Lecture Notes

Instructor: Samuel Bernard bernard@math.univ-lyon1.fr

link to the latest version: cellular_dynamics_and_complex_systems (see also the course webpage

Skills acquired Modelling cell population dynamics and complex systems. The most widely used dynamical system formalisms will be intriduced: Stochastic processes, ordinary and stochastic differential equation, and discrete systems. Emphasis will be put on qualitative study of dynamical systems and on the numerical methods and analysis.

Synopsis

- Birth/Death stochastic processes. Master equations, Langevin and Fokker-Planck equations, link with deterministic systems, examples
- Nonlinear ODEs. Existence/uniqueness, Hartman-Grobman theorem, linearisation and linear stability, classification of equilibria, bifurcations co-dimension 1 and 2: saddle-node, transcritical, pitchfork, Hopf, numerical analysis with XXPAUT, examples
- Discrete systems. Existence/uniqueness, linearisation and linear stability, comparison with ODEs, Poincaré map, bifurcations, chaos, examples
- Systems in large dimension. Coupled oscillators, Kuramoto model, numerical simulations
- Functional and delay differential equations. Existence/uniqueness, linearisation and linear stability, comparison with ODEs

Contents

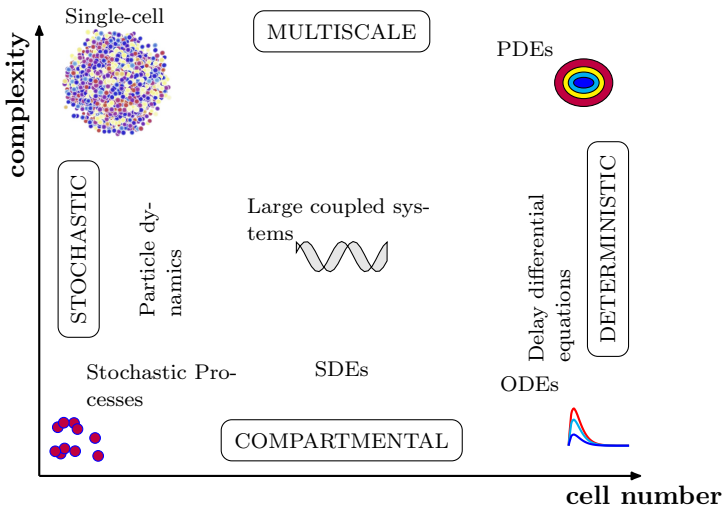


Figure 1. Modelling approaches in systems biology.

1 Birth/death processes

Birth and death are the two basic events that can occur in a cell population, no matter how complex the population is, so it makes sense to start here. In any finite size, or discrete, population, these event have a large part of randomness in their occurrence an their timing.

Cell survival and death depends on the environmental conditions (temperature, oxygen, nutrient, pH, mechanical stress, cytokines...), but cell intrinsic factors can lead to different outcomes in the same conditions. Mutations are mostly deleterious, and cells with damaged DNA will usually undergo programmed cell death, or apoptosis. In some case, mutations confer resistance to apoptosis, enabling cells to survive even with DNA damage.

Birth occurs through cell division, whereby a mother cell gives rise to two daughter cells. As with cell death, cell division is affected by the environment, but it is well

established the capacity for cells to divide depends also on their differentiation state. Most human tissues are organized hierarchically, where a small subset of cells, call stem cells, have the capability of self-renewing, that is, dividing to give rise to at least one stem cell. Stem cells also produce progenitor cells that will be able to proliferate through successive cell divisions. Some of the progenitors will also differentiate (acquire a stable phenotype) into mature cells and integrate the tissue to replace dead cells. Once differentiated, most cells lose their ability to divide. Heart muscle cells and neurons probably cannot divide. Red blood cells, which have lost their nucleus, cannot divide either. Once differentiated, lymphocytes can divide at high rate when activated during an immune response. After liver injury, hepatocytes can de-differentiate and divide again to heal. Even though differentiated cells can have the ability to divide, most tissue have stem cells to support regeneration. The extent at which human tissues renew vary by orders of magnitude depending on the tissue and the age of the person. White blood cells, part of the innate immune system, are renewed daily, while neurons of the cortex are never replaced. Skin, liver, epithelial cell in the gut, fat cells have renewal time ranging from days to years. In all tissues, controls are in place to ensure that cells do not accumulate mutations that would favor the development of tumors. This includes making stem cell division a rare event, limiting the number of division progenitors can undergo, and maintaining active survival factors within the tissue to make cells non-viable outside their natural environment.

Therapeutic strategies for heart failure or neurodegenerative disease include transplanting stem cells or reprogrammed stem cells to induce regeneration. Characterizing the mechanisms that allows or prevent regeneration these tissues is an area of active research.

By definition, cancer occurs when a subset of cells have evaded controls, and can survive, proliferate and migrate to other tissues.

1.1 Birth/death processes

Let $n(t)$ be the number of cells in a population. We assume that all cell are identical. We will track three events: cell death, cell division, and the recruitment of a new cell in the population. The last two event have the same effect, but cell division must depend on the number of cells $n(t)$, while recruitment is not necessary linked. We assume that events are independent in probability. The **propensity** or the **rate** of a birth (division or recruitment) is λ_n and the propensity of a death is μ_n. This means that, during a time interval Δt, the probability for a birth or a death to occur is

propensity
rate

$$\Pr(birth) = \lambda_n \Delta t + O(\Delta t^2).$$
$$\Pr(death) = \mu_n \Delta t + O(\Delta t^2).$$

Several events can happen during an interval Δt, but because they are independent, the probability of multiple events is of order Δt^k, $k \geq 2$. Taking Δt small enough ensures at most one event. With these events, the number of cells $n(t)$ is a positive-integer valued, piecewise constant, right-continuous **stochastic process** (a random

stochastic process

variable that depends on time).

What is the law of $n(t)$? Let $p_n(t)$ be the probability for the number of cells to be n at time t, for $n \geq 0$. Then

$$\begin{aligned} p_n(t+\Delta t) =& \lambda_{n-1} p_{n-1}(t)\Delta t \\ &+ \mu_{n+1} p_{n+1}(t)\Delta t \\ &+ p_n(t) - \big(\lambda_n + \mu_n\big) p_n(t)\Delta t + O(\Delta t^2). \end{aligned}$$

The number of cells n is non-negative. This means that the coefficient μ_0 must be equal to 0 (no death can occur). The coefficient λ_{-1} can also be set to 0. Collecting terms in Δt and dividing by Δt,

$$\frac{p_n(t+\Delta t) - p_n(t)}{\Delta t} = \lambda_{n-1} p_{n-1}(t) + \mu_{n+1} p_{n+1}(t) - \big(\lambda_n + \mu_n\big) p_n(t) + O(\Delta t).$$

Taking the limit $\Delta t \to 0$, we obtain the **master equation**

master equation

$$\frac{p_n(t)}{dt} = \lambda_{n-1} p_{n-1}(t) + \mu_{n+1} p_{n+1}(t) - \big(\lambda_n + \mu_n\big) p_n(t).$$

The master equation is a system of ODEs (of infinite dimension), and must be supplemented by appropriate initial conditions. Here we choose

$$p_n(0) = \delta_m n,$$

(1 if $m = n$ and 0 otherwise). The **probability generating function** is a helpful tool to solve the master equations, at least in simple cases. The probability generating function is

probability generating function

$$\varphi(z,t) = \sum_{n \geq 0} z^n p_n(t).$$

The partial derivatives of φ have nice properties:

- $\varphi(1,t) = 1$.
- $\partial^k \varphi(0,t)/\partial z = k! p_k(t)$.

1.1.1 Linear rates, no recruitment

We assume rates are linear: $\lambda_n = \lambda n$ and $\mu_n = \mu n$.

Then, we can derive the following PDE

$$\frac{d\varphi}{dt} = (1-z)(\mu - \lambda z)\frac{\partial \varphi}{\partial z}.$$

with initial condition $\varphi(z,0) = z^m$, which corresponds to our initial condition. The solution for φ is

$$\varphi(z,t) = \frac{\big[\mu - \lambda z - \mu(1-z)\varepsilon(t)\big]^m}{\big[\mu - \lambda z - \lambda(1-z)\varepsilon(t)\big]^m}, \tag{1}$$

$$\varepsilon(t) = \exp\big((\lambda - \mu)t\big). \tag{2}$$

In the following, we set $m = 1$. The expected value (denoted $\langle\cdot\rangle$) of $n(t)$ is

$$\langle n(t)\rangle = \sum_{n\geq 0} n p_n(t) = \frac{\partial \varphi(1,t)}{\partial z} = \varepsilon(t).$$

The variance of the size of the population $\sigma^2(t) = \langle \big(n(t) - \langle n(t)\rangle\big)^2\rangle$ is found by using the relationship $\langle n(n-1)\rangle = \partial^2\varphi(1,t)/\partial z^2$:

$$\sigma^2(t) = \frac{\lambda + \mu}{\mu - \lambda}\varepsilon(t)\big(1 - \varepsilon(t)\big).$$

The probability of extinction by time t is $p_0(t) = \varphi(0,t)$,

$$p_0(t) = \frac{\mu - \mu\varepsilon(t)}{\mu - \lambda\varepsilon(t)}.$$

What about the law of $n(t)$? The distribution of $n(t)$, conditional to $n(t) > 0$, is a **geometric law** with parameter

geometric law

$$p(t) = \frac{\mu - \lambda}{\mu - \lambda\varepsilon(t)}.$$

The geometric law has a probability function for cell number $k \geq 1$

$$\mathsf{Pr}(n(t) = k | n(t) > 0) = p(t)(1 - p(t))^{k-1}.$$

1.1.2 Linear rates and recruitment

We assume the death rate is linear: $\mu_n = \mu$, the division rate is linear and there is recruitment: $\lambda_n = \alpha + \beta n$.

