Assignment 3: Compartmental & Spatial models

Computational Biology 2020-2021

Deadline 02-05-2021

Introduction

So far we have worked with models that assumed **homogeneous concentrations**, meaning that the chemical proportions are the same throughout the whole model. But in biology, many processes are either happening in different compartments or are spatially separated (or both!). For instance, the transcription of genes in eukaryotes takes place in the cell nucleus (Figure 1). The transcripts encoding a protein (mRNA) are then transported to the endoplasmic reticulum, which is studded with ribosomes. These ribosomes can translate the mRNA strands into proteins. These proteins can be packaged into vesicles and transported to the Golgi apparatus, where they fuse with the Golgi membranes and are modified. Thereafter they are transported further to their final destination inside or outside the cell, and from there even to different tissues etc.

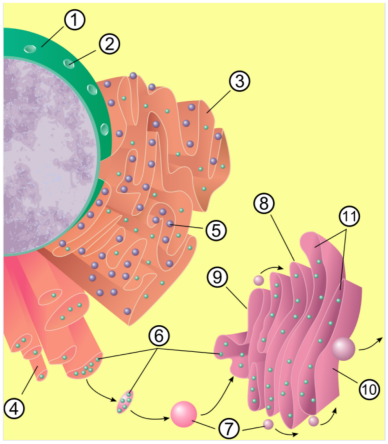

Figure 1: Eukaryotic cell organelles: 1. cell nucleus, 2. nuclear pore, 3. rough endoplasmic reticulum, 4. smooth endoplasmic reticulum, 5. ribosome, 6. protein being transported, 7. transport vesicle, 8. Golgi apparatus, 9. Cis face of Golgi apparatus, 10. Trans face of Golgi apparatus, 11. Cisternae of Golgi apparatus

If molecules diffuse freely and independently and if diffusion is much faster than chemical reactions, inhomogeneities will dissappear and substances may be described by concentrations averaged over a cell [1]. If molecules are not homogeneously distributed, for instance due to membranes, spatial location and structures need to be modeled. The spatiotemporal dynamics of substances and their concentrations can be modeled by different mathematical frameworks, which include compartmental models (e.g. modelling organelles) and reaction-diffusion equations.

Spatial processes are also found in populations of bacteria or animals. Each individual or a group can migrate and travel (long or short) distances. Think of the famous and largest terrestrial mammal migration in the Serengeti (which can influence the way predators attack or change feeding patterns etc.).

Reaction-Diffusion systems

The shapes and sizes of cells and/or compartments and spatial distribution of molecules inside of them can control how molecules interact to produce a certain cellular behaviour. Diffusion describes the space- and time-dependent concentration change of a substance. The reaction-diffusion system describes several substances that diffuse and participate in reactions. Combining a kinetic model for chemical reactions and the diffusion equation, a reaction-diffusion equation is obtained. Most of these models can only be solved numerically, i.e. with finite element methods or finite difference methods, because of their nonlinearity. The general reaction-diffusion equation is given by the equation below, where D_u is the diffusion constant of u and $f(u)$ is the function describing the reaction kinetics (formation and decay) of u. The forms of the reaction kinetics ($f(u)$) depend on the problem at hand.

$$\frac{\delta u}{\delta t} = D_u \nabla^2 u + f(u)$$

Reaction-diffusion systems can show various kinds of dynamic behaviour. A famous example is pattern formation, as shown in Figure 2. Alan Turing proposed the theory (in 1952) that the patterns we see in nature, such as pigmentation in animals, branching trees and skeletal structures are reflections of inhomogeneities in the underlying biochemical signalling [2]

Patterns can form spontaneously from systems that have a homogeneous steady state. The steady state must be stable against homogeneous concentration changes, but unstable against spatial variation (diffusion). In essence, diffusion is usually the stabilizing and homogenizing process, but Turing showed that from the interaction of two stabilizing processes, an instability could emerge.

