Physical Modeling of Complex Systems (2020)

List of Problems

1 Population Dynamics

1.1 Logistic growth

a) Solve exactly the logistic equation[1]

$$\dot{N} = \alpha N \left(1 - \frac{N}{K}\right) \tag{1}$$

starting from an initial population $N = N_0$.

b) With the help of a Matlab (or Mathematica, or whatever you like) code solve the same equation numerically by discretizing the differential equation to first order[2] in a small time step Δt using $\alpha = 3$ and $K = 10^3$. Consider $N_0 = 10$ and $N_0 = 10^5$. Plot the numerical and analytical solution as functions of time and verify that they overlap.

c) Perform a linear stability analysis by expanding Eq. (1) around the stable fixed point $N = K$ and deduce the long time behavior. What is the characteristic relaxation time to the stationary point? Plot $\log |N(t) - K|$ as a function of time and check that both the exact solution and that computed from discretization agree with the expected long time behavior.

1.2 Sustained Harvesting

Consider a population evolving following a logistic growth. The population is subject to harvesting (for instance fishing in a fish population). We consider two different models of harvesting:

$$\dot{N} = \alpha N \left(1 - \frac{N}{K}\right) - EN \tag{2}$$

$$\dot{N} = \alpha N \left(1 - \frac{N}{K}\right) - Y_0 \tag{3}$$

where the parameters α and K are fixed, while E and Y_0 can vary. We refer to Eq. (2) as *constant effort* harvesting, while to Eq. (3) as *constant yield* harvesting. We say that there is a *sustained harvesting* if a stable fixed point with $N^* > 0$ exists. The *yield* is the fraction of harvested population per unit of time, which is $Y = EN$ and $Y = Y_0$ in the cases (2) and (3) respectively.

a) Show[3] that for E and Y_0 sufficiently large the Eqs. (2) and (3) have no stable fixed points with $N^* > 0$. For lower E and Y_0 other fixed points appear. Discuss their nature (stable, unstable, half-stable?).

b) Consider the range of parameters in which a stable fixed point $N^* > 0$ is present in the two cases. Keeping α and K fixed what is the maximal yield possible?

c) Harvesting at a constant yield (Eq. (3)) is not a general good strategy. Can you explain why?

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[1] Hint: use the transformation $y = 1/N$ which maps Eq. (1) into a linear differential equation. This differential equation is known in mathematics as a Bernoulli equation.

[2] Although more sofisticated numerical techniques exist, for the purposes of this course it is sufficient to discretize the differential equation $\dot{N} = f(N)$ as $N(t + \Delta t) \approx N(t) + f(N(t))\Delta t$.

[3] This problem can be solved quite easily graphically. Plot on a graph the logistic term $y = \alpha N(1 - N/K)$ and find N^* from the intersection with the line $y = EN$ or $y = Y_0$.

1.3 Gompertz law

Another type of population growth model was developed by Gompertz. According to this model the number of individuals in the population follows the differential equation

$$\dot{N} = \alpha N \log\left(\frac{K}{N}\right) \tag{4}$$

a) Find an appropriate variable transformation and solve this differential equation exactly.

b) Plot the exact solution of Eq. (4) and compare it with that of Eq. (1) for the same initial condition and parameters α and K. Can you understand qualitatively the differences between the two models[4]?

1.4 Delays

In general it is easy to show that a first order non-linear differential equation $\dot{N} = f(N)$ cannot have oscillating solutions. However, oscillating solutions are possible if the equation contains some delay. Consider for instance a delay in the logistic growth:

$$\dot{N}(t) = \alpha N(t)\left(1 - \frac{N(t-T)}{K}\right) \tag{5}$$

where we fix the parameters to $T = 3$, $\alpha = 1$ and $K = 10^3$.

a) Solve the differential equation (5) numerically, using as initial condition $N(t) = 10$ for $t \leq 0$. Show that after an initial transient the solution follows an oscillating behavior at long times.

b) Repeat the numerical calculation for an initial condition $N(t) = 10^5$ for $t \leq 0$. Show that at long times the solution is the same as in (a), except for possibly a phase shift[5].

1.5 Rabbits versus Sheep

We consider the following model of two competing populations, which belongs to the class of Lotka-Volterra models[6]:

$$\begin{aligned} \dot{N} &= N(3 - N - 2M) && (6) \\ \dot{M} &= M(2 - N - M) && (7) \end{aligned}$$

The two populations follow a logistic growth[7], but compete for common resources. This interactions is described by the negative non-linear cross-terms.

a) Show that the system has three fixed points and determine their nature.

b) Determine the full phase portrait, eventually with help of numerical calculation. Conclude that in this model the two populations cannot coexist.

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[4] Hint: Compared the two left hand sides of Eqs. (4) and (1), to predict the rate of growth of the populations for small and large N's.

[5] This type of solution is known as *limit cycle* (more on this will follow)

[6] This example is taken from ithe book S. Strogatz, "Nonlinear dynamics and chaos" (Perseus, 1994)

[7] This is different from the basic LV model in which, in absence of competitors, one species grows exponentially and the other shrinks exponentially. Here in absence of competitors the two species has stable fixed points $N = 3$ and $M = 2$

1.6 Population model with delay: analytics

We consider the equation

$$\dot{N} = rN\left(1 - \frac{N(t-T)}{K}\right) \tag{8}$$

The population N follows logistic growth, but there is a time delay in the competition term, which can account for, for example, a maturation time, or a delayed effect of the species on its environment.

In problem 1.4 you are asked to solve this equation numerically. Here we will investigate the stability of the steady state analytically.

a) By suitable rescaling of N and t, show that the equation can be rewritten as

$$\frac{du}{ds} = u(1 - u(t-\tau)) \tag{9}$$

Naturally, the scaled delay time τ depends on r and T. From now on we will use u' to denote $\frac{du}{ds}$ and use t instead of s again.

b) For a delay equation, steady states are constant solutions where $u' = 0$. Since they are constant, $u(t) = u(t-\tau) = u^*$. Find the steady states.

c) As for ODEs, the stability of the steady states can be determined by considering the evolution of a small perturbation. This is done by setting $u = u^* + U$, where u^* is the steady state and $U(t)$ is the small perturbation, which is time dependent. By substituting into the equation and only keeping linear terms in U, show that, for the non-zero steady state, you find the following equation for U:

$$U' = -U(t-\tau) \tag{10}$$

d) The steady state is stable, if for any solution of the form $U = e^{\lambda t}$, the real part of λ is smaller than zero. Show that, by substituting this form into the linear equation above, we obtain the following condition on λ:

$$\lambda = -e^{-\lambda\tau} \tag{11}$$

e) Show graphically (by plotting both sides of the equation as function of λ) that any *real* solution of this equation has negative real part, for any value of τ.

f) To find complex solutions, take $\lambda = \mu + i\omega$. Substitute this into 11 and separate real and imaginary parts. One can show (you needn't) that for small τ, there are only solutions with $\mu < 0$, such that the steady state is stable. As τ increases beyond a threshold, values of λ with $\mu > 0$ appear in a so-called *Hopf* (or *Andronov-Hopf*) bifurcation. Find the threshold value for τ above which $\mu > 0$ by putting $\mu = 0$ and solving for ω and τ.

g) Finally go back to unscaled variables. By using your result for the instability threshold τ, show in the (r, T) plane for which values of r and T the solution is stable, and where it is oscillatory (unstable).

