Computational modeling of cell polarity

Dresden Summer School in Systems Biology, Summer 2018

We all began our journey as a mere, tiny single cell: a fertilized egg. A fertilized egg then goes through a spectacular orchestration of cell growth and division, cell differentiation, and morphogenesis leading to our complete development (see Fig. 1). These developmental principles are applicable to all multicellular organisms and are the subject of developmental biology (see Figs. 2 and 3). In biological systems, the process of cell division leads to replication of genetic material, and differentiation leads to diversification of cells based on their programmed task. The process of morphogenesis shapes the chemical, mechanical, and structural morphology of individual cells, tissues, organs, and the entire organism.

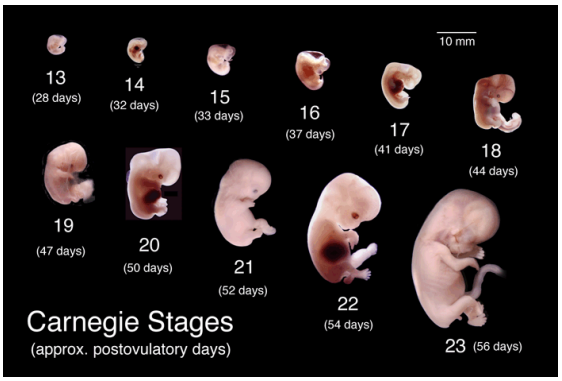

Figure 1: Development of a Human fetus development. Source: embryo.soad.umich.edu

Figure 2: Development of *Caenorhabditis elegans* starting from a single cell. Source: Ching-Sang lab, Queens University, Canada

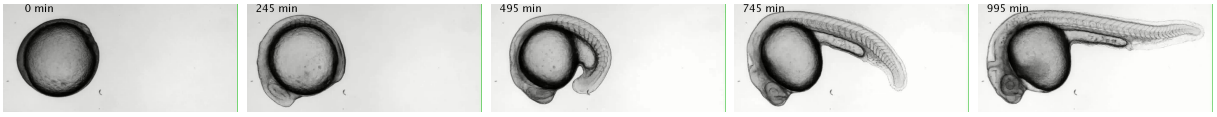

Figure 3: Development of *Zebrafish* starting from a single cell. Source: Schroeter et al, Dev. Dyn. (2008)

In 1952, in his seminal paper titled "*The chemical basis of morphogenesis*"the famous mathematician Alan Turing proposed that "a system of chemical substances, called morphogens, reacting together and diffusing through a tissue, is adequate to account for the main phenomena of morphogenesis.". Turing hypothesized that such a system can lead from an initial homogeneous state to a patterned state due to the inherent instability of the initial state. Turing, however, did suggest that such a model focusing only on reaction-diffusion processes is a simplification, an idealization, and will consequently be falsified, going on to suggest that a more realistic model should also include mechanical properties of biological entities. Recent experimental evidence in various model organisms like *Caenorhabditis elegans* (*C. elegans*) and *Drosophila* point at a coupled mechanochemical basis governing morphogenesis.

A key step in morphogenesis is the establishment of cell polarity. Cell polarity refers to the partitioning of a cell into spatially different domains. The spatial differences can be in shape, composition, or structure of the local cellular domains. Cell polarity, therefore, encodes spatial

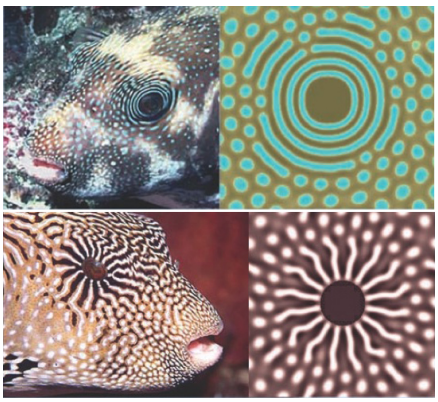

Figure 4: Patterns in nature. At the left the eye of a popper fishes. At right is a computer-generated image of a pattern generated by a Turing pattern simulation. From: Sanderson et al, Journal of Graphics (2006)

information in cells and enables them to carry out specialized functions. Classical examples of polarized cells include epithelial cells with apical-basal polarity that encode for whether a cell surface faces the interior or the exterior, neurons where polarity encodes for the direction of signal propagation, and migrating cells where polarity encodes the direction of migration. Another well-studied example of a polarized cell is the single-cell *C.elegans* embryo where cell polarity defines the head-tail axis, called the anterior-posterior axis of the *C. elegans* embryo. Establishment of cell polarity is crucial to the development of the embryo into an adult. The anterior-posterior polarity is achieved by segregation of proteins to the anterior and posterior poles of a single-cell embryo. This segregation process is mediated by differential stress induced across a thin cortical cytoskeleton layer (beneath the cell membrane), making it flow. This flow carries membrane-bound morphogens that also react together and diffuse on the membrane. Cell polarity establishment in a single cell *C. elegans* embryo is therefore a canonical example of a mechanochemical process.