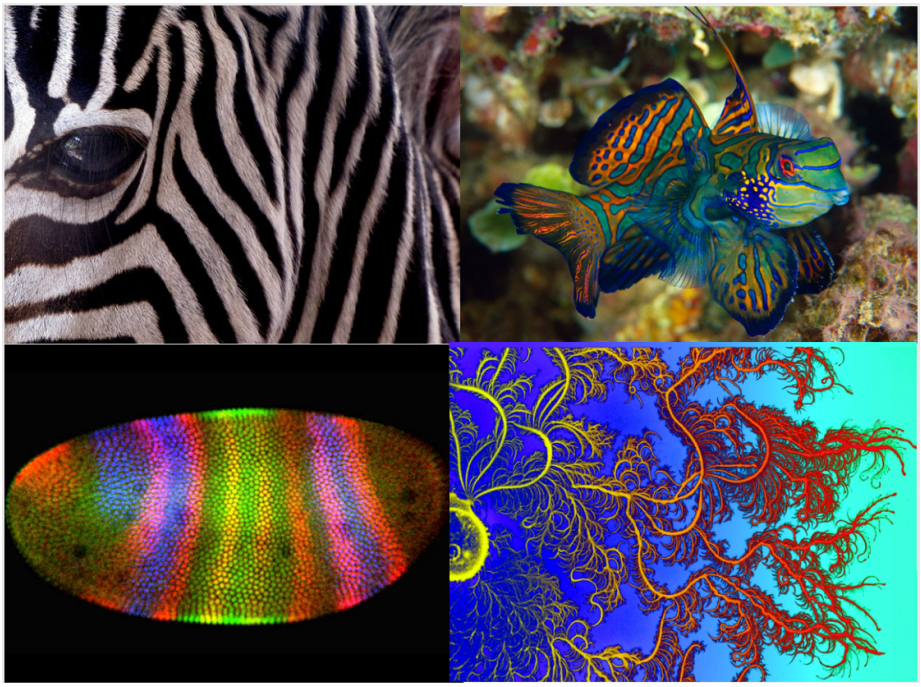

Figure 2: Pattern formation. Animal markings (top two pictures). Lower left: Drosophila melanogaster gene expression of different genes in patterns during embryogenesis. Lower right: single bacteria colony growing in chiral patterns in search for food.

The conditions described above can be full-filled in a simple reaction-diffusion system with two substances called the activator (u) and the inhibitor (v) (aka morphogens), as shown in Figure 3. If the inhibitor diffuses faster than the activator, the activator piles up in local regions in space, forming steady state patterns (dots or stripes). In other words, the inhibitor diffuses faster, inhibiting the production of the activator u over a long range (negative feedback dominated the long distance). Activator u will only spread locally, thus forming locally high concentrations (positive feedback dominates the short distance).

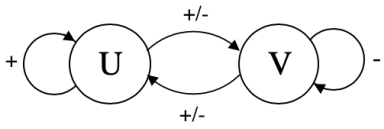

Figure 3: Activator and inhibitor graph

Compartmental modeling

A multi-compartmental model is a mathematical model used for describing how materials/energies are transported between different compartments of a system (e.g. cellular organelles). The compartments are assumed to each be homogeneous. It is assumed there is fast diffusion in the compartments, and if the compartments resemble each other and rapid mixing between them would not make a difference, they can be treated as a single compartment.

To make multi-compartmental modeling easier, certain assumptions can be made (that rarely exist in reality), by assuming a certain "topology". The two most known typologies are **closed models**, sinks and sources do *not* exist, and **open models**, where sinks and sources do exist.

In principle you can think of a multi-compartmental model as a set of blocks, each representing a compartment connected to each other in some way. Let us look at a simple example.