This type of equation has been used to explain periodic behavior in isolated populations, eg. without predator or competition.

1.7 Spruce budworm dynamics

We consider the equation

$$\dot{N} = rN\left(1 - \frac{N}{K}\right) - \frac{BN^2}{A^2 + N^2}. \tag{12}$$

This equation describes the dynamics of the spruce budworm population. The first term describes logistic growth, the second term describes predation by birds. Predation is nonlinear.

a) Plot the curve which shows predation as function of the number of worms. Start with $B = 1$ and $A = 2$:

$$f(N) = \frac{N^2}{4 + N^2}$$

Interpret the shape of this curve. How can you explain ecologically that the amount of predation levels off? Next, investigate the effect of the parameters A and B and describe.

b) Show that by rescaling the variables as

$$u = N/A \quad q = K/A \quad \rho = rA/B \quad s = Bt/A,$$

we can reduce the equation to

$$\frac{du}{ds} = \rho\left(1 - \frac{u}{q}\right) - \frac{u^2}{1 + u^2} \tag{13}$$

c) Analytically determine the stability of the zero steady state.

d) Graphically determine the steady states of this system, for example by looking at intersections of the curves

$$f(u) = \rho(1 - u/q) \quad \text{and} \quad f(u) = \frac{u}{1 + u^2}$$

Try different values of ρ and q. How many solutions are there in addition to the zero solution? How does this depend on ρ and q?

e) In reality, the worms grow faster when it is warmer. The value of r, and therefore of ρ, is temperature-dependent. Fix a number for q (for example $q = 10$), and vary ρ from low to high values. By determining (graphically) the steady states for increasing values of ρ, show that the population of budworms can suddenly jump to a large population when the temperature rises, for example in summer. What happens when after summer the temperature and therefore ρ slowly decrease? The phenomenon you observe is called a hysteresis phenomenon, and can have a huge impact on ecosystems.

f) Verify numerically your solution: solve the system starting with a low value of ρ and let it evolve to the non-zero steady state. Increase ρ a bit and solve again, using your previous steady state as initial condition. Continue doing this and plot the steady states as function of ρ.

g) (Difficult!) Determine the region in (ρ, q) space where three (non-zero) steady states exist. Hint: start from the graphical determination of the steady state as intersection of the two curves, and determine conditions for two of the intersection points to coalesce (in this case both the functions and their tangents are equal at the intersection point). Note: you will not find explicit expressions for ρ as function of q, but you can describe $\rho(\phi)$ and $q(\phi)$ as parameteric curves with ϕ as a parameter. Plot the region. What shape does it have?

1.8 Lotka-Volterra: predator-prey model and a more realistic extension

The classic predator-prey models is given by

$$\begin{aligned} \dot{N} &= aN - bNP \\ \dot{P} &= cNP - dP \end{aligned} \tag{14}$$

The solutions of this system are closed trajectories in the (N, P) plane, thus oscillations in time for both variables.

a) Show that the system, by adequately rescaling the variables and redefining parameters, can be rewritten as

$$\begin{aligned} u' &= u(1-v) \\ v' &= \gamma v(u-1) \end{aligned} \tag{15}$$

where $\gamma = d/a$.

b) This system is *conservative*. This means there is a conserved quantity (similar to the sum of kinetic and potential energy for a mechanical system). kind of energy conservation. Show that the function

$$H = \gamma u + v - \ln(u^{\gamma} v)$$

remains constant over time. This implies that many cyclic solutions exist together, and which one the system follows depends on the initial conditions. You can compare this to a pendulum, where the intial condition determines the amplitude of the periodic motion.

c) The Lotka-Volterra model is not realistic and has some undesireable features. For example, in the absence of predators, the prey population would grow unboundedly. Numerous extensions of the model have been proposed. One of them reads after suitable scaling:

$$\begin{aligned} u' &= u\left(1 - \frac{u}{q}\right) - \frac{uv}{1+u} \\ v' &= cv\frac{u}{1+u} - dv \end{aligned} \tag{16}$$

This model is also called the Rosenzweig-MacArthur model. Explain how these equations differ from the basic Lotka-Volterra model. Hint: in the Lotka-Volterra model, predation depends on u and v as uv. Here, the prey dependence is given by $u/(1+u)$.

What does this function look like, and what does it tell us about the capacity of predators to eat prey?

d) For this model, determine the steady states and their stability. First, take fixed parameters $c = 1$ and $d = 1/2$, but leave $q > 1$ undetermined and determine fixed points and their stability as function of q. You may find that there is a threshold value of q, above which the system's behavior changes markedly.

e) Run numerical simulations to check your stability results. You should find oscillatory behavior for large enough q. Does the amplitude of the oscillation depend on the initial condition? Contrast with the original Lotka-Volterra equations.

f) (Optional) take c and d as undetermined parameters and see how they influence the fixed points and their stability.

You will notice that increasing the carrying capacity of the prey, q, leads to bigger oscillations of the system. In real ecosystems, this actually increases the risk of extinction: large amplitude oscillations pass close to the $u = 0$ line, and when a little noise is added, the prey may go extinct. The phenomenon that increasing prey capacity may destabilize the ecosystem is sometimes called the *paradox of enrichment.*

2 Recap of concepts of non-linear dynamics

2.1 Classification of Linear Systems

Discuss the nature of the fixed point $x = y = 0$ of the following linear differential equations. Plot the trajectories in the vicinity of this fixed point. Indicate real eigenvectors in your sketch.

a)

$$\begin{cases} \dot{x} &= y \\ \dot{y} &= -2x - 3y \end{cases}$$

b)

$$\begin{cases} \dot{x} &= -3x + 4y \\ \dot{y} &= -x + y \end{cases}$$

c)

$$\begin{cases} \dot{x} &= -3x + 4y \\ \dot{y} &= -2x + 3y \end{cases}$$

2.2 Damped Harmonic Oscillator

The motion of a damped harmonic oscillator is described by $m\ddot{x} + b\dot{x} + kx = 0$, where $b > 0$ is the damping constant.

a) Rewrite the equation as a two-dimensional linear system.

b) Classify the fixed point at the origin and sketch the phase portrait. Be sure to show all the different cases that can occur, depending on the relative sizes of the parameters.

c) How do the results relate to the standard notions of overdamped, critically damped, and underdamped vibrations?

2.3 Phase portrait in two dimensions

We consider a system of two coupled non-linear differential equations

$$\begin{cases} \dot{x} &= f(x, y) \\ \dot{y} &= g(x, y) \end{cases} \tag{17}$$

Each solution of this system forms a continuous curve in the xy plane. Given an initial value (x_0, y_0) the curve is such that at any given points of coordinates (x, y), the vector with coordinates $(f(x, y), g(x, y))$ is tangent to it. The phase portrait is a geometric representation of the solutions of the system in the xy plane. An example of phase portrait is shown in Fig. 1. Note that two different solutions *never cross*! This is because we assume that the function $f(x, y)$ and $g(x, y)$ are sufficiently regular (it is sufficient that the functions are continuous with a continuous first derivative) so that given an initial value the solution of (17) is unique.