When there is recruitment, using the probability generating function is more tricky. Instead, we will work directly from the master equation, and find ODEs for the first two moments of $n(t)$. The first moment satisfies the ODE

$$\begin{aligned}\frac{d\langle n(t)\rangle}{dt} &= \frac{d}{dt}\sum_{n\geq 0} np_n(t)\\ &= \sum_{n\geq 0} n\frac{dp_n(t)}{dt}\\ &= \sum_{n\geq 0} n\big[\lambda_{n-1}p_{n-1}(t) + \mu_{n+1}p_{n+1}(t) - \big(\lambda_n + \mu_n\big)p_n(t)\big].\end{aligned}$$

On re-organising terms on the same indices, we obtain that

$$\frac{d\langle n(t)\rangle}{dt} = \sum_{n\geq 0}[\lambda_n - \mu_n]p_n(t) = \alpha + \beta\langle n(t)\rangle - \mu\langle n(t)\rangle.$$

The second moment $\langle n^2(t)\rangle$ satisfies the equation

$$\begin{aligned}\frac{d\langle n^2(t)\rangle}{dt} &= \sum_{n\geq 0} n^2\frac{p_n(t)}{dt}\\ &= \sum_{n\geq 0}(n+1)^2\lambda_n p_n(t) + (n-1)^2\mu_n p_n(t) - n^2(\lambda_n+\mu_n)p_n(t)\\ &= \sum_{n\geq 0} 2n(\alpha + \beta n - \mu n)p_n(t) + (\alpha + \beta n + \mu n)p_n(t)\\ &= 2\alpha\langle n(t)\rangle + 2(\beta-\mu)\langle n^2(t)\rangle + \alpha + (\beta+\mu)\langle n(t)\rangle.\end{aligned}$$

The variance $\sigma^2(t)$ of the population is

$$\begin{aligned}\frac{d\langle \sigma^2(t)\rangle}{dt} &= \frac{d\langle n^2(t)\rangle}{dt} - \frac{d\langle n(t)\rangle^2}{dt}\\ &= 2\alpha\langle n(t)\rangle + 2(\beta-\mu)\langle n^2(t)\rangle + \alpha + (\beta+\mu)\langle n(t)\rangle + 2\langle n(t)\rangle\frac{d\langle n(t)\rangle}{dt}\\ &= 2(\beta-\mu)\sigma^2(t) + (\beta+\mu)\langle n(t)\rangle + \alpha.\end{aligned}$$

Definition 1 [Coefficient of Variation] The coefficient of variation (CV) is defined as $\sigma/\langle n\rangle$. Compute it its limits when $t\to\infty$.

We have derived for the birth and death process closed form differential equations on **macroscopic** quantities: the mean population size $\langle n(t)\rangle$ and the variance $\sigma^2(t)$. The equation for the mean was uncoupled from the higher order moments, and this suggest that given a birth rate λ_n and a death rate μ_n, one could write down a macroscopic equation for the population density in a given domain V, $x = \langle n\rangle/V$,

macroscopic

$$\frac{dx}{dt} = \frac{1}{V}\lambda(xV) - V\mu(xV).$$

For instance, with the rates $\lambda_n = \alpha + \beta n$ and $\mu_n = \mu n$, the equation for the cell density is

$$\frac{dx}{dt} = \frac{\alpha}{V} + \beta x - \mu x.$$

This worked only because the rates are linear; nonlinear terms would make higher order moments of n appear in the equations. It is usual, when writing nonlinear population models based on ODEs, to neglect these higher order moments. This means that the population densities x obey deterministic system of equation that describes the production of new cells $P(x)$ (birth, recruitment) and the loss of cell $D(x)$ (death, loss through migration, differentiation or change):

$$\frac{dx}{dt} = P(x) - D(x).$$

For a system where $x \in \mathbb{R}^d$, the rate functions P and D are non-negative function from $\mathbb{R}^d$ to $\mathbb{R}^d$. The coefficient of the state vector x are the population densities (usually cell number per unit volume). Ideally the densities should be close to the mean of the underlying stochastic process. If noise (as defined by the coefficient of variation) is small, then it is reasonable to neglect σ^2 in front of $langlen\rangle$ and the deterministic system is a good approximation of the stochastic process.

As a rule of thumb, the noise acts on the system as

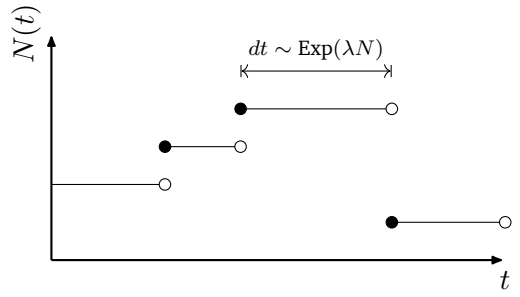
$$CV \approx \frac{1}{\sqrt{\langle n \rangle}}.$$

Therefore, as the population size goes to infinity, the noise should decrease to 0. This is a rule that should guide modelling only, and we can easily find examples where CV does not converges to 0 as the population goes to infinity.

When noise cannot be neglected, what can we do? One among many approaches is to expand the master equation and approximate it at the second order. This lead to an equation that will have two terms: one for the deterministic part, and one for the noise, or the stochastic part. The deterministic part will follow an equation similar to the one above, and the stochastic part will be described by a diffusion. The final equations have two different expressions: they can take the form of stochastic differential equations or deterministic convection-diffusion equations, called the Fokker-Planck equations.

1.2 Stochastic simulation algorithm (SSA)

In a discrete birth/death process, the variables are piecewise constant. If, for a given state at time t, we can generate the time of the next event, then this time is exact in the sense that the state cannot change before the time of the (known) next event.



Stochastic Simulation Algorithm

The **Stochastic Simulation Algorithm** is a numerical algorithm that takes advantage of the discrete nature of jumps in $N(t)$. For a n-dimensional birth/death process $N(t) \in \mathbb{N}^n$, we need the define

- the initial conditions $N_0 \in \mathbb{N}^n$ at time $t_0 \in \mathbb{R}$, such that $N(t_0) = N_0$,
- a list of all events, numbered from 1 to r,
- for each event k, $k \in \{1, ..., r\}$, the propensity $\lambda_N^{(k)}$. The propensities can have nonlinear dependence on the population size N, but cannot depend on the occurrence of other events; event probabilities are independent.
- the law of birth or death conditional to event k, given a population size N before the event, $\mathsf{Pr}(\text{add } j \text{ individuals}) = w_k^{(N)}(j)$, $j \in \mathbb{Z}$.

The propensites define a memoryless process. That is, the time to the next event has an exponential distribution. Neglecting all other events, the time τ_k to event k has an exponential distribution with parameter $\lambda_k^{(N)}$. When the r events are considered together, the time τ to the next event will be just $\min_{1 \le k \le r}\{\tau_k\}$. This is because during the interval $[t, t+\tau)$, the event probabilities are independent. At time t, the law of τ is a exponential with parameter $\lambda^{(N(t))}$, with

$$\lambda^{(N)} = \sum_{k=1}^{r} \lambda_k^{(N)}. \tag{3}$$

Independence also ensures that no two events can occur at the same time. When the event k is realised, the solution to the process will be $N(t+\theta) = N(t)$ for $\theta \in [0, \tau)$, and $N(t+\tau) = j$, with probability $w_k^{(N(t^-))}(j)$. The probability to choose event k is proportional to its propensity $\lambda_k^{(N)}$. After re-normalization,

$$\mathsf{Pr}(\text{choose event } k) = \frac{\lambda_k^{(N)}}{\lambda^{(N)}}. \tag{4}$$

A realization of $N(t)$ can be computed iteratively, by advancing in time by steps of size τ.

