcription factor binding site of the gene.



The following model is commonly used to describe activator controlled gene transcription:

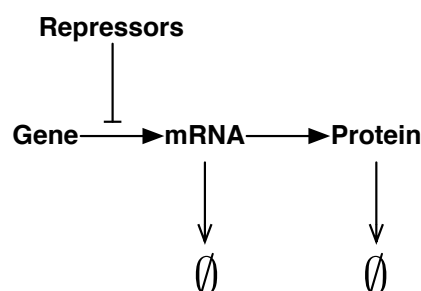
$$\dot{m} = k_1 \frac{A^n}{K^n + A^n} - d_1 m \quad (35)$$

$$\dot{p} = k_2 m - d_2 p \quad (36)$$

where $m = [mRNA]$, $p = [Protein]$, $A = [Activator]$, $k_1 =$ maximal transcription rate, $K =$ activation coefficient, $n =$ Hill coefficient (= number of activators that need to cooperatively bind the promoter to trigger the activation of gene expression).

Gene transcription regulation by repressors

Consider the case of a gene whose transcription is **repressed** by the cooperative binding of repressors to the transcription factor binding site of the gene.



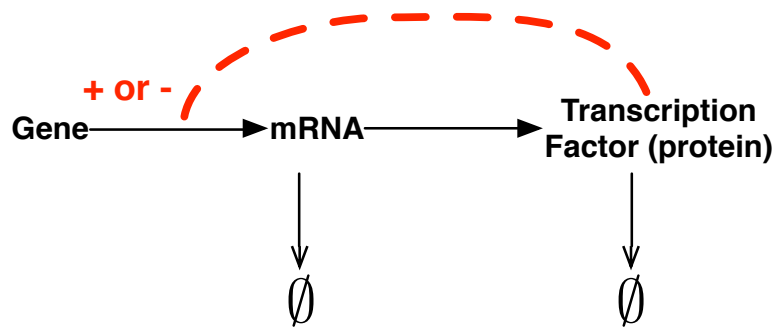
The following ODE model describes repressor-controlled gene transcription:

$$\dot{m} = k_1 \frac{K^n}{K^n + R^n} - d_1 m \quad (37)$$

$$\dot{p} = k_2 m - d_2 p \quad (38)$$

where $m = [mRNA]$, $p = [Protein]$, $R = [Repressor]$, $k_1 =$ maximal transcription rate, $K =$ repression coefficient, $n =$ Hill coefficient (= number of repressors that need to cooperatively bind the promoter to trigger the inhibition of gene expression).

Auto-activation and auto-inhibition



$$\dot{m} = k_1 f(p) - d_1 m \quad (39)$$

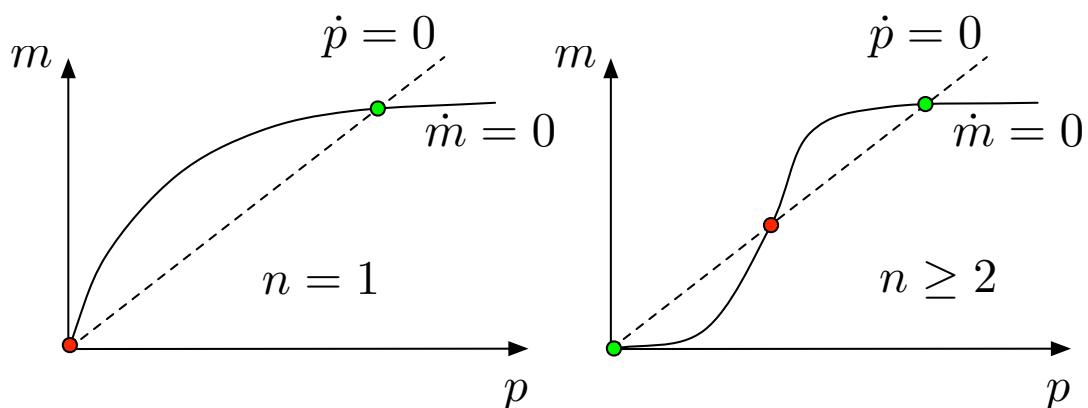
$$\dot{p} = k_2 m - d_2 p \quad (40)$$

where $f(p) = f^+(p) = \frac{p^n}{K^n + p^n}$ (monotonically increasing Hill function) for an auto-activating action of the transcription factor p , and $f(p) = f^-(p) = 1 - f^+(p) = \frac{K^n}{K^n + p^n}$ (monotonically decreasing Hill function) for an auto-inhibiting action of the transcription factor p .