In order to sketch the phase portrait one can start from the analysis of the *nullclines*, which are the curves in the (x, y) plane for which $\dot{x} = 0$ or $\dot{y} = 0$. The intersection of the nullclines are the fixed points of the problem. In addition the nullclines divide the plane in regions with different signs of $\dot{x}$ and $\dot{y}$ and a solution cross the nullclines parallel to the x or y axes.

As an example we consider the following system As an example we consider the following system

$$\begin{cases} \dot{x} &= x - y \\ \dot{y} &= 1 - e^{x} \end{cases} \tag{18}$$

a) Draw the two nullclines and identify the fixed points.

b) Find the signs of $\dot{x}$ and $\dot{y}$ in the four regions of the xy-plane partitioned by the nullclines.

c) On the basis of the results stketch a plausible form of a phase portrait. Include the nullclines in your graph.

d) Confirm these findings by plotting the numerical solutions, obtained by Matlab or other tools, from the discretization of the (18) using in particular as initial conditions $(x, y) =(1, 2)$, $(1, 1.5)$, $(-1, -2)$ and $(-1, -1.2)$.

2.4 Poincaré-Bendixson Theorem

(This is problem 7.3.1 from the book of Strogatz)

The Poincaré-Bendixon theorem states that if a closed set R of the plane without a fixed point there is a trajectory $\vec{x}(t)$ which remains confined in R, then R contains a periodic orbit. To apply this theorem one should constract a trapping region, i.e. to find R such that all trajectories at the boundary flow inside it.

Consider the system

$$\begin{cases} \dot{x} = x - y - x\,(x^2 + 5y^2) \\ \dot{y} = x + y - y\,(x^2 + y^2) \end{cases} \tag{19}$$

we construct a trapping region for this system, which is an annulus $R = \{(x, y) \text{ with } r_1 \leq \sqrt{x^2 + y^2} \leq r_2\}$

a) Using the linear stability analysis classify the fixed point in $(0, 0)$.

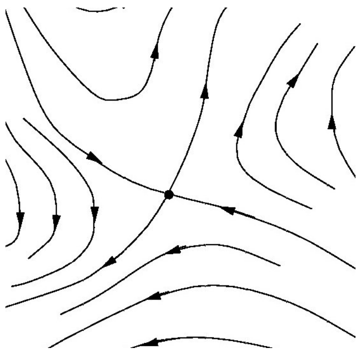

Figure 1: Example of a phase portrait of a two dimensional system. In this case the fixed point is a saddle node.

b) Rewrite the system in polar coordinates, using $r\dot{r} = x\dot{x} + y\dot{y}$ and $\dot{\theta} = (x\dot{y} - y\dot{x})/r$.

c) Using the Equation for $\dot{r}$ determine the circle of maximal radius, r_1, centered on the origin such that all trajectories have a radially outward component on it (eg $\dot{r} > 0$).

d) Determine the circle of minimal radius, r_2, centered on the origin such that all trajectories have a radially inward component on it (eg $\dot{r} < 0$).

e) Having constructed the trapping region we can then apply the Poincaré-Bendixon theorem. We know then that the system has a closed orbit. By solving the system (19) numerically, show that the closed orbit is a limit cycle contained in the trapping region $r_1 \leq r \leq r_2$. Show that the limit cycle is stable by plotting the numerical solutions of Eq. (19) using as initial values $r < r_1$, $\theta = 0$ and $r > r_2$, $\theta = 0$.

3 Quasi steady state approximation

3.1 Quasi steady-state approximation: a linear example

When dealing with N coupled first order differential equations, one can use of the so-called *quasi-steady-state approximation*. This approximation can be applied if one variable evolves much faster than the others. Let us suppose that $x_1(t)$ is the "fast" variable. We take then $\dot{x_1} = 0$, from which one obtains $x_1(t)$ as a function of all other $N-1$ variables. In this way we reduce the problem to a system of $N-1$ equations. The procedure is known in mathematics as singular perturbation theory.

As an example of this method, consider the following system of linear differential equations

$$\begin{cases} \dot{x} &= -3x + y \\ \dot{y} &= 100(2x - y) \end{cases}$$

with the given initial conditions $x(0) = 1$ and $y(0) = 0$.

a) Identify the "fast" and the "slow" variable.

We now rewrite this system of linear equations in matrix form as

$$\dot{\Omega}(t) = M\Omega(t)$$

with $\Omega(t) = \begin{pmatrix} x(t) \\ y(t) \end{pmatrix}$. M is a 2×2 matrix.

Note that this linear system of differential equations can be solved exactly. The solution can be expressed in terms of eigenvectors and eigenvalues of M (facultative).

Eventually, the equations can be integrated numerically as follows

$$\Omega(t + \Delta t) \approx \Omega(t) + \Delta t M\Omega(t) + \mathcal{O}(\Delta t^2) \tag{20}$$

b) Use Eq. (20) to trace the trajectories of $x(t)$ and $y(t)$ (with a sufficiently small Δt to avoid numerical rounding errors, and using the initial conditions given above).

c) Apply the quasi-steady-state approximation to Eq. (20) now by setting $\frac{dy}{dt} = 0$ and expressing $y(t)$ as a function of $x(t)$.

b) Plot the solutions of the quasi-steady-state approximation from (c) and compare them with the numerical exact solution of (b). Do the steady-state solution approximates well the full solution at all times?

3.2 Enzymatic degradation

In many situations a chemical X is degraded, meaning that it breaks into fragments which do not participate to the reactions anymore. *Spontaneous* degradation of X, i.e. a reaction $X \to \emptyset$ is described in the mass action kinetics by a term $-\alpha x$, where x is the concentration of X, and α the degradation rate. Synthesis and degradation of a chemical are described by the equation

$$\frac{dx}{dt} = \beta - \alpha x \tag{21}$$

where β is the creation rate, which can eventually depend on other chemical concentrations. For the time being we take β as a constant.

We consider here a different type of degradation due to the effect on an "enzyme" E on X. The enzymatic degradation is described by the following reactions

$$E + X \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} EX \xrightarrow{k'} E \tag{22}$$

which describe binding of X to the enzyme E and the formation of a complex EX, through a reversible reaction, followed by the irreversible degradation of X. Once degradation has occurred the free enzyme is released.

Use the quasi steady state approximation, i.e. assume that the complex EX is rapidly formed, to find a new form of degradation term replacing the αx in Eq. (21).

3.3 Two subunit enzyme

We consider an enzyme which is formed by two subunits and which we denote as EE. Each subunit is capable of transforming a substrate S in a product P. The reactions are:

$$EE + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} EES \tag{23}$$

$$EES \xrightarrow{k_3} EE + P \tag{24}$$

$$EES + S \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} SEES \tag{25}$$

$$SEES \xrightarrow{k_4} EES + P \tag{26}$$

We consider the steady state approximation for the formation of the two complexes EES and SEES.

a) Consider the following choice of rates: $k_1 = 2k_2$, $k_{-2} = 2k_{-1}$, $k_4 = 2k_3$. Argue that this choice corresponds to the case of two subunits acting independently from each other. Show that the system follows the usual Michaelis-Menten kinetics:

$$\frac{dp}{dt} = \frac{v_{\max} s}{K_m + s} \tag{27}$$

and determine the parameters $v_{\max}$ and K_m as functions of k_1, k_{-1} and k_3.

b) Find the equation governing the product formation for arbitrary values of the parameters. Express this equation as a function of the Michaelis-Menten constants $K_{m1} = (k_{-1} + k_3)/k_1$ and $K_{m2} = (k_{-2} + k_4)/k_2$ of the interaction of the enzyme with the first and second substrate.

c) Show that in the limit $K_{m1} \to \infty$ and $K_{m2} \to 0$ such that $K_{m1}K_{m2} \to const.$ one finds Hill kinetics with a Hill exponent equal to 2.