The algorithm goes as follows

```
################## SSA algorithm #################
# input:
#   N0: array of integers of size n, initial conditions
#   t0: real value, initial time
#   T : positive real value, time interval
# output:
#   N: array of integers of size n, the solution at N(t0 + T)
N = N0;
t = t0;
  while ( t < t0 + T ) {
    lambda = sum(lambda_k);
    tau = draw from exponential distribution with parameter lambda;
    k = draw from distribution with probabilities lambda_k/lambda;
    j = draw from distribution with probabilities w_k_j;
    N = N + j;
    t = t + tau;
  }
```

Notes. Parameters `tau`, `k`, `j` are drawn from specific distributions that can be easily reproduced using only a standard pseudo-random number generator by using the reciprocal of the repartition function. If the random variable X has a repartition function $F(x) = \mathsf{Pr}(X < x)$ and U is random variable with a uniform density on the $[0, 1]$ interval, then the random variable $F^{-1}(U)$ has the same distribution as X. The time to the next event can be computed with these steps

```
### Generate an exponential covariate ###
  u = rand01(); # u drawn from a uniform distribution on [0,1]
  tau = -log(u)/lambda; # log: natural log
  return tau;
```

For discrete probability laws, the repartition function is piecewise constant, and cannot be inverted. However, the repartition functon induces a partition of the unit interval. The i-th sub-interval has the size of the i-th probability. This means that drawing a integer i with probability p_i is equivalent to identifying which sub-interval contains a random variable drawn from a uniform distribution in the unit interval.

```
### Generate a discrete covariate ###
# p: array of size I of probabilities, p[i] = prob(choose i)
#    If needed, the values of i are rescaled between 1 and I
  u = rand01();  # u drawn from a uniform distribution on [0,1]
  c = cumsum(p); # c array with right-ends of sub-intervals
  i = find_first( u < c ); # find first index i such that u < c[i]
  return i;
```

The algorithm can be adapted for distributions with an infinite number of possibe values.

1.3 Links

Solutions for the birth and death process: Kendall (1948) On the Generalized "Birth and Death" Process.

Moment closure and the stochastic logistic equation model (Nåsell, 2003).

Stochastic equations in Matlab: An algorithmic introduction to numerical simulation of stochastic differential equations.

2 Dynamical systems approach to ODEs

dynamical systems

phase portait

linear stability

global stability analysis

Bifurcation analysis

The **dynamical systems** approach focuses on the qualtiative behaviour of the solutions, by opposition to the quantitative behaviour of the solution. As such, for a dynamical system described by ordinary differential equations, the aim will be to re-construct the **phase portait** and how it is modified by changes in the system parameters. Re-construction of the phase portrait relies on a combination of **linear stability** analysis, nonlinear **global stability analysis**, and geometrical and numerical methods. **Bifurcation analysis** studies the changes in the topological structure of the phase portrait.

2.1 Linear systems

Let n be a positive integer, A be a n-by-n real matrix, c be a vector in $\mathbb{R}^n$, t_0 and T in $\mathbb{R}$ and $x : [t_0, t_0 + T] \to \mathbb{R}^n$. The equations

$$\frac{dx}{dt}(t) = Ax(t), \tag{5}$$

$$x(t_0) = c. \tag{6}$$

linear system of ordinary differential equations

phase space

trajectory

orbit

phase portrait

dynamical system

vector field

form a **linear system of ordinary differential equations**. The vector x_0 is the initial condition. The **phase space** is the space in which the solution $x(y)$ lies, here it is $\mathbb{R}^n$. A **trajectory** or an **orbit** is the curve in the phase space defined by the solution x for $t \in [t_0, t_0 + T]$. The **phase portrait** is defined as the set of all trajectories generated by all initial conditions and all values of T (trajectories include curves with negative values of T).

The **dynamical system** defined by the system (5, 6) is the map $\phi : \mathbb{R} \times \mathbb{R}^n \to \mathbb{R}^n$, which, for $(t, c) \in \mathbb{R} \times \mathbb{R}^n$, is defined by the solution $x(t; c)$, where $x(0; c) = c$.

The right-hand-side Ax of equation (5) defines a **vector field** in the phase space.

Theorem 1 (Fundatmental theorem for linear systems) *The system (5, 6) has a unique solution* $x(t) = e^{At}c$.

In particular, if $c = 0$, the solution $dx/dt = 0$ and $x(t) = 0$ for all t. The value $x = 0$ is an **equilibrium point**.

equilibrium point

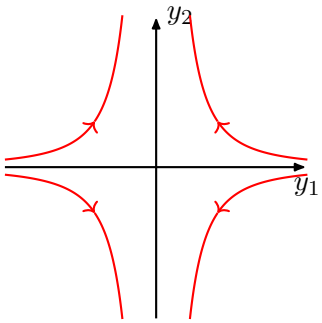
For $n = 2$, there are only four distinct phase portraits. Let PBP^{-1} be a Jordan decomposition of A, with P an invertible matrix, and B is an upper triangular matrix. The eigenvalues of A have either distinct real values λ, μ, repeated values $\lambda \in \mathbb{R}$, or complex conjugate values $\nu, \bar{\nu}$. The eigenvalue matrix B has one of the following form:

$$\begin{pmatrix} \lambda & 0 \\ 0 & \mu \end{pmatrix}, \qquad \begin{pmatrix} \lambda & 1 \\ 0 & \lambda \end{pmatrix}, \qquad \begin{pmatrix} \nu & 1 \\ 0 & \bar{\nu} \end{pmatrix}. \tag{7}$$

After a change of coordinates $y = P^{-1}x$, the phase portrait associated to the linear system is one of the following.

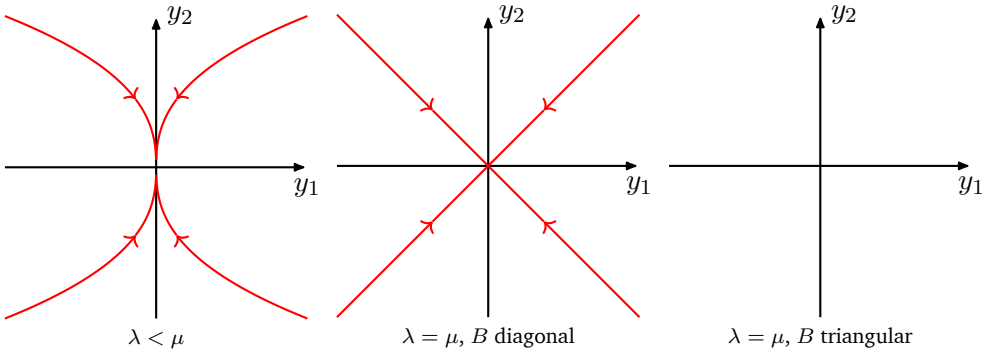
Case I—Distinct eigenvalues of opposite signs. Assume $\lambda < 0$ and $\mu > 0$. The equilibrium point $x = 0$ is a **saddle**.

saddle



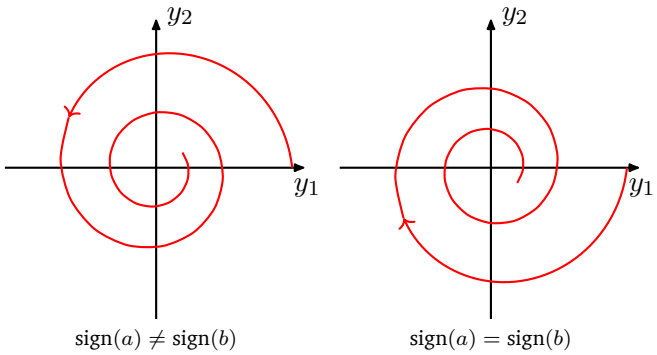
Case II—Eigenvalues of the same sign. Assume $\lambda \leq \mu < 0$. The equilibrium point $x = 0$ is a **node**.

node



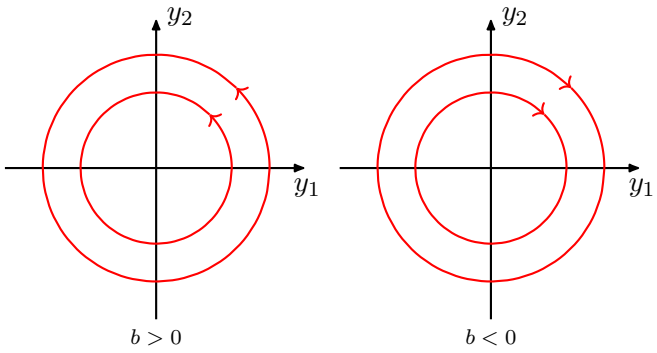
Case III—Complex eigenvalues. Assume $\nu = a + ib$, with a and b real, $a, b \neq 0$. The equilibrium point $x = 0$ is a **focus**.

focus



Case IV—Pure imaginary eigenvalues. Assume $\nu = ib$, for a real value b. The equilibrium point $x = 0$ is a **centre**.

centre



For $n \geq 1$, the phase space can be decomposed as a direct sum of linear subspaces associated to subset of eigenvalues with different signs. Denote $w_j = u_j + iv_j$ the j-th eigenvector and $\lambda_j = a_j + ib_j$ the j-th eigenvalue. The **stable subspace** E^S is the linear span of the eigenvectors associated to eigenvalues with negative real part.

stable subspace

$$E^S = \text{Span}\{u_j, v_j : a_j < 0\}. \tag{8}$$

The **unstable subspace** E^U is the linear span of the eigenvectors associated to eigenvalues with positive real parts.

unstable subspace

$$E^U = \text{Span}\{u_j, v_j : a_j > 0\}. \tag{9}$$

The **centre subspace** E^C is the linear span of the eigenvectors associated to eigenvalues with zero real parts.

centre subspace

$$E^C = \text{Span}\{u_j, v_j : a_j = 0\}. \tag{10}$$

The following statement are equivalent

- For all $c \in \mathbb{R}^n$, $\lim_{t\to\infty} e^{At}c = 0$ and for $c \neq 0$, $\lim_{t\to-\infty} |e^{At}c| = +\infty$.
- There exists positive constants M, c such that for all x_0, $|e^{At}x_0| < Me^{-ct}|x_0|$.
- The eigenvalues of A all have negative real parts.