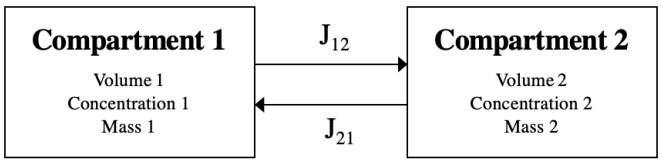

Figure 4: Schematic representation of a compartmental model

Let's assume we are looking at a compartmental model with an exchange of substances, e.g. ions/enzymes. We can in general denote the concentration in a compartment i as c_i with $i = 1, ..., n$, where n is the total number of compartments. The reaction rate of this compound would then be described by the equation below, where the parameter α_i is related to the volume of compartment i.

$$\frac{dc_i}{dt} = \alpha_i(\sum_{j \neq i} J_{ji} - \sum_{j \neq i} J_{ij})$$

The set of ODEs corresponding to the model described in Figure 4 would then be:

$$\begin{cases} \frac{dc_1}{dt} = \alpha_1(J_{21} - J12) \\ \frac{dc_2}{dt} = \alpha_2(J_{12} - J_{21}) \end{cases}$$

Continuing dynamic analysis

Last assignment we analysed the phase plane and talked about different kinds of fixed points. In this assignment we will discuss two phenomena in the phase plane of dynamic systems: limit cycles and chaos, both often seen in nature.

Limit cycles

Periodicity is often seen phenomenon in nature. You can think about human sleep cycles, to oscillations in populations of animal and or the concentration of insulin in our blood [3]. The fact that these oscillations are not easily interrupted by a changed environment indicates that there is a dynamic phenomenon at play, a phenomenon we call a limit cycle.

A **limit cycle** is an isolated closed trajectory in the phase plane. [4] **Closed** in such a way that a point moving along the cycle will return to its starting position at **fixed time intervals**. This means that the trajectory cannot contain any equilibrium points. **Isolated** means that neighbouring trajectories are not closed and approach the limit cycle for either $t \to \infty$ or $t \to -\infty$. This means that there exists at least one trajectory that spirals into or out of the limit cycle, depending on the stability of the limit cycle. Figure 5 shows the three different stabilities in a two-dimensional phase plane.

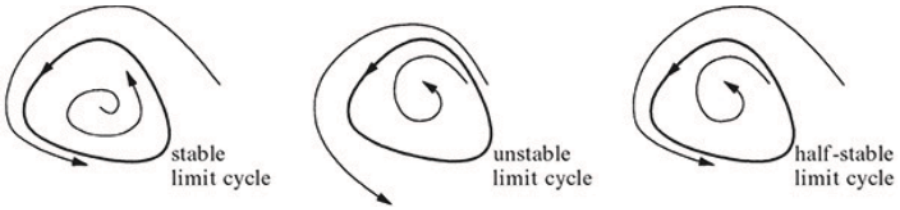

Figure 5: Caption

Remember that we already saw periodic solutions in the two-dimensional phase plane when we discussed **centers** in the last assignment. Centers are fixed points surrounded with a family of closed orbits. This means that these orbits are not isolated, which distinguishes them from limit cycles.

Examples using polar coordinates

An easy and straightforward example of a limit cycle can be created in the two-dimensional phase plane using polar coordinates. Remember that polar coordinated allow us to write the x(t) and y(t) as functions of the radius ($r(t)$) and the angle ($\theta(t)$), as shown in the equations below.

$$\begin{cases} x(t) = r(t)cos(\theta(t)) \\ y(t) = r(t)sin(\theta(t)) \end{cases}$$

This means that we can write the following set of ODEs, where $f(r)$ is an arbitrary function. Since $\frac{d\theta}{dt}$ is a positive constant, we know that the trajectory will rotate around {0,0} in clockwise direction at a distance of r. This means that we obtain closed orbits if r is constant, so for the values of r^* for which $f(r^*) = 0$.

$$\begin{cases} \frac{dr}{dt} = f(r) \\ \frac{d\theta}{dt} = 1 \end{cases}$$

The following figure shows four systems, all with a closed orbit at $r^* = 1$ (as indicated in green). The plots on top show the phase plots of the system, the plots below those show the corresponding $f(r)$ for different values of r. The latter determines the characteristics of the closed orbit. Check for yourself how the three limit cycles and the center follow from the different $f(r)$.