3.4 Messenger RNA dynamics

In the description of gene networks in the course we have neglected mRNA production. We consider here a model in which both mRNA and protein productions are taken into account. These are described by the following linear differential equations

$$\frac{dy}{dt} = f_m - \alpha_m y \tag{28}$$

$$\frac{dY}{dt} = py - \alpha Y \tag{29}$$

where y is the mRNA concentration and Y the protein concentration. f_m is the mRNA production rate while α_m and α represent the degradation rates of mRNA, protein respectively. Equation (28) assumes that the rate of protein production is proportional to the mRNA concentration.

a) What is the general solution of Eqs. (28,29) given the initial conditions $y(0) = Y(0) = 0$?

b) Now consider the limit $\alpha_m \gg \alpha$, i.e. the mRNA degrades much faster than the protein. Take this limit in the general solution of Eqs. (28,29). What does this limit correspond to?

4 Motifs

From *Wikipedia*: Network motifs are connectivity-patterns (sub-graphs) that occur much more often than they do in random networks. Most networks studied in biology, ecology and other fields have been found to show a small set of network motifs; surprisingly, in most cases the networks seem to be largely composed of these network motifs, occurring again and again.

4.1 Motifs in the E. Coli Gene Regulatory Network

The Regulatory Network of the bacteria E. Coli can be found in `http://itf.fys.kuleuven.be/~enrico/Teaching/coliInterFullVec.txt` This list contains per row three numbers: x, y and z, where x and y are numbers identifying two proteins. The z is instead 1, 2 or 3, where 1 means protein X is an activator for protein Y, while 2 means protein X represses protein Y and the 3 means that the type of interaction is unknown. As an example, the first row of the file is 3 4 2 which means the protein 3 represses the protein 4. In the file `http://itf.fys.kuleuven.be/~enrico/Teaching/coliInterFullNames.txt` you will find a "dictionary" to assign to each number a protein name: for instance protein 3 is acrAB and protein 4 is acrR.

a) By analyzing the above given files determine the number of nodes (N) and the number of edges (E) of the network.

b) Determine the number of selfregulating[8] proteins N_{self} and distinguish the number of activators (N^a_{self}) and repressors (N^r_{self}).

c) Calculate analytically $\langle N_{\text{self}} \rangle$ the average number of selfregulating nodes in a random network with the same number of nodes and edges as the above network. Conclude that selfregulation is a *network motif*.

d) Another interesting regulation pattern is the Feed Forward Loop (FFL) shown in Fig. 2. How many FFLs can you detect in the above file? Show that FFLs occurr more often in the above file than in a random network[9]. Thus FFLs are *network motifs* as well.

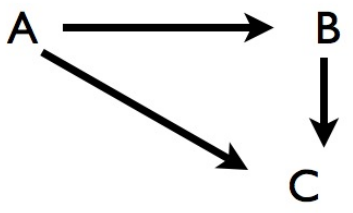

Figure 2: The Feed Forward Loop.

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[8] Those which interact with themselves; these are lines in the file with the same numbers in the first two columns, as eg. the second line of the file 6 6 3.

[9] This number can be calculated analytically. But you can also generate your own random network with the same number of nodes and edges as the above. You can then compute the average number of FFLs in many randomly generated networks, to check if this number matches with your analytical result.

4.2 Positively autoregulated protein

As shown in the previous problem autoregulation is a network motif. We consider the case of a positively autoregulated protein whose production is governed by the following differential equation

$$\frac{dX}{dt} = \frac{\beta X^n}{X^n + K^n} - \alpha X \tag{30}$$

Here the first term is a Hill function with Hill coefficient n. The $n = 1$ is the Michaelis-Menten kinetics.

a) Non-dimensionalize Eq. (30) by rescaling appropriately X and the time. Show that the dynamics is governed by a single parameter which is a combination of α, β and K.

b) Consider the case $n = 1$. For which values of α, β and K has Eq. (30) a fixed point with $X = X^* > 0$? Is this fixed point stable or unstable?

c) Solve numerically Eq. (30) using $\alpha = \beta = 1$ and $K = 1/4$, taking as initial value $X(0) = 10^{-3}$. Plot on the same graph your numerical solution with the solution of the non-regulated protein synthesis i.e.

$$\frac{dX}{dt} = \beta - \alpha X \tag{31}$$

using the same parameters and initial condition. From the analysis of the graph of the solution of Eq. (30) and from the analytical solution of Eq. (31) determine the *response time*[10] for the two cases and show that positive autoregulation leads to a longer response time compared to the non-regulated case.

d) We consider now the case $n = 2$. For which values of α, β and K does Eq. (30) show bistability?

4.3 Negatively autoregulated protein

We consider the case of a negatively autoregulated protein whose production is governed by the following differential equation

$$\frac{dX}{dt} = \frac{\beta K^n}{X^n + K^n} - \alpha X \tag{32}$$

a) Numerical solution for $n = 3$ and $n = 8$

b) Compare with the boolean approximation

c) In the case of delay we expect

$$\frac{dX}{dt} = \frac{\beta K^n}{X(t-\tau)^n + K^n} - \alpha X \tag{33}$$

solve numerically again.

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[10] We recall that the response time is the time for the system to reach half of the stationary value concentration

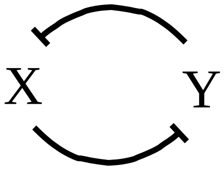

Figure 3: Two mutually repressing Transcription Factors. This module is known as *Genetic Toggle Switch*.

4.4 Genetic Toggle Switch

We consider two transcription factors mutually repressing each other as illustrated in Figure 3. This system can become bistable and thus can be considered as a genetic switch [11]. To understand qualitatively bistability consider the case in which the concentration of X is high: the production of Y is then repressed, so Y has a low concentration. If this happens Y cannot repress X, which then maintains its high concentration. The other possibility is a symmetric situation in which the role of X and Y is interchanged. Bistability occurs only for some specific choice of model and parameters.

We consider the following model

$$\frac{dX}{dt} = f(Y) - \alpha X \tag{34}$$

$$\frac{dY}{dt} = f(X) - \alpha Y \tag{35}$$

where $f()$ is a repressor Hill functions characterized by the three parameters β, K and n

$$f(X) = \frac{\beta K^n}{X^n + K^n} \tag{36}$$

a) Perform a non-dimensionalization of Eqs. (34, 35).

b) Show that if the Hill coefficient is $n = 1$ the Eqs. (34, 35) have a single fixed point (X^*,Y^*) with $X^* = Y^*$. There is thus no bistability.

c) Consider now the case $n = 2$. Show that if $\beta > 2\alpha K$ the Eqs. (34, 35) have three fixed points: one symmetric ($X^* = Y^*$) and two asymmetric ($X^* > Y^*$ and $Y^* > X^*$). Show also that there is a single symmetric fixed point ($X^* = Y^*$) if $\beta < 2\alpha K$.