2.2 Nonlinear systems

Let n be a positive integer, c a vector in $\mathbb{R}^n$, t_0 and T in $\mathbb{R}$ and $x : [t_0, t_0 + T] \to \mathbb{R}^n$, and $f : \mathbb{R}^n \to \mathbb{R}^n$. The equations

$$\frac{dx}{dt} = f(x), \tag{11}$$

$$x(t_0) = c. \tag{12}$$

form a **nonlinear system of ordinary differential equations**. The vector c is the initial condition.

nonlinear system of ordinary differential equations

The point $\bar{x}$ is an equilibrium point or a fixed point if $f(\bar{x}) = 0$. Let A be the n-by-n matrix defined by $A = \mathbf{D}f(\bar{x})$, where $\mathbf{D}f$ is the Jacobian matrix of f:

$$\mathbf{D}f = \begin{pmatrix} \frac{\partial f_1}{\partial x_1} & \frac{\partial f_1}{\partial x_2} & \cdots & \frac{\partial f_1}{\partial x_n} \\ \frac{\partial f_2}{\partial x_1} & \frac{\partial f_2}{\partial x_2} & \cdots & \frac{\partial f_2}{\partial x_n} \\ \cdots & & & \\ \frac{\partial f_n}{\partial x_1} & \frac{\partial f_n}{\partial x_2} & \cdots & \frac{\partial f_n}{\partial x_n} \end{pmatrix}. \tag{13}$$

The notation $\mathbf{D}f(\bar{x})$ means that the Jacobian matrix is evaluated at the point $\bar{x}$. The coefficients of A are

$$a_{ij} = \left.\frac{\partial f_i}{\partial x_j}\right|_{x=\bar{x}}. \tag{14}$$

The following theorem establishes that if the Jacobian matrix has no eigenvalue with zero real part, then the phase portrait of the linear system is **topologically equivalent** to the phase portrait of the nonlinear system, in a neighbourhood of the equilibrium point. Topological equivalent means that there exist a continuous transformation H with a continous inverse (a **homeomorphism**) that 1) maps trajectories from one system to the other, and 2) preserves time orientation in the sense that if a trajectory goes from x_1 to x_2, then it goes from $H(x_1)$ to $H(x_2)$. If, in addition, the homeomorhism preserves time parametrization, then the to systems are said to be **topologically conjugate**. While topological equivalence requires the direction of time to be preserved, topological conjugacy requires H not only to map trajectories, but corresponding points on the trajectories at the right times.

topologically equivalent homeomorphism

topologically conjugate

Let E be an open subset of $\mathbb{R}^n$ containing the origin, let $f : E \to E$ be continuously differentiable, and let ϕ_t be the flow if the system (11). Suppose that $f(0) = 0$, and let the Jacobian matrix $A = \mathbf{D}f(0)$. The next result is the **Hartman-Grobman Theorem**, taken from [15].

Hartman-Grobman Theorem

Theorem 2 *If A has no eigenvalues with zero real part, then there exists a homeomorhism H of an open open subset U of E containing the origin to an open subset V of $\mathbb{R}^n$ containing the origin such that there is an open interval $I_0 \subset \mathbb{R}$ containing zero such that for all $x_0 \in U$ and $t \in I_0$,*

$$H \circ \phi_t(x_0) = e^{At} H(x_0). \tag{15}$$

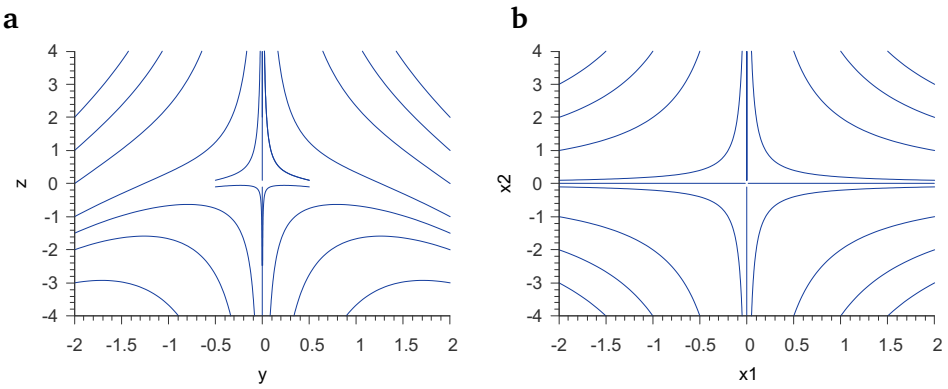


Figure 2. Illusration of the phase portrait of the system $y' = -y, z' = z + y^2$ (**a**), and its linearized system $x_1' = -x_1, x_2' = x_2$ (**b**).

That is, H maps trajectories of the nonlinear system onto the trajectories of the associated linear system, in a neighbourhood of the origin, and preserves the parameterization in time. The linear system is locally (in time and space) topologically conjugate to the nonlinear system (Figure 2).

The importance of this theorem lies in the fact that the asymptotic behaviour of the trajectories of the nonlinear system can be characterized locally by the linearized system around a equilibrium.

stable

Definition 2 A equilibrium $\bar{x}$ of the system (11) is **stable** if for all $\varepsilon > 0$, there exists $\delta > 0$ such that for all x_0 in a neighbourhood $B_\delta(\bar{x})$ of size δ centred at $\bar{x}$, the solution $\phi_t(x_0)$ remains in a neighbourhood $V_\varepsilon(\bar{x})$.

asymptotically stable

Definition 3 A equilibrium $\bar{x}$ of the system (11) is **asymptotically stable** if it is stable, and there exists $\delta > 0$ such that for all x_0 in a neighbourhood $B_\delta(\bar{x})$ of size δ centred at $\bar{x}$, $\lim_{t\to\infty} \phi_t(x_0) = \bar{x}$.

unstable
neutrally stable

An equilibrium is **unstable** if it is not stable. An stable equilibrium that is not asymptotically stable is sometimes called **neutrally stable**.

The Hartman-Grobman theorem ensures that an equilibrium $\bar{x}$ of the system (11) is asymptotically stable if the origin of the associated linear system $x' = \mathbf{D}f(\bar{x})$ is asymptotically stable.

For a linear system with a matrix A, the origin is stable if and only if A has no eigenvalue with a positive real part. The origin is asymptotically stable if and only if all eigenvalues have a negative real part. The origin is neutrally stable if A has eigenvalues with zero real parts, but none with positive real parts. The stability of the four types of planar equilibria can therefore be characterized by the location of the eigenvalues

- A saddle is always unstable.
- A node is aymptotically stable if all eigenvalues are negative (the usual case), and is unstable if all roots are positive.
- A focus is stable if the real parts of the eigenvalues are negative, and in unstable

if they are positive.

- A centre is always neutrally stable.

The planar equilibrium types for linear systems can be extended to nonlinear systems. For an equilibrium, we distinguish the stability and type associated to the nonlinear system (nonlinear equilibrium), and the stability and type associated to the linearized system (linear equilibrium). A nonlinear equilibrium is an asymptotically stable node if the linear equilibrium is an asymptotically stable node. A nonlinear equilibrium is an asymptotically stable focus if the linear equilibrium is an asymptotically stable focus. A nonlinear equilibrium is a saddle if and only if it is a linear saddle. However, if the equilibrium is a linear centre, the nonlinear equilibrium can be stable, asymptotically stable or unstable. Indeed, the Hartman-Grobman theorem says nothing about the qualitative structure of the nonlinear system when the Jacobian matrix possesses eigenvalues with zero real parts. We note however that is there are eigenvalues with positive real parts, the equilibrium is always unstable, regardless of the existence of a centre subspace.

Example 1 The equation $x' = -x^2$ has an equilibrium $\bar{x}$ the origin. It is unstable, because for an initial condition $x_0 < 0$ the solution diverges from 0. The linearized equation, $x' = 0$, has a centre, which is neutrally stable. We say that the equilibrium is a nonlinear saddle and a linear centre.

Example 2 The equation $x' = -x^3$ has a nonlinear asymptotically stable node at the origin, but the origin is only a linear centre.

These two examples reveal the importance of the nonlinear terms in the nonlinear stability of linear centres.