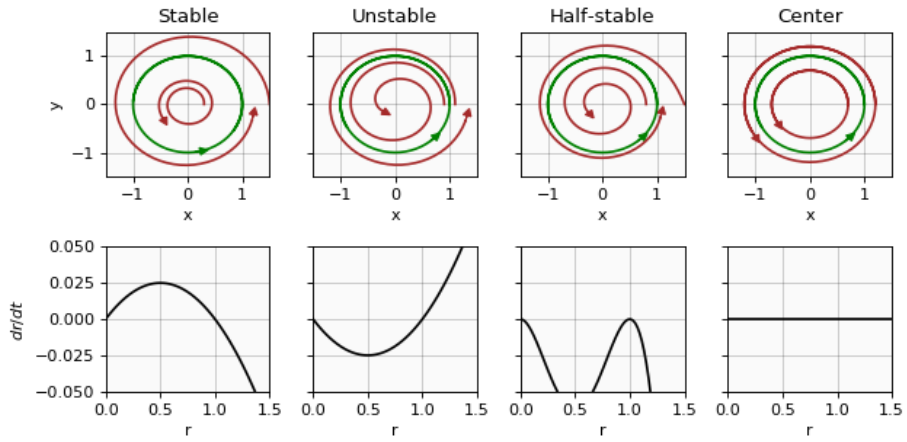

Figure 6: Three limit cycles and one center constructed with polar coordinates

Chaos

So far we discussed how trajectories develop as $t \to \infty$. They can approach attractors over time, such as stable equilibrium points or stable orbits. Trajectories can also be stuck from the beginning in for example an equilibrium. But then there is also the case that a trajectory does not settle down for either of those. In this case we talk about **chaos**.

Chaos is **aperiodic** long-term behaviour in a **deterministic** system that exhibits sensitive dependence on initial conditions. [4]. Aperiodic means that there are trajectories that do not end up in either a closed orbit or an equilibrium point. A deterministic system always returns the same results for the same set of initial conditions, such as our sets of ODEs.

Lorenz Map

A famous example of chaotic behaviour is Lorenz' strange attractor. When we solve this three-dimensional system we obtain a trajectory as shown in figure 7 and 8. It starts near the origin and then either swings left or right, where it spirals around for an unpredictable amount of times before it swings back to the other side. The trajectory never crosses itself. In other words, it never returns in the same position which means that it shows aperiodic behaviour.

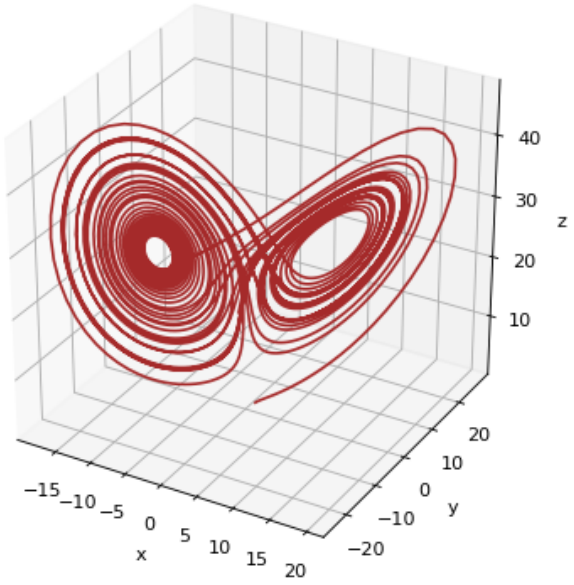

Figure 7: Lorenz strange attractor $\sigma = 10, \beta = \frac{8}{3}, \rho = 28, \{x_0, y_0, z_0\} = \{1, 1, 1\}$