   Hint: To get a qualitative picture use a graphical solution by plotting the two nullclines on the XY plane. As function of the parameters one may have one or three intersections between the nullclines. To find the bifurcation value show first that asymmetric fixed points are characterized by the relation $X^*Y^* = K^2$. *Use this relation to prove that asymmetric fixed points exist only for some choice of the parameters.*

d) Compute the Jacobian matrix of the system. Show that the the symmetric fixed point is stable if $\beta < 2\alpha K$, while it becomes a saddle node if $\beta > 2\alpha K$. Show that the asymmetric fixed points are always stable.

e) Draw the phase portrait of the system.

---

[11] The properties of an artificially synthesized Genetic Toggle Switch was discussed by Gardner et al. in Nature **403**, 339 (2000), see `http://www.nature.com/nature/journal/v403/n6767/pdf/403339a0.pdf`

4.5 Negatively autoregulated cascade

Study the dynamics of the negatively autoregulated cascade shown in Fig. 4. In this simple motif the protein X represses the production of Y. Both X and Y negatively regulate their own promoters. We assume logic input functions with threshold levels K_X, K_Y and K_{XY} for the action of X on its own promoter, of Y on its own promoter and of X on Y , respectively. For simplicity we take the production rates are all equal to β.

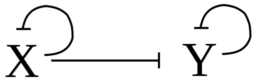

Figure 4: Negatively autoregulated cascade.

a) At time $t = 0$, X begins to be produced starting from $X(0) = 0$, while Y is at its stationary level $Y(0) = K_Y$. What is the dynamics of X and Y? What are the response times of X and Y?

b) At time $t = 0$, the production of X stops after a long period of production, the concentration decays from its initial steady-state level. What are the dynamics of X and Y? What are the response times of X and Y?

5 Non-linear Oscillators and limit cycles

5.1 Brusselator (was an optional exercise)

The Brusselator is a model described by the coupled differential equations

$$\frac{dx}{dt} = a + x^2 y - (b+1)x \tag{37}$$

$$\frac{dy}{dt} = bx - x^2 y \tag{38}$$

where a and b are positive constants.

a) Trace the nullclines and show that the system has a unique fixed point.

b) In a two dimensional systems one distinguishes two types of oscillators depending on the sign patterns of the Jacobian: the substrate-depletion and activator-inhibitor oscillators. To which of these two does the Brusselator belong?

c) Consider a fixed value of b and a varying a. From the shape of the nullclines determine in which parameter range the Jacobian has the correct sign pattern for limit cycles to arise from a Hopf bifurcation. Determine analytically the values of a and b at the Hopf bifurcation.

d) By solving numerically the differential equations show that inside the above region there is a limit cycle solution.

5.2 The Goodwin model

The Goodwin model[12] is one of the simplest models of biological oscillators. This model is described by the following three differential equations:

$$\frac{dx}{dt} = \frac{1}{1+z^p} - bx \tag{39}$$

$$\frac{dy}{dt} = b(x-y) \tag{40}$$

$$\frac{dz}{dt} = b(y-z) \tag{41}$$

(in non-dimensionalized form). Note that there is only one non-linear term in the model describing repression of the variable z on x.

a) Show that the equations have a unique fixed point.

b) Show that the model fixed point undergoes a Hopf bifurcation for $p > 8$ (this is an unrealistically high value for the cooperativity parameter p), while there is no Hopf bifurcation for $p < 8$.

c) Show by numerical integration of the equations (39, 40,41) that in the region of parameters in which the fixed point is unstable there is a limit cycle. For this purpose plot the trajectories of the solutions of the differential equations in the xy, yz and xz planes using different initial conditions.

---

[12] See: B. Goodwin, Nature **209**, 479 (1966)

We consider now a generalized Goodwin model with N components

$$\begin{aligned}
\frac{dx_1}{dt} &= \frac{1}{1+x_N^p} - bx_1 && (42)\\
\frac{dx_2}{dt} &= b(x_1 - x_2) && (43)\\
\frac{dx_3}{dt} &= b(x_2 - x_3) && (44)\\
&\dots && (45)\\
\frac{dx_N}{dt} &= b(x_{N-1} - x_N) && (46)
\end{aligned}$$

d) Show that the system has a unique fixed point. Find, for a given N, the minimal value of p for which Hopf bifurcation is possible.

5.3 The Repressilator

We consider a mathematical model of the repressilator as in the paper by M. B. Elowitz and S. Leibler (Nature **403**, 335 (2000)) `http://www.elowitz.caltech.edu/publications/Repressilator.pdf`

The repressilator is a synthetic genetic regulatory network consisting of three genes connected in a feedback loop, such that each gene represses the next gene in the loop, and is repressed by the previous gene. The model is given in terms of 6 coupled differential equations:

$$\begin{aligned}
\frac{dm_i}{dt} &= -m_i + \frac{\alpha}{1+p_j^n} + \alpha_0 && (47)\\
\frac{dp_i}{dt} &= -\beta(p_i - m_i) && (48)
\end{aligned}$$

where m_i is the mRNA concentration and p_i is the protein concentration of the three species. In the above equations the mRNA production from gene i is regulated by protein j with $i = 1, 2, 3$ and $j = 2, 3, 1$ respectively. The equations are written in dimensionless units.

a) What is the physical meaning of the three parameters α, α_0 and β?

b) Show that the only steady state of the system is the symmetric one, i.e. that satisfying $p_1 = p_2 = p_3 = m_1 = m_2 = m_3 = p$.

c) Show that the linearization of the equations around the steady state give:

$$\frac{dz}{dt} = Az \tag{49}$$

where the six dimensional jacobian matrix is

$$A = \begin{pmatrix} -I & XC \\ \beta I & -\beta I \end{pmatrix} \tag{50}$$

and where $X = -\alpha n p^{n-1}/(1+p^n)^2$ (as in the paper), while I is the 3×3 identity matrix and C is the cyclic permutation matrix:

$$C = \begin{pmatrix} 0 & 1 & 0 \\ 0 & 0 & 1 \\ 1 & 0 & 0 \end{pmatrix} \tag{51}$$

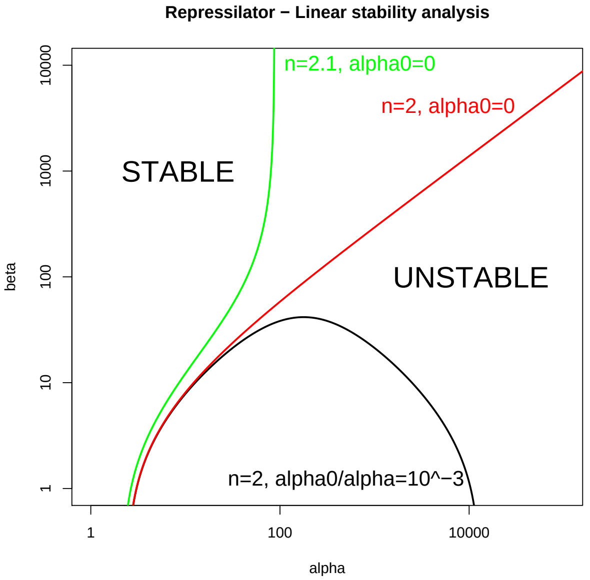

Figure 5: Linear stability analysis of the repressilator for different values of the parameters n, α and α_0. Notice that the unstable region grows when n is increased.