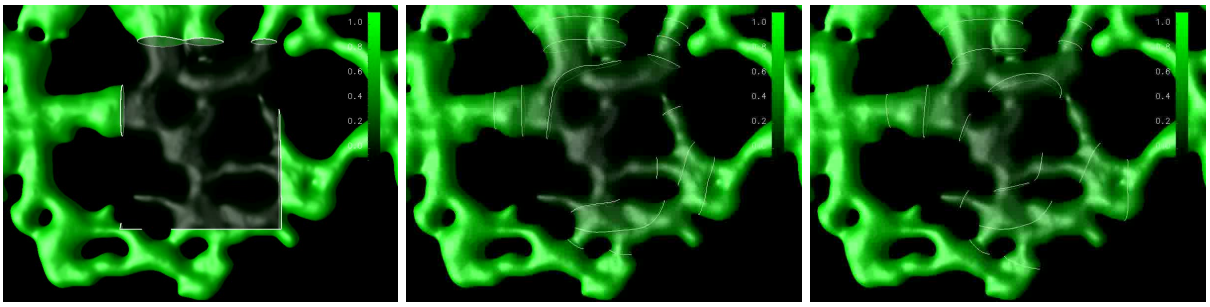

Figure 5: Simulation of diffusion in the endoplasmic reticulum using continuum particle methods. Source: Sbalzarini et al, Biophys. J. (2006)

During the tutorial sessions, we will focus on developing a quantitative model, subsequently analyzing, simulating and validating the model for cell polarity establishment in a single-cell *C. elegans* embryo. Simulating any realistic biological model requires robust numerical methods and is integral to understanding dynamics of many biological processes (see Fig. 5). Numerical methods like continuum particle methods, finite differences, finite volumes, and finite elements are used to solve continuum models formulated as partial differential equations. On the other hand, discrete models can be simulated using cellular automata, agent based methods, and discrete particle methods.

1 Anterior-posterior polarity in *C. elegans* through PAR proteins

As mentioned earlier, during the establishment of cell polarity in *C. elegans*, some proteins get segregated between the anterior and posterior poles of the single-cell embryo. The proteins that segregate are the PARs (abbreviation for PARtitioning-defective). Fig. 6 shows the embryo before and after the establishment of cell polarity. Establishment of cell polarity is a result of formation of two distinct membrane domains, the so called anterior and posterior PAR domains. These domains consist of distinct proteins shown in Fig. 6 in blue and red, respectively.

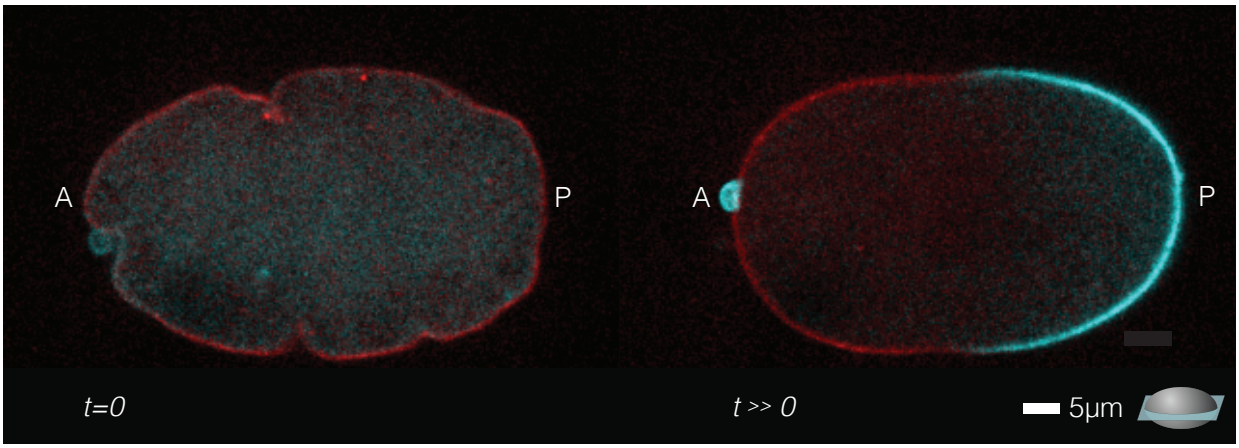

Figure 6: Fluorescence microscopy image of the midplane cross-section showing PAR polarity in a single-cell *C. elegans* embryo. Left: the unpolarized state. Right: polarized state.