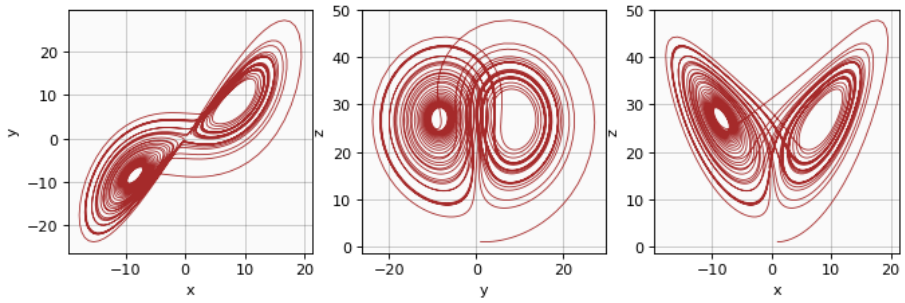

Figure 8: Lorenz strange attractor in 2D

Analysing these systems can be tricky since it is hard to find order in these chaotic results. One method is to focus on a single feature that re-appears over time. In our example we will pick the height of the peaks in z, as shown in figure 4. Lorenz had the idea that $z_{max}(n)$ should predict $z_{max}(n+1)$ and checked this by plotting $z_{max}(n+1)$ vs. $z_{max}(n)$ in a **Lorenz map**. This map indeed shows that the peaks of z appear to fall on a curve, implying that there exists a function $z_{max}(n+1) = z_{max}(n)$ which would appear as $t \to \infty$.

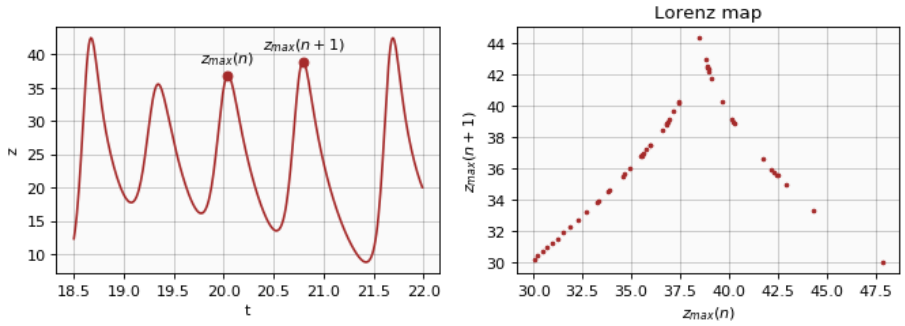

Figure 9: z over time and the corresponding Lorenz map

Note that Lorenz maps are only one of the methods to analyse chaotic behaviour and does not work this nicely for all chaotic system. Another widely used method for these kind of systems is the Poincaré map, which we will not discuss here.

Question 1: Complex calcium oscillations

We will start this week with building a multicompartmental model of intracellular calcium oscillations. Oscillatory changes of cytosolic calcium concentrations (Ca) in response to agonist stimulation are experimentally well observed in various living systems (see paper Marhl et al., 2000 on canvas). In the following model we will look at complex behaviour of calcium oscillations, including bursting and chaos. Figure 10 schematically shows the cellular model system, including the Endoplasmic Reticulum (ER), mitochondria and calcium binding proteins in the cytosol, which all can be seen as calcium stores.