Let λ be an eigenvalue of A with eigenvector $(\delta m, \delta p)$. Show that the following relation is verified:

$$C\delta p = \frac{(\lambda+\beta)(\lambda+1)}{\beta X}\delta p \tag{52}$$

d) The Eq. (52) relates the eigenvalues of the matrix C to the eigenvalues of the matrix A. Given Γ eigenvalue of C express λ as a function of Γ, solving a second order equation.

e) With the help of the result of the previous point derive the stability condition given in the paper, which is that the steady state becomes unstable if[13]:

$$\frac{(\beta+1)^2}{\beta} < \frac{3X^2}{4+2X} \tag{53}$$

f) Plot the phase boundary between unstable and stable fixed points in the $\alpha - \beta$ plane for i) $n = 2$, $\alpha_0 = 0$, ii) $n = 2$, $\alpha_0 = 0$, iii) $n = 2$, $\alpha_0/\alpha = 10^{-3}$. You should obtain a graph as that shown in Fig. 5. (See Figure 1b in M. B. Elowitz and S. Leibler, *A synthetic oscillatory network of transcriptional regulators*, Nature **403**, 335 (2000)).

g) With the help of the stability condition, find a set of parameters for which the repressilator oscillates. Plot the $p_i(t)$ obtained from the numerical discretization of Eqs.(47) and (48).

---

[13] Instability occurs if the eigenvalues of A gets a positive real part. You will find that this is equivalent to prove that $Re\sqrt{z} > 1$, with z a complex number. Use then the representation $z = |z|e^{i\phi}$ to work out the previous relation

5.4 A synthetic genetic oscillator

J. Hasty *et al.* (Phys. Rev. Lett. **88**, 148101, (2002) [14]) considered a model of a synthetic genetic oscillator. The oscillator contains two genes CI and Lac, whose proteins concentrations are denoted by X and Y, respectively. The two genes are engineered to have the same promoter region. Transcription initiates when two CI dimers are bound to the promoter. If a Lac tetramer is bound to the promoter transcription is stopped. CI acts thus as an *activator* and Lac as a *repressor*. Although there is a large number of chemical reactions involved, which are described using mass action kinetics, the system is mapped onto a two coupled differential equations describing the time evolution of the protein concentrations of CI and Lac. Use the reactions given in Table I of the paper and the quasi steady state approximation to obtain the dimensionless Eqs. (2) of the paper.

5.5 Delays in protein synthesis

A simple model of protein synthesis producing robust limit cycle type of oscillations is the following[15]:

$$\frac{dY(t)}{dt} = \frac{k_1 S K_d^p}{K_d^p + Y^p(t-\tau)} - \frac{k_2 E_T Y(t)}{K_m + Y(t)} \tag{54}$$

Here the protein undergoes enzymatic degradation of a Michaelis-Menten form and E_T is the total concentration of the enzyme. The synthesis term is described by a Hill function with coefficient p and has a delay: the protein produced at time t depends on its concentration at time $t - \tau$. We use the choice of parameters as in the paper by Novak and Tyson: $p = 2$, $K_m/K_d = 1$, $S/K_d = 1$, $k_1 = k_2 E_T/K_d = 1$ min^{-1} and $\tau = 10$ min.

a) Solve numerically the differential equation (54) and show that the solution is oscillatory of limit cycle type[16].

b) Estimate the period of the oscillation; check if your result matches that of the paper of Novak and Tyson.

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[14] This paper can be downloaded from: `http://biodynamics.ucsd.edu/pubs/articles/Hasty02.pdf`

[15] This model comes from the paper by B. Novak and J. Tyson, Nat Rev Mol Cell Biol **9**, 981 (2008); `http://www.nature.com/nrm/journal/v9/n12/full/nrm2530.html`

[16] To show that the solution is a limit cycle you can start from different initial conditions and show that the system reaches the same solution, it may eventually have a phase shift.

6 Chaos

6.1 The Lorenz system

The Lorenz system is given by

$$\dot{x} = \sigma(y - x) \tag{55}$$
$$\dot{y} = rx - y - xz \tag{56}$$
$$\dot{z} = xy - bz \tag{57}$$

with σ, r, b parameters.

1. Find the coordinate transformation that transforms the waterwheel equations into the Lorenz system.
2. Examine the linear stability of the non-zero fixed points (C^+, C^-). What is the characteristic equation that you get?
3. Look for solution of the form $\lambda = i\omega$ with ω real. Calculate for which value of r there is a Hopf bifurcation, where there is a pair of pure imaginary eigenvalues.

6.2 The Rössler system

The Rössler system is given by

$$\dot{x} = -y - z \tag{58}$$
$$\dot{y} = x + ay \tag{59}$$
$$\dot{z} = b + z(x - c) \tag{60}$$

with a, b, c parameters. Notice that this system only contains one nonlinear term, whereas the Lorenz system has two nonlinear terms.

1. Numerically explore the dynamics of the Rössler system for $a = b = 0.2$. Plot some time series and phase space plots for changing values of c. Also draw an orbit diagram in function of c.
2. Calculate the fixed points of the system and examine their linear stability (for $a = b = 0.2$ and changing values of c).
3. Similarly as for the Lorenz system, one can try to obtain a one-dimensional map for this system. Calculate successive local maxima of $x(t)$ for a chaotic time series. Plot x_{n+1} in function of x_n. What type of curve do you obtain?

6.3 The logistic map

The logistic map

$$x_{n+1} = rx_n(1 - x_n)$$

can be derived by scaling from a typical growth model with a certain carrying capacity. The behavior of the map is strikingly different from the behavior of the corresponding differential equation.

1. Simulate the above map with initial conditions x_0 in the range [0-1], for different parameters r between 0 and 4. Look at both time series and cobwebb diagrams. What different behaviors do you see?
2. Determine the steady states of the equation and their stability.
3. Draw an orbit diagram in function of r. Approximately determine values of r for which the behavior changes. The behavior of the logistic map for increasing r is called the period-doubling route to chaos.

6.4 The sine and tent map

The sine map is given by

$$x_{n+1} = rsin\pi x_n$$

with r and x between 0 and 1.
Another well-known map is called the tent map, defined by

$$x_{n+1} = rx_n$$

for $x \in [0, 1/2]$ and

$$x_{n+1} = r - rx_n$$

for $x \in [1/2, 1]$ and this for r between 0 and 2.

1. Similarly as for the logistic map, draw an orbit diagram in function of r. Approximately determine values of r for which the behavior changes.
2. Compare these orbit diagrams between the different maps. When you observe a period-doubling cascade to chaos, then calculate the distance in r between consecutive period-doubling bifurcations, and estimate the following quantity based on the first period-doubling bifurcations: $\delta = \frac{r_n - r_{n-1}}{r_{n+1} - r_n}$.

7 Synchronization

7.1 The period of a nonuniform oscillator

The oscillation period of the Adler system is given by the integral $T = \int_{-\pi}^{\pi} \frac{d\theta}{\omega - a\sin\theta}$, where $\omega > a > 0$. Evaluate this integral as follows.