PAR polarity module as a two species system. The posterior PAR domain consists of three protein species (PAR-1, PAR-2, LGL-1). Three other protein species (PAR3, PAR6, PKC-3) make up the anterior PAR domain (see Fig. 7). These anterior and posterior PAR complexes can therefore be effectively modeled as a two species: making the PAR polarity module a two-species system. These species can bind to the membrane and also can be found in the cytoplasm.

PAR complexes react between them. PAR complexes in the membrane can interact between each other. Upon colliding with a member of the other species, the corresponding PAR complex gets pulled back to the cytosol. This constitutes a mutual inhibition of the PAR complexes in the membrane (see Fig. 8). Additionally, the cytosolic PAR complexes can spontaneously bind to the membrane. Similarly, membrane-bound PAR complexes can unbind spontaneously.

Denoting anterior PAR membrane-bound concentration by A, cytoplasmic anterior PAR concentration by A_{cyto}, posterior PAR membrane-bound concentration by P and cytoplasmic posterior

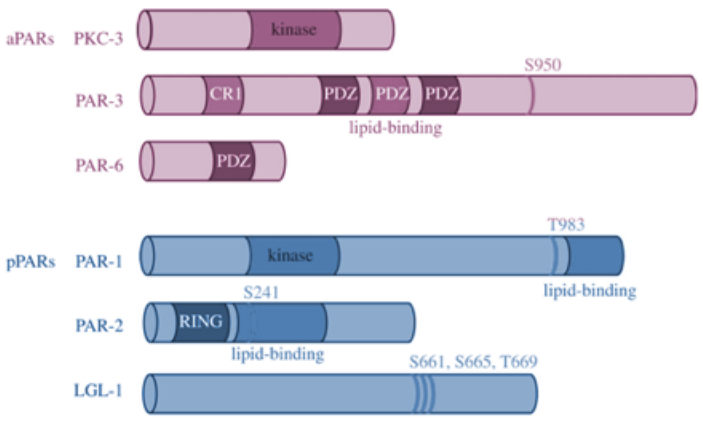

Figure 7: Anterior and posterior PAR complexes. Red proteins and cyan proteins lead to the formation of the aPAR and pPAR complexes. From: Motegi and Seydoux, Phil Trans R Soc B (2013).

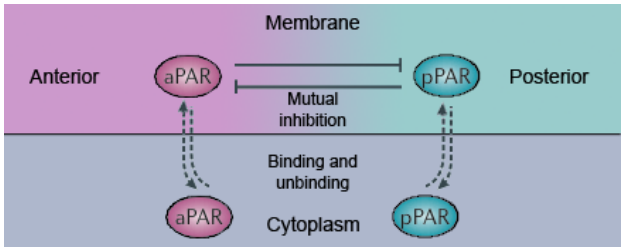

Figure 8: Schematic of the PAR complexes reactions.

PAR concentration by $\mathrm{P}_{\mathrm{cyto}}$, the PAR reaction system is

$$\begin{aligned} \mathrm{A} &\xrightarrow{k_{\mathrm{offA}}} \mathrm{A}_{\mathrm{cyto}} \\ \mathrm{A}_{\mathrm{cyto}} &\xrightarrow{k_{\mathrm{onA}}} \mathrm{A} \\ \mathrm{P} &\xrightarrow{k_{\mathrm{offP}}} \mathrm{P}_{\mathrm{cyto}} \\ \mathrm{P}_{\mathrm{cyto}} &\xrightarrow{k_{\mathrm{onP}}} \mathrm{P} \\ \mathrm{A} + \alpha\,\mathrm{P} &\xrightarrow{k_{\mathrm{AP}}} \mathrm{A}_{\mathrm{cyto}} + \alpha\,\mathrm{P} \\ \mathrm{P} + \beta\,\mathrm{A} &\xrightarrow{k_{\mathrm{PA}}} \mathrm{P}_{\mathrm{cyto}} + \beta\,\mathrm{A} \end{aligned} \tag{1}$$

where the k's are macroscopic reaction rates, α and β are unknown stoichiometries.

Stability of dynamical systems. As you have seen in the lectures, systems of differential equations can exhibit multiple different stability properties. To investigate this further, you will now analyze a very simple system of equations for its stability - the harmonic oscillator, which can be physically realized e.g. as spring pendulum. The dynamical equation governing the pendulum is:

$$\ddot{x} = \frac{k}{m} x, \tag{2}$$

where x is the elongation, k the spring constant and m the mass.

By integration, one second-order differential equation can be reformulated as a system of two first-order differential equations:

$$\dot{x} = y \tag{3}$$

$$\dot{y} = -\frac{k}{m}x \tag{4}$$

We will now investigate simple systems like this a bit more and then move on to the reaction system in (1).

Question 1: Stability analysis

a) Solve this system analytically as well as numerically and plot the $\dot{x}, \dot{y}$ plane for a few values of m and k. How can you interpret this result? Does the system evolve in a clockwise or counterclockwise manner?

b) Moving to a more complicated system:

$$\dot{x} = y \tag{5}$$

$$\dot{y} = x - x^3, \tag{6}$$

Can you find the fixed points? Are they stable? Make a 3-dimensional sketch of the area around these fixed points and have a close look at the determinant of the Jacobian at those points!