In higher dimensions, linear equilibria can combine several planar types, for instance a stable focus and an unstable saddle. Regardless of the dimension, negative (real) eigenvalues play no role in determining the stability and type of equilibrium. The characterization will be based on the dominant eigenvalues, that is, those with the largest real parts. If the dominant eigenvalue is real and positive, we will call the equilibrium a saddle. If it is negative, we will call the equilibrium a node. If the dominant eigenvalues are complex with non zero real parts, we will call the equilibrium a focus. If the dominant eigenvalues are imaginary, we will call the equilibrium a linear centre.

Linear subpaces E^C, E^S and E^U can be generalized to nonlinear systems. Assume $f(0) = 0$, and let k, j, and m be the number of eigenvalues of $\mathbf{D}f(0)$ with negative, positive and zero real parts, respectively. The **stable manifold** of an equilibrium $\bar{x}$, denoted W^S is a k-dimensional manifold tangent to E^S containing all values x_0 in $\mathbb{R}^n$ such that $\phi_t(x_0) \to \bar{x}$ when $t \to \infty$. The **unstable manifold** of an equilibrium $\bar{x}$, denoted W^U is a j-dimensional manifold, tangent to E^U, containing the values x_0 in $\mathbb{R}^n$ such that $\phi_t(x_0) \to \bar{x}$ when $t \to -\infty$. The **centre manifold** is a m-dimensional manifold tangent to E^C. These manifold are invariant under the flow ϕ.

stable manifold

unstable manifold

centre manifold

2.3 Bifurcations

Bifurcation analysis is a set of methods to study changes in the topological structure

Bifurcation

of the phase portrait of a dynamical system with respect to changes in system parameters. By the Hartman-Grobman theorem, the local topological structure around an equilibrium cannot change unless the equilibrium becomes a centre. Bifurcations will then usually occur when the dynamical system is modified so that eigenvalues of the linearized system cross the imaginary axis. Bifurcations at nonlinear equilibria include: transcritical bifurcations, saddle-node bifurcations, pitchfork bifurcations, and Hopf bifurcations. Bifurcations can also occur far from equilibirum points. In such cases, the linear phase portrait is not sufficient to re-construct the nonlinear phase portrait and nonlinear methods have to be used. Global bifurcations include: homoclinic and heteroclinic bifucations, and saddle-node bifurcations on invariant cycles. We first study bifurcations at equilibria.

For each bifurcation type, it will be useful to look at a generic, archetypical system. This generic system is called the normal form. Since the bifurcation will occur at a linear centre, it is enough to look at what happens at the center manifold, which is usually of low dimension compared to the dimension of the full system. Eigenvalues can cross the imaginary axis at 0, in such case the centre manifold will be of dimension 1, or they can cross as pairs of complex values, in such case the centre manifold will be of dimension 2.

Around an equilibirum, the system 11 can be decomposed into a linear part Ax and a nonlinear part $F(x)$,

$$\frac{dx}{dt} = Ax + F(x), \tag{16}$$

The goal is to make a suitable invertible nonlinear transformation to remove as many linear and quadratic terms (and higher order terms if possible). This simplified form is called the **normal form**. Once this is done, the higher order terms can be neglected, as they will not affect the qualitative structure of the phase portrait.

normal form

2.3.1 Saddle-node bifurcation

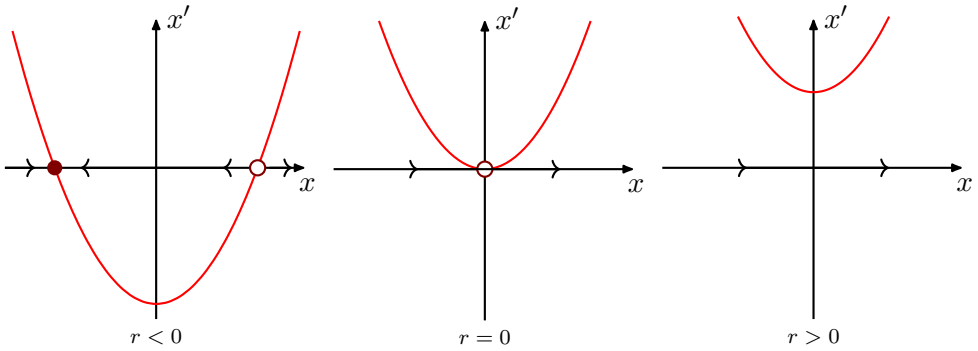
The normal form the the **saddle-node bifurcation** is the one-dimensional equation

saddle-node bifurcation

$$\frac{dx}{dt} = r + x^2. \tag{17}$$

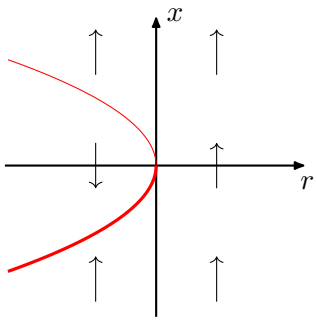
The parameter r is called the **bifurcation parameter**. As this parameter changes the phase portrait undergoes qualitative changes: the appearance/disappearance of two equilibria. The bifurcation point $r = 0$. At this point there is a single equilibrium $\bar{x} = 0$.

bifurcation parameter



The **bifurcation diagram** is the one parameter-family of phase portraits with respect to the bifurcation parameter. The bifurcation diagram is usually represented graphically, with the bifurcation parameter on the x-axis, and a suitable projection of the phase space on the y-axis. The normal form of the saddle-node bifurcation is one-dimensional, so the whole phase space can be put on the y-axis. Only the most important trajectories should be present on the diagram. In one-dimensional systems, these are equilibria, and possible the directions of other trajectories. Equilibra will appear as curves.

bifurcation diagram



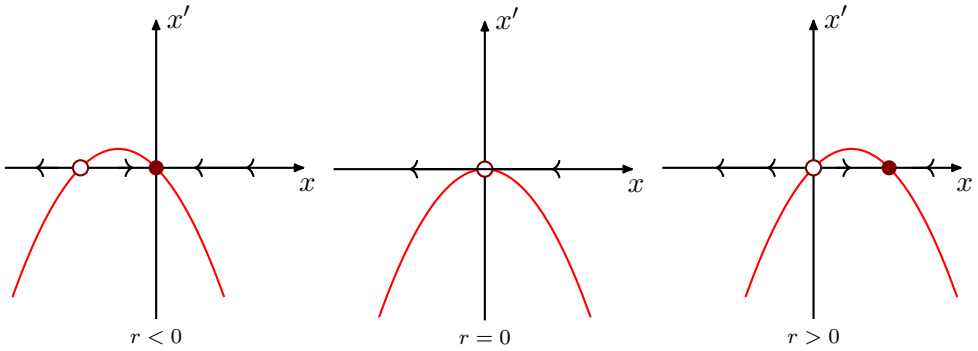
2.3.2 Transcritical bifurcation

The normal form the the **transcritical bifurcation** is the one-dimensional equation

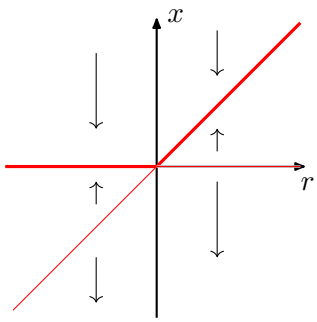
transcritical bifurcation

$$\frac{dx}{dt} = rx - x^2. \tag{18}$$

As r changes the phase portrait undergoes qualitative changes: the exchange of stability of two equilibria. The bifurcation point $r = 0$. At this point there is a single equilibrium $\bar{x} = 0$.



The bifurcation diagram is



This is a common bifurcation in biological models that include "threshold" effect. **Nucleation**, a process of initiation is self-organization, can often be described in simple models by a transcritical bifurcation [6]. Below threshold, organization is unlikely to occur, and the system remains at a stable basal state, corresponding to the zero equilibrium in the normal form. At the bifurcation point The organized state, represented by the equilibrium $\bar{x} = r$, is unstable. $(r = 0)$ the organized state merges with the basal state, and acquires stability for $r > 0$.

Nucleation

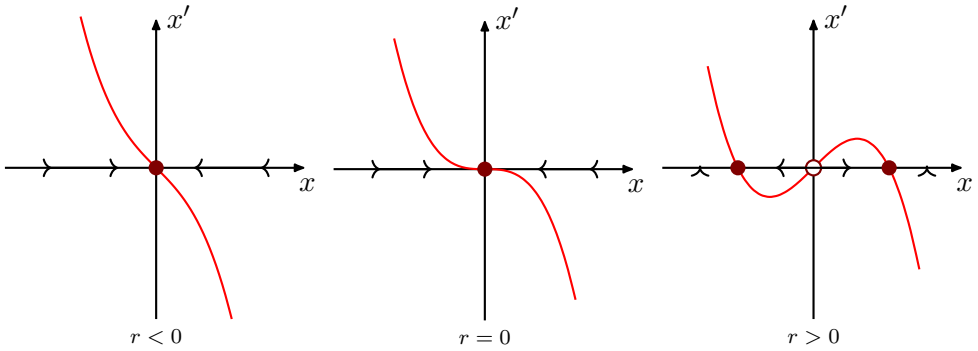
2.3.3 Pitchfork bifurcation

The normal form the the **pitchfork bifurcation** is the one-dimensional equation

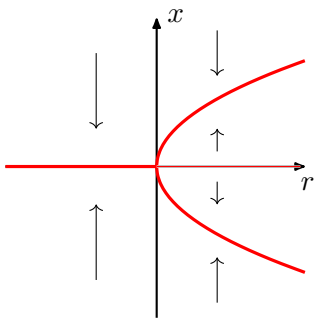
pitchfork bifurcation

$$\frac{dx}{dt} = rx - x^3. \tag{19}$$

As r changes the phase portrait undergoes qualitative changes: the exchange of stability of two equilibria. The bifurcation point $r = 0$. At this point there is a single equilibrium $\bar{x} = 0$.



