1 Adding spatial dynamics

So far, in the project introduction sheet we have explored the reaction dynamics of the PAR proteins. Through their interactions they are pushed off, or transfered onto the membrane. Via analysis of the reaction system we have found criteria for the reactions and parameters for the reaction system to be bi-stable, i.e., that the system exhibits two different stable steady states. However, this analysis has completely ignored the critical spatial component that is at the core of our problem, *polarity*.

Our system starts in a spatially homogeneous state, i.e. the concentrations of the PAR proteins do not depend on where on the surface of the embryo they are. Nevertheless, the final polarized state is characterized by a heterogeneous PAR distribution, with two distinct spatial domains with very different PAR concentrations in the membrane.

Understanding the *spatial* and *temporal* dynamics of this transition from a spatially homogeneous to a polarized state is the main research task that you as a group of ambitious systems biologists are here to investigate.

1.1 Seeing is believing

Question 1: Actively observe

In the Git repository we have provided a video `par_time_evolution.mov`. The video shows PAR proteins through time in a cross section of the embryo. Have a look at it and notice what a very dynamic process this transition is!

Play only the first second of the video a few times (multiple frames). You can see that although there is no spatial pattern, the concentrations fluctuate randomly around their homogeneous state. Recall from your lectures, these fluctuations in movement are modeled by a process known as *diffusion*.

Now, let the video run to the end, watch the membrane (edge) of the embryo through time. Now, watch what is happening in the cytosol (inside) of the embryo. There are *flows* occuring both at the surface and within the embryo that coincide with the establishment of PAR polarity!

1.2 Diffusion

As we can note from inspecting the video, there is diffusion occurring in both the membrane and the cytosol. The combined reaction and diffusion situation is shown in the schematic Fig. 1, where we have proteins coming on and off the membrane and diffusing in both, the membrane and the cytosol.

Do you need to model both the membrane and cytosol? If you were to model the cytosol as a reservoir what would you have to assume about the relative diffusion rates (time scales) in the membrane vs. the cytosol? You are free to make your own assumptions, but make sure you consider their consequences or implications! (Hint: Have a look at the following paper: http://www.ncbi.nlm.nih.gov/pubmed/18805921)

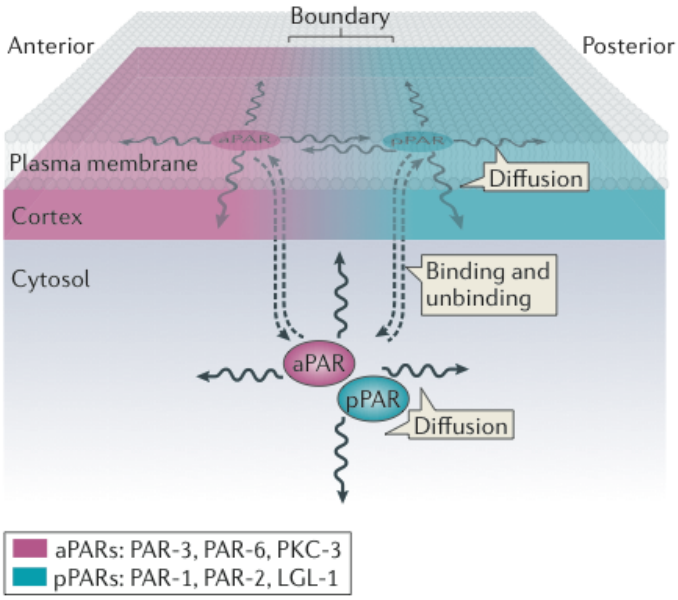

Figure 1: Illustration of membrane diffusion of PAR proteins, their mutual inhibitory interactions, and cytosolic exchange.

1.3 Flows

Cortical flows trigger the establishment of PAR polarity. In the embryo, the transition from the unpolarized state to the polarized state is, however, not a spontaneous concentration fluctuation induced transition. Rather, it is triggered by flows on the cell membrane, which in turn result from a flow of the actomyosin cortex right beneath the membrane (see Fig. 2).