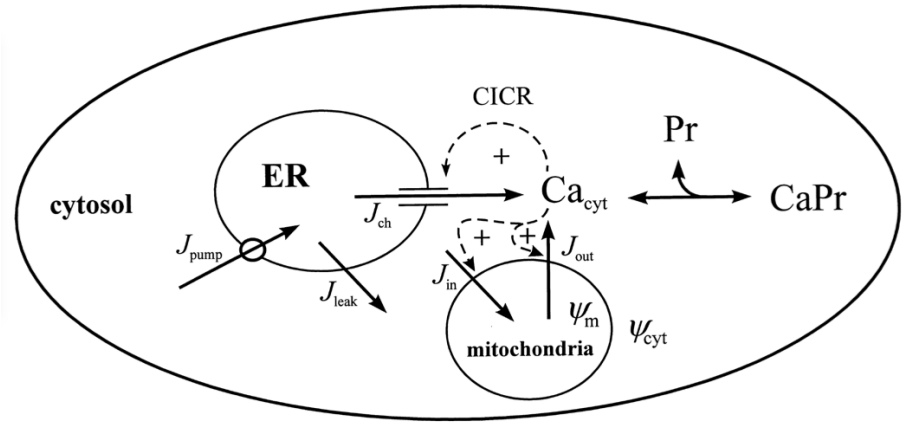

Figure 10: Schematic representation of the model system. Includes the Endoplasmic Reticulum (ER), mitochondria and calcium binding proteins (Pr) in the cytosol.

The following equations describe the rates of change of calcium in the model.

$$\begin{cases} \frac{d[Ca_{cyt}]}{dt} & = J_{ch} + J_{leak} - J_{pump} + J_{out} - J_{in} + k_{-}[CaPr] - k_{+}[Ca_{cyt}][Pr] \\ \frac{d[Ca_{ER}]}{dt} & = \frac{\beta_{ER}}{\rho_{ER}}(J_{pump} - J_{ch} - J_{leak}) \\ \frac{d[Ca_m]}{dt} & = \frac{\beta_m}{\rho_m}(J_{in} - J_{out}) \end{cases}$$

The system contains two conserved moieties: the total concentration of cellular calcium (C_{tot}) and the total concentration of calcium-binding protein (Pr_{tot}).

$$Ca_{tot} = [Ca_{cyt}] + \frac{\rho_{ER}}{\beta_{ER}}[Ca_{ER}] + \frac{\rho_m}{\beta_m}[Ca_m] + [CaPr]$$
$$Pr_{tot} = [Pr] + [CaPr]$$

The fluxes of the model are given by the following equations.

$$
\begin{aligned}
J_{pump} &= k_{pump} Ca_{cyt} \\
J_{ch} &= k_{ch} \frac{Ca_{cyt}^2}{K_1^2 + Ca_{cyt}^2} (Ca_{ER} - Ca_{cyt}) \\
J_{leak} &= k_{leak} (Ca_{ER} - Ca_{cyt}) \\
J_{in} &= k_{in} \frac{Ca_{cyt}^8}{K_2^8 + Ca_{cyt}^8} \\
J_{out} &= (k_{out} \frac{Ca_{cyt}^2}{K_3^2 + Ca_{cyt}^2} + k_m) Ca_m
\end{aligned}
$$

(a) Describe the system on a molecular level.

(b) Describe the model mathematically.

(c) Let us assume that due to a genetic mutation, the Ca^{2+} channel proteins are not transcribed and translated into a functional protein. How would you rewrite the equations of the model? What do you expect to happen?

(d) Use the conserved moieties to reduce the number variables in the set of ODEs to three independent variables.

In this exercise we will analyse the system for different values of k_{ch}. The other parameters are given in the table below.

Parameter	Value
Total concentration	
Ca_{tot}	90 μM
Pr_{tot}	120 μM
Geometric parameters	
ρ_{ER}	0.01
ρ_{m}	0.01
β_{ER}	0.0025
β_{m}	0.0025
Kinetics parameters	
k_{pump}	20 s^{-1}
k_{leak}	0.05 s^{-1}
k_{in}	300 μM s^{-1}
k_{out}	125 s^{-1}
k_{m}	0.00625 s^{-1}
k_+	0.1 μM^{-1} s^{-1}
k_-	0.01 s^{-1}
K_1	5 μM
K_2	0.8 μM
K_3	5 μM

(e) Build the model in python and plot the calcium concentrations in all three compartments over time ($t = 0 - 300$) for $k_{ch} = 3900s^{-1}$ using $\{Ca_{cyt}(0), Ca_{ER}(0), Ca_m(0)\} = \{0.3, 0.2, 1\}$ as initial conditions.

(f) Describe the behaviour of the system in your result.