Stability of reactions systems. Now, let us focus in reactions systems like the one we need to model. From the reactions (1) it is possible to obtain the set of ODEs that govern its dynamics. Consider only the aPAR complex and its reactions:

$$\begin{aligned} \mathrm{A} &\xrightarrow{k_{\mathrm{offA}}} \mathrm{A_{cyto}} \\ \mathrm{A_{cyto}} &\xrightarrow{k_{\mathrm{onA}}} \mathrm{A} \end{aligned} \tag{7}$$

Using the law of mass action kinetics we can write the following equations for the concenrations of A and $\mathrm{A_{cyto}}$:

$$\frac{d\mathrm{A}}{dt} = -k_{\mathrm{offA}}\mathrm{A} + k_{\mathrm{onA}}\mathrm{A_{cyto}}, \tag{8}$$

$$\frac{d\mathrm{A_{cyto}}}{dt} = k_{\mathrm{offA}}\mathrm{A} - k_{\mathrm{onA}}\mathrm{A_{cyto}}, \tag{9}$$

First notice this two equations are redundant, so extra information is needed to find the solution. But, the fact that there is neither degradation nor creation of A or $\mathrm{A_{cyto}}$ means that the total amount of aPAR complexes remains constant (denoted by N_{A}):

$$\frac{d\mathrm{A}}{dt} + \frac{d\mathrm{A_{cyto}}}{dt} = 0 \tag{10}$$

$$\tag{11}$$

Parameters	Measured values
V_{cyto}	2.5×10^4 μm^3
Ω_{memb}	4.4×10^3 μm^2
N_{A}	2.4×10^5 molecules
N_{P}	9.8×10^4 molecules
D_{A}	0.28 $\mu\text{m}^2\text{s}^{-1}$
D_{P}	0.15 $\mu\text{m}^2\text{s}^{-1}$
k_{offA}	3.24×10^{-3} s^{-1}
k_{offP}	7.19×10^{-3} s^{-1}
k_{onA}	6.29×10^{-3} $\mu\text{m}\,\text{s}^{-1}$
k_{onP}	7.682×10^{-2} $\mu\text{m}\,\text{s}^{-1}$
k_{AP}	? $\mu\text{m}^{\alpha+1}\text{s}^{-1}$
k_{PA}	? $\mu\text{m}^{\beta+1}\text{s}^{-1}$
α	?
β	?

Table 1: Measured physical constants.

In order to translate this concentrations to number of aPAR complexes - which is the remaining constant - we need to remember that A is present only in the membrane and A_{cyto} only in the cytoplasm. With this in mind, the conservation equation looks as follows:

$$N_{\text{A}} = \text{A}\Omega_{\text{memb}} + \text{A}_{\text{cyto}} V_{\text{cyto}}, \tag{12}$$

where Ω_{memb} is the membrane surface area and V is the volume of the cytoplasm. We can then replace A_{cyto} from (12) into (8), and obtain the solution. This will be useful when we take into account diffusion of PAR complexes in the membrane, but being careful with A and its dependence on its spatial distribution in the membrane.

Question 2: PAR Reactions stability

Now let us go to the full reaction model

a) Explore the stability of the PAR complexes reaction system. Maybe plot the nulclines or linearize the system and check the eigenvalues of the Jacobian to see to mutual inhibitory interactions between the PARs.

b) Does the model exhibit multistability? Can this be achieved by first-order reactions alone? Or does one need higher-order interactions between the PAR complexes?

Guideline for the tutorial sessions

We want you to have fun and learn new things. To add to the excitement, we want to get your competitive juices flowing. At the end of the summer school, we will assess your group's performance and give prizes to the three groups that had the most fun. We will assess your efforts on both your group's ability to model the PAR system, to explain experimental measurements, and taking the initiative and exploring the problems set above and beyond..

We will consider the following criteria:

- Originality/Creativity,
- Simplicity and elegance of the model,
- Simplicity, elegance and quality of the numerical method,
- Distance of model prediction from experimental data, and
- Novel insights on pattern formation,
- Computational efficiency (runtime) of your simulation.
- Consideration of additional modeling insights, limitations, assumptions, or inferences.

We will also consider:

- Quality of your final presentation, and
- Quality of software, that is, user friendliness, user interface, visualizations, and own implementation efforts.

The tutors are available any time to help and consult. Do not hesitate to ask them. You can also reach the tutors through Github chat (*https://gitter.im/SysBioSummerSchool/Talk*). The tutors are as eager to learn from you as you are from them. And the most important thing: **Enjoy Dresden and Have Fun!**