The bifurcation diagram reveals why this bifrucation is called “pitchfork”.



The normal form of the pitchfork bifurcation involves a third-degree term, because the quadratic term is absent. This absence means that the pitchfork bifurcation requires a specific model structure to appear. Thus, unlike the transcritical and the saddle-node bifurcations, the pitchfork bifurcation is not generic and will not play a major role in the qualitative analysis of biological systems. The pitchfork bifurcation is an example of a co-dimension 2 bifurcation, which, loosely stated, requires two bifrucation parameter to appear: one to set the quadratic term to zero, and one to change the number of equilibria.

2.3.4 Hopf bifurcation

The three previous bifurcations (saddle-node, transcritical, and pitchfork) occured as one real eigenvalue crosses zero, and involved only equilibria. The **Hopf bifurcation** occurs when a pair of dominant complex conjugate eigenvalues cross the imaginary axis at a non-zero value. At the bifurcation, the origin goes from a stable focus to an unstable focus. In the generic nonlinear case, which the normal form captures, a single **limit cycle** appears. A limit cycle is a non-constant, closed trajectory, which attracts or repel neighbouring trajectories. Limit cycles are a type of periodic solutions.

Hopf bifurcation

limit cycle

The normal form for the Hopf bifurcation is best expressed in polar coordinates. Let z be a complex value , let λ be a real number, and b a complex number. The normal form is

$$\frac{dz}{dt} = z\big((\lambda + i) + b|z|^2\big). \tag{20}$$

The complex value z can be re-expressed as $z = re^{i\theta}$, where r is a positive real number, and θ is a real number. Let $b = \alpha + i\beta$, with α, β real numbers. The normal form becomes

$$\frac{dr}{dt} = \lambda r + \alpha r^3, \tag{21}$$

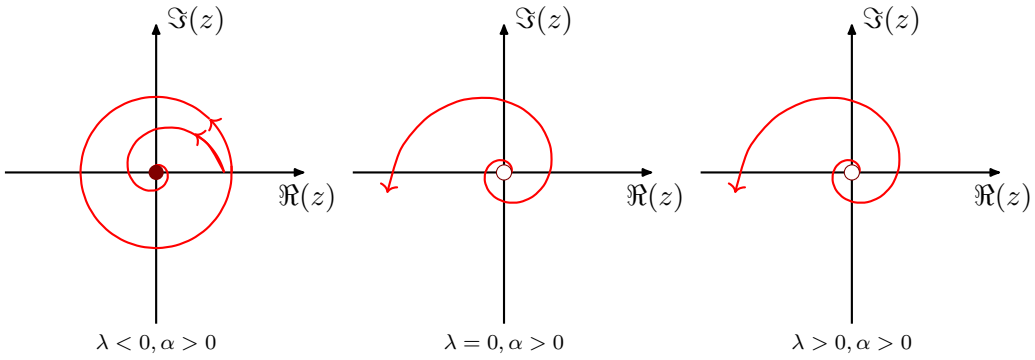
$$\frac{d\theta}{dt} = 1 + \beta r^2. \tag{22}$$

There is a always an equilibrium at the origin ($r = 0$, θ undetermined). When λ and α are of opposite signs (this implies $\alpha \neq 0$), there is a second equilibrium on r:

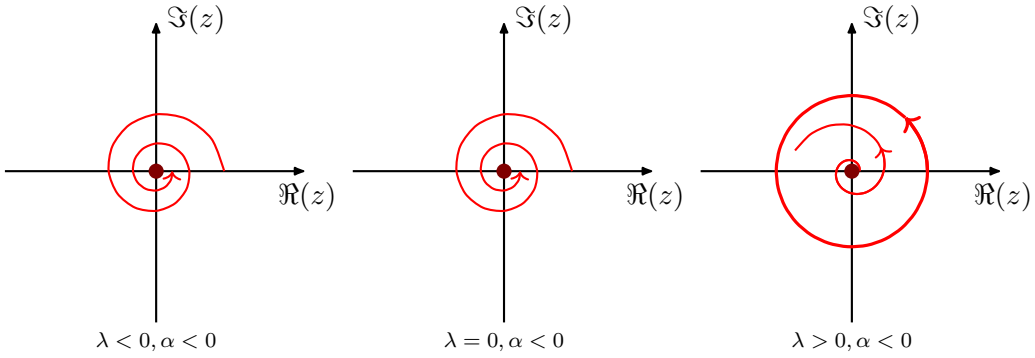
$$\bar{r} = \sqrt{-\frac{\lambda}{\alpha}}. \tag{23}$$

When $r = \bar{r}$, $\theta(t) = \theta_0 + (1 + \beta\bar{r}^2)t$. The trajectories are not at equilibirum in the plane, but evolve along a circle of radius $\bar{r}$ at constant speed $1 + \beta\bar{r}^2$. For the bifurcation analysis, we will use λ as the bifurcation parameter, and we will assume that $\beta > 0$. We will distinguish two cases: I) $\alpha > 0$ and II) $\alpha < 0$. Because we are concerned with equilibrium solutions on r only, stability analysis reduces to a one-dimensional problem. The Jacobian matrix at $r = 0$ is $A_0 = \lambda$, and the matrix at $\bar{r} > 0$ is $A_{\bar{r}} = -2\lambda$.

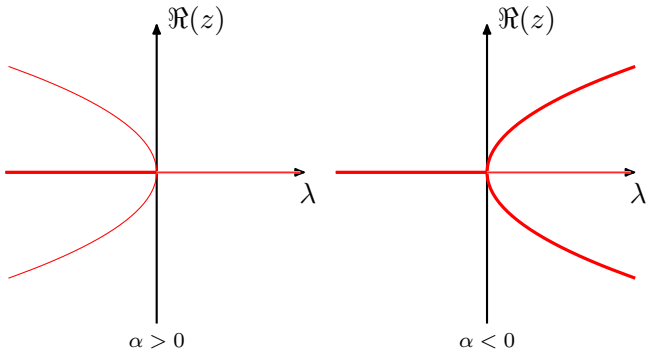
Case I—$\alpha > 0$. The equilibrium $\bar{r}$ exists for $\lambda < 0$. The origin is an asymptotically stable focus. At $\lambda = 0$, the origin is a linear centre, and the nonlinear stability must be determined from the nonlinear equation $r' = \alpha x^3$. The positive sign of α implies that the origin is unstable. When λ is positive, the origin is an unstable focus. The positive equilibrium $\bar{r}$, which exists for $\lambda < 0$, is unstable. In the plane, the equilibrium corresponds to an unstable limite cycle: it is a closed trajectory that repels nearby trajectories.



Case I—$\alpha < 0$. The equilibrium $\bar{r}$ exists for $\lambda > 0$. The origin is an unstable focus. At $\lambda = 0$, the origin is a linear centre, and the nonlinear stability must be determined from the nonlinear equation $r' = \alpha x^3$. The negative sign of α implies that the origin is asymptotically stable. When λ is negative, the origin is an unstable focus. The positive equilibrium $\bar{r}$, which exists for $\lambda > 0$, is asymptotically stable. In the plane, the equilibrium corresponds to an asymptotically stable limite cycle: it is a closed trajectory that attracts nearby trajectories.



We are now ready to draw the bifurcation diagrams. Because the phase space is planar, we must choose a one-dimensional representation for the bifurcation diagram. One choice would be to use r, but the real or the imaginary part of z are also sensible choices. Here we will use a projection of the phase space on the real part of z. For limit cycles, it is customary to draw the mininum and the maximum of the trajectory. Here these are $\pm\bar{r} = \pm\sqrt{-\lambda/\alpha}$.



The Hopf bifurcation occurs at $\lambda = 0$. When α is positive, the bifurcation is called a **subcritical Hopf bifurcation**, and when α is negative, the bifurcation is called a **supercritical Hopf bifurcation**.

subcritical Hopf bifurcation

supercritical Hopf bifurcation

2.3.5 Global bifurcations

Case study: Tumor-immune interaction (pdf, French).

Case study: Tumor-immune interation, numerical simulations with XPPAUT (pdf, French).