1. Let $u = \tan\frac{\theta}{2}$. Solve for θ and express $d\theta$ in terms of u and du.
2. Show that $\sin\theta = 2\frac{u}{1+u^2}$.
3. Express T as an integral with respect to u.
4. Reduce the integral to the following form: $T = \int_{-\infty}^{\infty} \frac{dx}{r+x^2}$
5. This integral also describes the time spent in a bottleneck generated close to a saddle-node bifurcation. Such bifurcation is given by $\dot{x} = r + x^2$, with r small and proportional to the distance from the bifurcation. Evaluate this integral by using $x = \sqrt{r}\tan\alpha$ and using the identity $1 + \tan^2\alpha = \sec^2\alpha$.

7.2 Triangle wave in firefly model

When using the Adler equation to model the behavior of the fireflies, the sinusoidal form of the firefly's response function was chosen somewhat arbitrarily. Consider the alternative model $\dot{\Phi} = \Omega, \dot{\theta} = \omega + Af(\Phi - \theta)$, where $f(\phi)$ is a triangle wave using

$$\phi, \quad \text{for } -\pi/2 \le \phi \le \pi/2 \tag{61}$$

$$\pi - \phi, \quad \text{for } \pi/2 \le \phi \le 3\pi/2 \tag{62}$$

and this extended periodically outside this interval.

1. Graph $f(\phi)$
2. Find the range of entrainment.
3. Assuming that the firefly is phase-locked to the stimulus, find a formula for the phase difference ϕ^*.
4. Find a formula for the period T of the drifting solutions.

8 Traveling wave solutions of reaction diffusion model

8.1 Fisher-Kolmogorov equation

We consider the Fisher-Kolmogorov equation

$$\frac{\partial u}{\partial t} = \frac{\partial^2 u}{\partial x^2} + u(1-u) \tag{63}$$

and consider traveling wave solutions of this equation, i.e. solutions of the type $u(x,t) = f(x-ct)$, with boundary conditions $\lim_{z\to-\infty} f(z) = 1$ and $\lim_{z\to+\infty} f(z) = 0$.

a) Using the phase portrait method show that there is a minimal velocity c_{min} for a wavelike solution and determine the value of c_{min}.

b) Consider now an interval $[-20, 20]$ and an initial function at $t = 0$

$$u_{in}(x) = \frac{e^{-x^2}}{2} \tag{64}$$

By discretization of Eq. (67) in space and time[17] show that the solution evolves to a traveling wave with the minimal velocity[18] c_{min}.
Note: To test your numerical integration scheme you can first "turn off" the reaction part and to simulate only the diffusion equation, with the initial condition (64). You can compare the numerical solution with the exact analytical expression obtained from the solution of the diffusion equation.

c) An approximated solution can be found by the following change of variable $\xi = z/c$. Defining $g(\xi) = u(z)$, t he Fisher-Kolmogorov equation becomes

$$\frac{1}{c^2} g''(\xi) + g'(\xi) + g(\xi)\,(1 - g(\xi)) = 0 \tag{65}$$

where the prime indicate the derivative with respect of ξ. As the minimal velocity is $c_{min} = 2$ we can assume that the second derivative term is small and write:

$$\frac{dg}{d\xi} = -g(1-g) \tag{66}$$

Solve the previous equation using the separation of variables and compare this solution with the wave found in (b) by numerical integration.

---

[17] To discretize the equation split the interval $[-20, 20]$ in N points and consider $u_n(t)$ the value of the function at point n. These satisfy the set of equations:

$$\begin{aligned}
\frac{du_1}{dt} &= \frac{1}{\Delta x^2}\left(u_2(t) - u_1(t)\right) + u_1(t)(1-u_1(t)) \\
\frac{du_n}{dt} &= \frac{1}{\Delta x^2}\left(u_{n+1}(t) - 2u_n(t) + u_{n-1}(t)\right) + u_n(t)(1-u_n(t)) \qquad n = 2, 3 \dots N-1 \\
\frac{du_N}{dt} &= \frac{1}{\Delta x^2}\left(u_{N-1}(t) - u_N(t)\right) + u_N(t)(1-u_N(t))
\end{aligned}$$

where $\Delta x = x_{n+1} - x_n$. The equations are integrated numerically in time.

[18] The convergence to the minimal velocity is known to be very slow as discussed in this paper: E. Brunet, B. Derrida, Shift in the velocity of a front due to a cut-off Phys. Rev. E 56, 2597-2604 (1997). So the wave velocity that you determine in your numerical calculation can be somewhat smaller than c_{min} (something like 10% smaller).

8.2 Traveling waves in bistable systems

The homogeneous steady states in the Fisher-Kolmogorov model are unstable ($u = 0$) and stable ($u = 1$). We consider here the following model:

$$\frac{\partial u}{\partial t} = \frac{\partial^2 u}{\partial x^2} + u(u-a)(1-u) \tag{67}$$

with $0 < a < 1$. In this case there are two stable homogeneous fixed points $u = 0$ and $u = 1$, and an unstable one $u = a$. We look for solutions $u(x,t) = f(x - ct)$, with boundary conditions $\lim_{z\to-\infty} f(z) = 1$ and $\lim_{z\to+\infty} f(z) = 0$. We fix $a = 1/4$.

a) Using the phase portrait method show that there is a unique velocity c^* for a wavelike solution. Determine the value of c^* numerically as follows: in the plane (u,v), with $v = u'$ we seek for a trajectory connecting the two saddle nodes $(1,0)$ and $(0,0)$. Start from $(1,0)$ and determine the eigenvalues of the Jacobian $\lambda_\pm$. Use an initial point (u_0, v_0) in the vicinity of $(1,0)$ along the repulsive eigenvector (that corresponding to $\lambda_- < 0$) and an initial guess for c. Follow the flow in the phase plane (u,v). If c is too small the trajectory will cross the u-axis before reaching the origin. If c is too large it will flow to infinity. In this way different values of c could be tested until the right (heteroclinic) trajectory connecting the two saddle nodes is generated.

b) (Facultative) - Using appropriate intial conditions $u(x)$ at time $t = 0$ show numerically that the solution evolves in a traveling wave with the velocity determined in (a).

8.3 Special solution of the Fisher-Kolmogorov equation

a) Show that

$$u(z) = \frac{1}{(1 + Ae^{z/\sqrt{6}})^2} \tag{68}$$

where A is an arbitrary constant and $z = x - ct$, is a traveling wave solution of the Fisher-Kolmogorov equation:

$$\frac{\partial u}{\partial t} = \frac{\partial^2 u}{\partial x^2} + u(1-u) \tag{69}$$

with wave velocity equal to $c = 5/\sqrt{6}$.

b) Plot the solution (68) in the two dimensional phase space (u,v), with $v = du/dz$. This corresponds to a heteroclinic orbit connecting the two fixed points $(1,0)$ to $(0,0)$. (see `https://en.wikipedia.org/wiki/Heteroclinic_orbit`).

c) Compare the solution (68) with that obtained from numerical integration in the exercise 8.1. Describe the differences in the two waves.

9 Additional problems

9.1 Hopf bifurcation and polar coordinates

Consider the system

$$\begin{aligned} x' &= px - y - ax(x^2+y^2) \\ y' &= x + py - ay(x^2+y^2) \end{aligned} \tag{70}$$

1. Perform a stability analysis of the equilibrium state $(0,0)$. Show that for a certain threshold value of p, the equilibrium becomes unstable. At this threshold value, the system undergoes a *Hopf bifurcation*.

2. Transform the system to polar coordinates (r,θ) with $x = r\cos\theta$ and $y = r\sin\theta$, derive ODEs that describe how r and θ change over time.