Auto-activation

$$\dot{m} = k_1 \frac{p^n}{K^n + p^n} - d_1 m \quad (41)$$

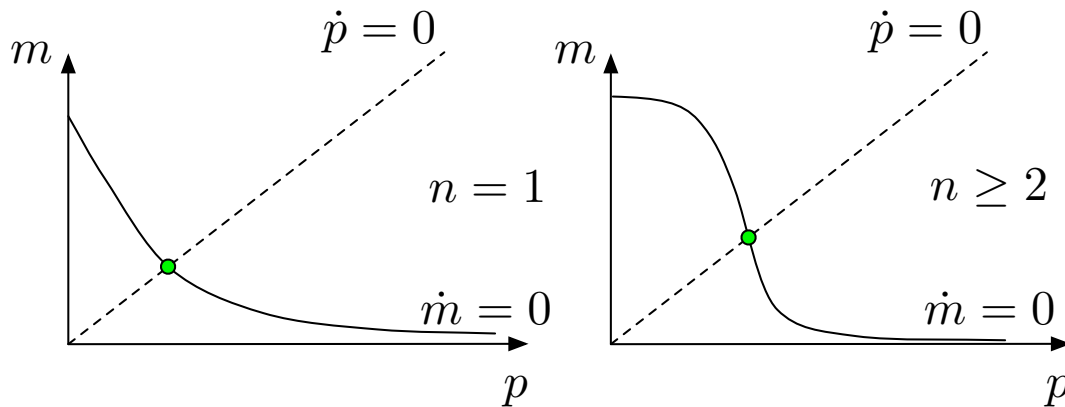
$$\dot{p} = k_2 m - d_2 p \quad (42)$$



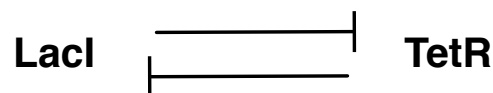
Auto-repression

$$\dot{m} = k_1 \frac{K^n}{K^n + p^n} - d_1 m \quad (43)$$

$$\dot{p} = k_2 m - d_2 p \quad (44)$$



The toggle switch



$$\dot{m}_L = k_{L,1} \frac{K_T^{n_T}}{K_T^{n_T} + p_T^{n_T}} - d_{L,1} m_L$$

$$\dot{p}_L = k_{L,2} m_L - d_{L,2} p_L$$

$$\dot{m}_T = k_{T,1} \frac{K_L^{n_L}}{K_L^{n_L} + p_L^{n_L}} - d_{T,1} m_T$$

$$\dot{p}_T = k_{T,2} m_T - d_{T,2} p_T$$

where m_L (resp. m_T) is the concentration of *LacI* (resp. *TetR*) mRNA, and p_L (resp. p_T) is the concentration of *LacI* (resp. *TetR*) protein.

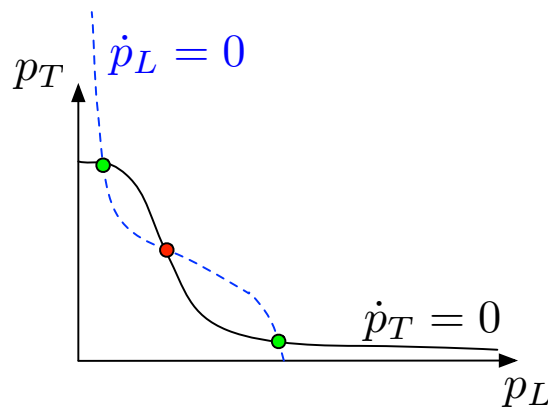
The toggle switch (cont')

Using a quasi-stationary assumption for the mRNA dynamics, i.e., $\dot{m}_L \approx 0$ and $\dot{m}_T \approx 0$, we obtain a model of order 2 whose equations are:

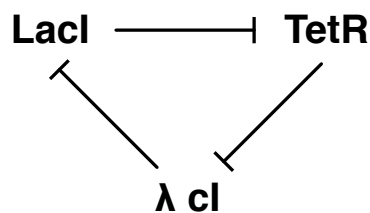
$$\dot{p}_L = k_{L,2} \frac{k_{L,1}}{d_{L,1}} \frac{K_T^{n_T}}{K_T^{n_T} + p_T^{n_T}} - d_{L,2} p_L \quad (45)$$

$$\dot{p}_T = k_{T,2} \frac{k_{T,1}}{d_{T,1}} \frac{K_L^{n_L}}{K_L^{n_L} + p_L^{n_L}} - d_{T,2} p_T \quad (46)$$

For example, for $n_L = n_T = 2$, $k_{L,1} = k_{T,1} = 10$, and all other parameters equal to 1 the phase plane looks like this:



The repressilator: a synthetic genetic oscillator



The corresponding model is of order 6 and can be written as (after non-dimensionalisation):

$$\dot{m}_i = -m_i + \frac{\alpha}{1 + p_j^n} + \alpha_0 \quad (47)$$

$$\dot{p}_i = -\beta (p_i - m_i) \quad (48)$$

where $(i, j) = \{(Lacl, cl), (TetR, Lacl), (cl, TetR)\}$.

For certain values of the parameters, this system exhibits limit cycle oscillations

Time evolution of protein concentrations for the repressilator