3 Systems in large dimension

4 Discrete dynamical systems

5 Delay differential equations

Models of self-regulating systems often include discrete delays in the feedback loop to account for the finite time required to perform essential steps before the loop is closed. Such mathematical simplifications are especially welcome in biological applications, where knowledge about the loop steps is usually sparse. This includes maturation and growth times needed to reach reproductive age in a population [10, 12], signal propagation along neuronal axons [4], and post-translational protein modifications [3, 14]. Introduction of a discrete delay in an ordinary differential equation can destabilize steady states and generate complex dynamics, from limit cycles to chaos [11]. Although the linear stability properties of scalar equations with single discrete delays are fairly well characterized, lumping intermediate steps into a delayed term can produce broad and atypical delay distributions that deviate from discrete delays, and it is still not clear how that affects the stability of the equation [5].

The delayed feedback differential equation of the form

$$\dot{x} = F\Big(x, \int_0^\infty x(t-s)d\eta(s)\Big)$$

is a model paradigm in biology and physics [1, 2, 7, 13, 14, 16]. The first argument of F is the instantaneous part of the loop and the second one, the delayed or retarded part, which closes the feedback loop. The function η is a cumulative probability distribution function, it can be continuous, discrete, or a mixture of continuous and discrete elements. In most cases, the stability of the above equation is related to its linearized equation about one of its steady states $\bar{x}$,

$$\dot{x} = -ax - b\int_0^\infty x(t-s)d\eta(s) \tag{24}$$

where the constants a and $b \in \mathbb{R}$ are the negatives of the derivatives of the instantaneous and the delayed parts of F at $x = \bar{x}$,

$$a = -\frac{\partial}{\partial x}F(x,y)\Big|_{x=y=\bar{x}} \quad \text{and} \quad b = -\frac{\partial}{\partial y}F(x,y)\Big|_{x=y=\bar{x}}.$$

Let B be the vector space of continuous and bounded functions on $[-\infty, 0] \to \mathbb{R}$. With the norm $||\phi|| = \sup_{\theta\in[-\infty,0]} |\phi(\theta)|$, $\phi \in B$, B is a Banach space.

Consider the linear retarded functional differential equation

$$\dot{x} = -ax - b\int_0^\infty x(t-s)d\eta(s) \tag{25}$$

with real constants a and b. We assume that η is a cumulative probability distribution function: $\eta : [0, \infty) \to [0, 1]$ is monotone nondecreasing, right-continuous, $\eta(s) = 0$ for $s < 0$ and $\eta(+\infty) = 1$. The corresponding probability density functional $f(s)$ is

given by the generalized derivative $d\eta(s) = f(s)ds$. The following definitions and Theorem follow from Stépán [17].

Definition 4 [Solution] The function $x : \mathbb{R} \to \mathbb{R}$ is a solution of equation (25) with the initial condition

$$x_\sigma = \phi,\ \sigma \in \mathbb{R},\ \phi \in B, \tag{26}$$

if there exists a scalar $\delta > 0$ such that $x_t \equiv x(t+\theta) \in B$ for $\theta \in [-\infty, 0]$ and x satisfies Eqs. (25) and (26) for all $t \in [\sigma, \sigma + \delta)$.

The notation $x_t(\sigma, \phi)$ is also used to refer to the solution of equation (25) associated with the initial conditions σ and ϕ.

Definition 5 [Stability] The trivial solution $x = 0$ of equation (25) is stable if for every $\sigma \in \mathbb{R}$ and $\varepsilon > 0$ there exists $\delta = \delta(\varepsilon)$ such that $||x_t(\sigma, \phi)|| < \epsilon$ for any $t \geq \sigma$ and for any function $\phi \in B$ satisfying $||\phi|| < \delta$. The trivial solution $x = 0$ is called asymptotically stable if it is stable, and for every $\sigma \in \mathbb{R}$ there exists $\Delta = \Delta(\sigma)$ such that $\lim_{t\to\infty} ||x_t(\sigma, \phi)|| = 0$ for any $\phi \in B$ satisfying $||\phi|| < \Delta$.

Definition 6 [Characteristic equations] The function $D : \mathbb{C} \to \mathbb{C}$ given by

$$D(\lambda) = \lambda + a + b \int_0^\infty e^{-\lambda s} d\eta(s),$$

is called the characteristic function of the linear equation (25). The equation $D(\lambda) = 0$ is called the characteristic equation of (25).

The following theorem [8, 17] gives a necessary and sufficient condition for the (linear) asymptotic stability of $x = 0$.

Theorem 3 *Suppose that there exists $\nu > 0$ such that the following inequality is satisfied:*

$$\int_0^\infty e^{\nu s} d\eta(s) < \infty. \tag{27}$$

The solution $x = 0$ of equation (25) is (exponentially) asymptotically stable if and only if all roots of the characteristic equation $D(\lambda) = 0$ have $\Re(\lambda) < 0$.

In particular, when the delay is bounded, i.e. when there is $h > 0$ such that $d\eta(s) = 0$ for all $s > h$, the condition is satisfied, and asymptotic stability is determined by the characteristic equation.

5.1 Discrete Delay Differential Equations

When η represents a single discrete delay (η a heaviside function), the asymptotic stability of the zero solution of equation (25) is fully determined by the following theorem, originally due to Hayes [9]. Let $\eta(s) = \mathbb{1}_{[\tau,+\infty)}$, for a constant $\tau > 0$ then equation (25) simplifies to

$$\dot{x} = -ax - bx(t - \tau). \tag{28}$$

The generalised differential of η is a Dirac mass centered at τ: $d\eta(s) = \delta(s - \tau)ds$.

Theorem 4 (Hayes) *Let the delay probability density be $f(s) = \delta(s-\tau)$, a Dirac mass at τ. The zero solution of equation (25) is asymptotically stable if and only if $a > -b$ and $a \geq |b|$, or if $b > |a|$ and*

$$\tau < \frac{\arccos(-a/b)}{\sqrt{b^2 - a^2}}.$$

More generally, the following statements always hold for any delay distribution:

(i) When $a \leq -b$, the characteristic equation of equation (25) has a positive real root.

(ii) When $a \geq |b|$ and $a > -b$, the characteristic equation of equation (25) has no root with positive real part.

Proof The delay τ being bounded, we can use the characteristic equation to study the asymptotic statibility of equations (28). This means that we are looking for exponential solutions, just as in the case of ordinary differential equations. Assume there is a solution $x(t) = \exp(\lambda t)$, for some complex value λ. Then, the characteristic equation is

$$\begin{aligned} \dot{x} = \lambda x(t) &= -ax(t) - bx(t-\tau), \\ \lambda e^{\lambda t} &= -ae^{\lambda t} - be^{\lambda(t-\tau)}, \\ \lambda &= -a - be^{-\lambda\tau}. \end{aligned}$$

The characteristic equation is trancendental, and possesses an infinity of roots for $\tau > 0$, always in pair of complex conjugates. When $\tau = 0$, there is a single root located at $\lambda = -a - b$. This root is negative when $a > -b$, zero when $a = -b$ and positive when $a < -b$. By continuity of the characteristic equation in τ, roots cannot appear in the right-half complex plane. Roots $\lambda = \mu + i\omega$ must be located on the following curve (figure 3),

$$\omega = \pm\sqrt{b^2 e^{-2\mu\tau} - (\mu + a)^2}.$$

When τ is continuously increased from zero, the only way stability can change is when roots cross the imaginary axis, i.e. when $\Re(\lambda) = 0$.

For $a = -b$, the dominant root $\lambda = 0$ for all $\tau \geq 0$. For $a < -b$, there exists a positive root $\lambda > 0$ for all $\tau \geq 0$. For $a > -b$ and τ sufficiently small, all roots have negative real parts. If there is a critical value τ^* such that a pair of roots crosses the imaginary axis, then the delay can destabilise the equilibrium. We obtain , after setting $\lambda = i\omega$, and separating the real and imaginary parts of the characteristic equation,

$$\begin{aligned} a + b\cos(\omega\tau) &= 0, \\ \omega - b\sin(\omega\tau) &= 0. \end{aligned}$$