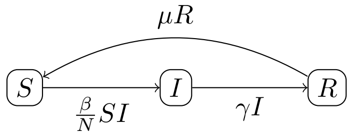
3. Analyze the resulting system, and especially the r equation. What are the steady states for r, and what kind of solution does this describe in the (x,y) plane?

You will find periodic solutions, of which the amplitude depends on p as $\sqrt{p}$. This is typical for a *supercritical* Hopf bifurcation.

9.2 Epidemic model

In this problem you are asked to analyze a model which describes an epidemic. Typically, in epidemic modeling, the population is divided into different classes or compartments. We consider three compartments: S, the susceptible (healthy) population, I, the infected population and R, the recovered population. The recovered population has temporary immunity, but people can lose this immunity and go back to the susceptible class.

Schematically:



The expressions above the arrows describe the rates by which people go from one compartment to the other. The equations describing this system are:

$$\begin{aligned} S' &= -\frac{\beta}{N}SI + \mu R \\ I' &= -\frac{\beta}{N}SI - \gamma I \\ R' &= \gamma I - \mu R \end{aligned} \tag{71}$$

1. Interpret: why is the rate by which people become infected proportional to SI/N?

2. Show that the total population stays constant (nobody dies, nobody is born). We take the total population size to be N. Use this fact to eliminate the R variable and write the system as a two variable system.

3. Choose $\beta = 2$, $\gamma = 1$, $mu = 1$ and draw the phaseplane together with some trajectories.

4. For arbitrary β, γ, μ, determine the steady states and their stability analytically. Interpret your results.

You will find that the existence and stability of a steady state where the disease is endemic (ie. there is always a certain number of infected people at equilibrium) depends on the ratio β/γ. This value is called R_0, the average reproduction number. This is one of the most important concepts in epidemiological modeling. The value of R_0 is equal to the average number of people an infected person can infect when it is introduced in an otherwise completely susceptible population. Highly contagious diseases have high R_0 numbers. Having an estimate of this number is crucial to implement vaccination measures, for example.

9.3 Beyond QSSA: matched asymptotic expansions

We take another look at the enzymatic reaction

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C \xrightarrow{k_2} P + E,$$

where we assume that there is a lot more substrate than enzyme. This leads to Michaelis-Menten kinetics in the quasi-steady state approximation.

After nondimensionalization, the equations for this system are

$$\begin{aligned} u' &= -u + (u + K - \lambda)v \\ \epsilon v' &= u - (u + K)v. \end{aligned} \tag{72}$$

Here $u = s/s_0$, $v = c/e_0$ are the normalized amounts of substrate and enzyme-substrate complex. The parameter ϵ is equal to e_0/s_0 and is by assumption small. The initial values to be used are $u(0) = 1$ and $v(0) = 0$.

Because ϵ is small, one usually takes $v' = 0$, from which the Michaelis-Menten formula

$$v = \frac{u}{u + K}$$

derives.

a) Simulate the system numerically for $K = 2, \lambda = 1, \epsilon = 0.1$. Plot, on a single graph as function of t, u, v and $u/(u + K)$. Does the QSSA approximate v well at all times?

There is an issue around $t = 0$. This can be seen, for example, by looking at the initial conditions. The QSSA $v \approx u/(u + K)$ would give $v(0) = 1/(1 + K)$, whereas in the original system $v(0) = 0$. This shows that something is missing. In this exercise we will derive an analytical approximation which is valid at *all times*.

b) Solve system 72 for $\epsilon = 0$. The second equation gives the QSSA for v. Substitute this into the first equation and solve for u by separation of variables. You will find an implicit equation for u. You will also find that there is one free parameter left. This solution is called the *outer layer*

c) Next we switch the time variable. Set $s = t/\epsilon$. Note that this timescale is suitable for studying what happens around $t = 0$: when t ranges from 0 to 1, for example, s ranges from 0 to $1/\epsilon$. Show that the new equation, with time variable s, are

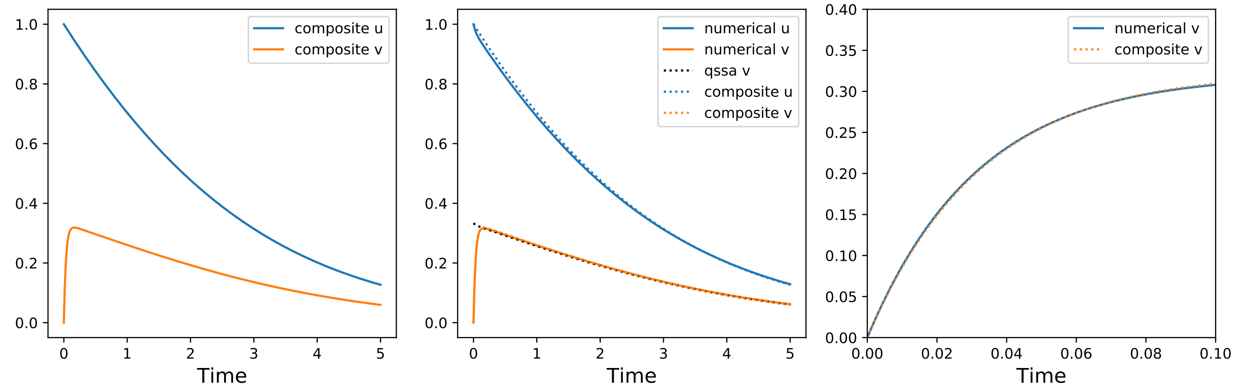


Figure 6: Left: composite expansions for u and v. Middle: comparison of the composite expansion with the numerically obtained result and the QSSA. Right: zoomed version of the composite and numerical solution of v, for small times.

$$\begin{aligned}\frac{du}{ds} &= \epsilon(-u + (u + K - \lambda)v) \\ \frac{dv}{ds} &= u - (u + K)v.\end{aligned} \tag{73}$$

d) Solve the system for $\epsilon = 0$ exactly, using the initial conditions $u(0) = 1$ and $v(0) = 0$ of the original system. Call the resulting functions of s $U(s)$ and $V(s)$. The solution is called the *initial layer*.

e) The outer layer still has one unknown parameter, which can be fixed by a so-called *matching procedure*. We ask that $U(s), V(s)$ for $s \to \infty$ are equal to $u(t), v(t)$ for $t \to 0$. Use this to fix the remaining parameter.

f) Now we have $U(s)$ and $V(s)$ with $s = t/\epsilon$ which are valid in the beginning, and $u(t)$ and $v(t)$ which are valid for large times. They overlap: $U(\infty) = u(0)$ and $V(\infty) = v(0)$.

The *composite expansion* is given by

$$\begin{aligned}u_c(t) &= U(t/\epsilon) + u(t) - \text{overlap} \\ v_c(t) &= V(t/\epsilon) + v(t) - \text{overlap}.\end{aligned}$$

Determine the formulas for u_c and v_c (note that you will have to leave $u_(t)$ as it is in the formulas, since this is only determined implicitly).

g) Plot your composite solution and compare with the exact solution of part (a). You will need for each timestep to solve the implicit equation for u. You can use the built in solve commands in Python or Matlab for this. The Figure below shows an example. In the middle plot you can see that the composite formula and the numerical solution are visuall indistinguishable for v! Try different values of ϵ. When does the approximation break down?