(g) Identify the three phases in these oscillations and elaborate on them on a molecular level.

(h) Create the three 2D-phase plots and analyse them. Identify any possible closed orbits and describe them.

(i) Create the 3D-phase plot and check if your conclusions in (g) still stand.

(j) Now repeat the steps you took in (e) - (i) for $k_{ch} = 4000s^{-1}$.

(k) Now repeat the steps you took in (e) - (i) for $k_{ch} = 2830s^{-1}$.

(l) Create the Lorenz map based on the peaks in Ca_m for the three values of k_{ch} for t = 100 - 1000. Elaborate on your results. (Hint: The find_peaks-function might come in handy)

(m) Check your predictions made in (c).

Question 2: Schnakenberg model

In this exercise we will create Turing-patterns using the Schnakenberg model (check Maine et al., 2000 on canvas). It describes a fast diffusing substrate v that is consumed by a slow diffusing activator u.

$$\begin{cases} \frac{\delta u}{\delta t} = D_u \nabla^2 u + c_1 - c_{-1} u + c_3 u^2 v \\ \frac{\delta v}{\delta t} = D_v \nabla^2 v + c_2 - c_3 u^2 v \end{cases}$$

(a) Describe the model on a molecular level.

(b) Describe the model mathematically.

We will first solve the model in a one-dimensional space. We use a 1xN grid to describe how the concentrations of u and v change over time on a line of length L.

We solve the system over time using Eulers method, where we use the i to indicate the location on the grid.

$$\begin{cases} u_i(t + \Delta t) = u_i(t) + \Delta t(D_u \nabla^2 u_i + c_1 - c_{-1} u_i + c_3 u_i^2 v_i) \\ v_i(t + \Delta t) = v_i(t) + \Delta t(D_v \nabla^2 v_i + c_2 - c_3 u_i^2 v_i) \end{cases}$$

We use the finite difference method to approach the value for the Laplace-operator (∇^2). For this 1D-system, we will use following equation, where $dx = L/N$

$$\nabla^2 z_i = \frac{(z_{i-1} + z_{i+1} - 2z_i)}{dx^2}$$

(c) Build and solve the one-dimensional Schnakenberg model with periodic boundaries for $c_1 = 0.1, c_{-1} = 1, c_2 = 0.9, c_3 = 1, D_u = 0.0004, D_v = 0.016, L = 1, N = 100$ for t = (0 - 35) using $\Delta t = 0.001$. As initial conditions you should use

$$\{u_i(0), v_i(0)\} = \begin{cases} \{1, 3\} & \text{for } i = 5 \\ \{0, 0\} & \text{for } i \neq 5 \end{cases}$$

(d) Show how the concentrations of u and v develop over time. (Hint: The function pyplot.imshow() might come in handy.)

(e) Elaborate on your results.

Now we will solve the system in en two-dimensional space using an NxN grid of length L. Our Laplace-operator is now defined by the following equation, where i and j indicate the location on the grid.

$$\nabla^2 z_{(i,j)} = \frac{z_{(i-1,j)} + z_{(i+1,j)} + z_{(i,j-1)} + z_{(i,j+1)} - 4z_{(i,j)}}{dx^2}$$

(f) Build and solve the two-dimensional Schnakenberg model with periodic boundaries using the same parameters as in (c). Use random initial conditions for u and v, respectively around 1 and 3.

(g) Show how the concentrations of u and v change over time by plotting the grid for both of them at different timepoints.

(h) Elaborate on your results.

References

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[2] Maini, P.K. et al. (2012). Turing's model for biological pattern formation and the robustness problem. Interface Focus, 2: 487-496.

[3] Schmitz, O., Rungby, J., Edge, L., Juhl, C. B., On high-frequency insulin oscillations, Ageing Research Reviews, Volume 7, Issue 4, 2008, Pages 301-305

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[5] Marhl, M., et al. (2000). Complex calcium oscillations and the role of mitochondria and cytosolic proteins. Biosystems, 57: 75-86.