The equations can be solved for ω by summing up the squares for get rid of the trigonometric functions. Therefore, there is a pair of imaginary roots when

$$\tau = \tau^* = \frac{\arccos(-a/b)}{\omega},$$

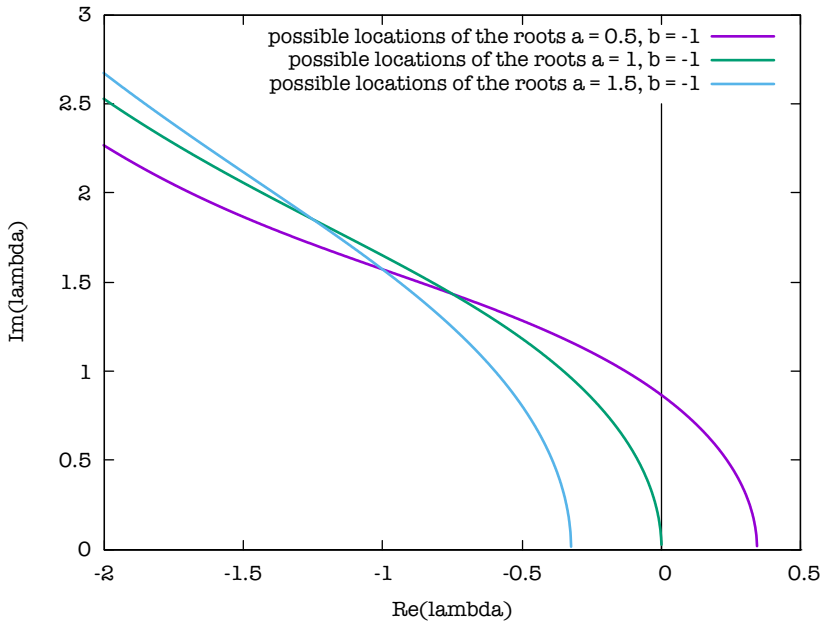


Figure 3. Possible locations of the roots of the characteristic equations, for $a = 0.5, 1.0$ and 1.5, and $b = -1$.

where $\omega = \sqrt{b^2 - a^2}$. To finish the proof, it remains to show that the pair of imaginary roots becomes, and stay positive, when $\tau > \tau^*$. To do that, we need to check that the derivative $d\Re(\lambda)/d\tau$ is always positive at $\lambda = \pm i\omega$. The derivative of λ wrt to τ is obtained implicitly by differentiating the characteristic equation. Let $\lambda' = d\lambda/d\tau$, we have

$$\lambda' + be^{-\lambda\tau}\Big(-\tau\lambda' - \lambda\Big) = 0.$$

At an imaginary root, $i\omega + a + be^{-i\omega\tau} = 0$, so

$$\lambda'\Big(1 + \tau a + i\omega\tau\Big) = i\omega\big(-a - i\omega\big).$$

It follows that

$$\begin{aligned}
\lambda' &= \frac{i\omega\big(-a - i\omega\big)}{\Big(1 + \tau a + i\omega\tau\Big)}, \\
&= \frac{\big(-ia\omega + \omega^2\big)\big(1 + \tau a - i\omega\tau\big)}{(1 + \tau a)^2 + \omega^2\tau^2}, \\
&= \frac{\omega^2 - i\big(a\omega + a^2\tau\omega + \omega^3\big)}{(1 + \tau a)^2 + \omega^2\tau^2}.
\end{aligned}$$

The real part of the derivative is strictly positive, since $\omega^2 = b^2 - a^2$. This completes the proof.

Note When τ increases further, there will be several other pairs of root crossing to the right half-complex plane. None of these roots can cross back to the left half-plane. Another way to look a the stability of equation 28 is by fixing the value of τ and finding the region of stability in the (a, b)-plane. This is called a **stability chart** (figure 4). The characteristic equation can be solved parametrically for a and b:

stability chart

$$b(\omega) = \frac{\omega}{\sin(\omega\tau)},$$
$$a(\omega) = -\omega\frac{\cos(\omega\tau)}{\sin(\omega\tau)}.$$

The parameters have a periodic denominator. The zeros of the denominator delimit branches of the parametric curve (a, b). Only branches with $b > 0$ are relevant here, and these branches are well-ordered. The first branch corresponds to the interval $\omega \in [0, \pi/\tau)$, and this is the branch that determines the boundary of stability (figure 4, it dashed curve).

6 Tools and software

- XPPAUT oldish but still widely used
- MATCONT Matlab package for ODEs
- DDE-BIFTOOL Matlab package for delay differential equations
- PyDSTool Dynamical systems in Python (ODEs and algebraic differential equations, hybrid systems). Based on numpy et scipy

References

[1] M. Adimy, F. Crauste, and S. Ruan. A mathematical study of the hematopoiesis process with applications to chronic myelogenous leukemia. *SIAM J. Appl. Math.*, 65(4):1328–1352, 2005.

[2] F.M. Atay. Distributed delays facilitate amplitude death of coupled oscillators. *Phys. Rev. Lett.*, 91(9):94101, 2003.

[3] S. Bernard, B. Čajavec, L. Pujo-Menjouet, M.C. Mackey, and H. Herzel. Modelling Transcriptional Feedback Loops: The Role of Gro/TLE1 in Hes1 Oscillations. *Philos. Trans. R. Soc. London, Ser. A*, pages 1155–1170, 2006.

[4] S.A. Campbell. Time delays in neural systems. In A.R. McIntosh and V.K. Jirsa, editors, *Handbook of Brain Connectivity*, pages 65–90. Springer, 2007.

[5] S.A. Campbell and R. Jessop. Approximating the Stability Region for a Differential Equation with a Distributed Delay. *Math. Mod. Nat. Phenom.*, 4(2):1–27, 2009.

[6] Leah Edelstein-Keshet, William R Holmes, Mark Zajac, and Meghan Dutot. From simple to detailed models for cell polarization. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 368(1629):20130003, 2013.

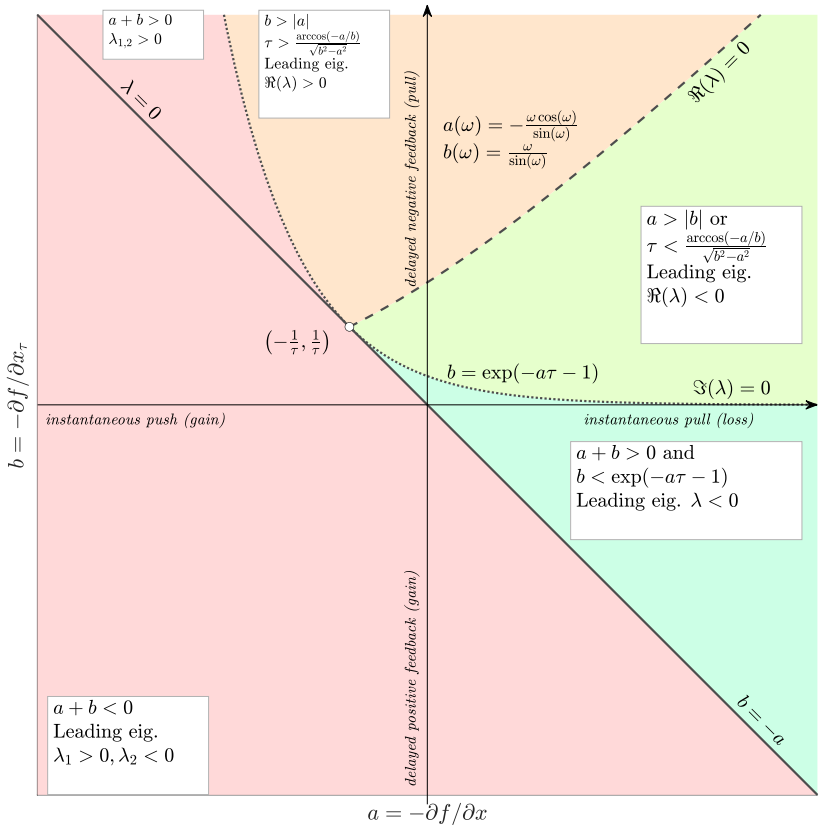


Figure 4. Stability chart for the linear delay differential equation $x' = -ax + bx_\tau$ with discrete delay $\tau = 1$. The region of stability is in green, while the region of instability is in red.

[7] C.W. Eurich, A. Thiel, and L. Fahse. Distributed delays stabilize ecological feedback systems. *Phys. Rev. Lett.*, 94(15):158104, 2005.

[8] J.K. Hale. Functional differential equations with infinite delays. *J. Math. Anal. Appl.*, 48(1):276–283, 1974.

[9] ND Hayes. Roots of the transcendental equation associated with a certain difference-differential equation. *J. Lond. Math. Soc.*, 25:226–232, 1950.

[10] G.E. Hutchinson. Circular causal systems in ecology. *Ann. N.Y. Acad. Sci.*, 50(4):221–246, 1948.

[11] Y. Kuang. *Delay differential equations: With applications in population dynamics*. Academic Pr, 1993.

[12] M. C. Mackey. Unified hypothesis of the origin of aplastic anaemia and periodic hematopoiesis. *Blood*, 51:941–956, 1978.

[13] U. Meyer, J. Shao, S. Chakrabarty, S.F. Brandt, H. Luksch, and R. Wessel. Distributed delays stabilize neural feedback systems. *Biol. Cybern.*, 99(1):79–87, 2008.

[14] N.A.M. Monk. Oscillatory expression of Hes1, p53, and NF-κB driven by transcriptional time delays. *Curr. Biol.*, 13(16):1409–1413, 2003.

[15] Lawrence Perko. *Differential equations and dynamical systems*, volume 7. Springer Science & Business Media, 2013.

[16] K. Rateitschak and O. Wolkenhauer. Intracellular delay limits cyclic changes in gene expression. *Math. Biosci.*, 205(2):163–179, 2007.

[17] G. Stépán. *Retarded dynamical systems: stability and characteristic functions*. Longman Scientific & Technical New York, 1989.

Index