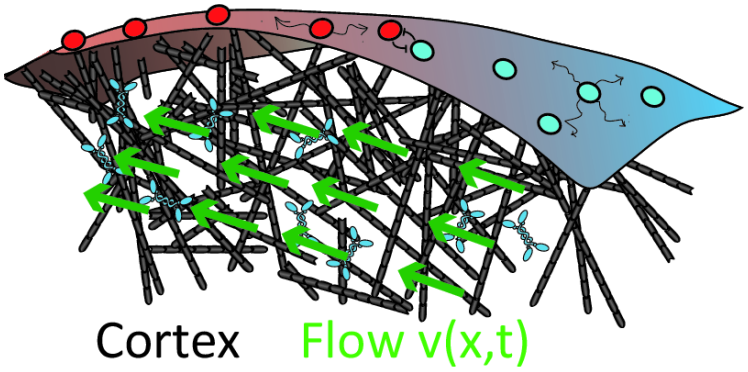

Figure 2: Illustration of membrane diffusion of PAR proteins aided by cortical flow, their mutual inhibitory interactions, and cytosolic exchange.

In summary, ***the PAR complexes react, diffuse, and get advected in the PAR polarity system*** as summarized in Fig. 3.

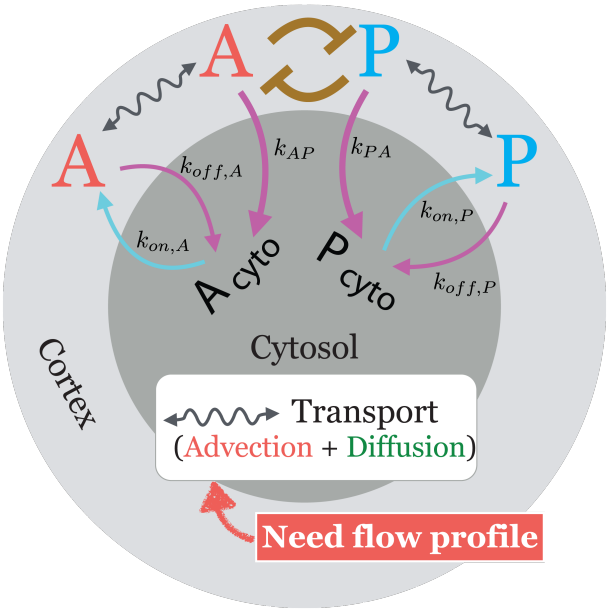

Figure 3: Summary of the two-state PAR polarity system.

2 Build a model

Question 2: Play a modeler: model formulation

Formulate a model for the PAR polarity system to explain interesting features shown by the experimental data (see video and later the datasets outlined in the experimental data handout).

How are you going to model the system? Think about the following areas:

Continuous vs. Discrete Models

- Are you going to model concentrations fields of the individual proteins, or model explicitly individual protein molecules? (PDEs, cellular automata or hybrid methods?)
- How will you represent the spatial domain (a grid? Particles?)
- How will you track the total amount of proteins?

Stochastic vs. Deterministic

- How will you model the reactions: rule based events, deterministic reaction rates or stochastic reactions?
- How will you then model the diffusion of the proteins (continuous diffusion? Random walk on a lattice?)
- How will you model the flow, will you use a continuous flow field? Smooth or noisy fields?

Dimension: 1D/2D/3D

- How are you going to represent your embryo? Will you assume certain symmetries?
- Are you going to explicitly model the cytosol? (See discussion of diffusion above!)

3 Move into cyberspace - Simulations

Question 3: Take biology to cyberspace: numerical method

Most realistic models for biological processes cannot be solved analytically. Solve your model numerically to get aPAR and pPAR concentrations in space and time. Developing a numerical method for a two-dimensional computational domain will help you in later tasks (It will also make you get more out of your adventures in Dresden!).

a) Making statements about the model using a numerical method without verification is a crime. So, verify your numerical method. Demonstrate that your numerical method solves your model of cell polarity correctly. You could, for example, do this by simplifying your model so that an analytical solution becomes available. You could then compare the solution obtained from your numerical method against this analytical solution for the simplified model (Or can you come up with sanity checks that the results are logically consistent!). Please feel free to come up with other ways.

b) Play an engineer. For what values of k_{AP}, k_{PA}, α, and β would the *C. elegans* embryo survive?

c) Without validating your model using it to make statements about cell polarity in *C. elegans* is also considered a crime. So, validate your model! Compare the numerical solution against experimental data. How accurately does your model explain the measurements? Does it show all the qualitative features? What about quantitative ones?

4 Investigate

The research process does not end with the formulation of a model and a working simulation, this is only the beginning... Explore the questions below regarding both your theoretical model and simulation results, to find out what more can you discover!

Question 4: Play a tinkerer: explore your model (optional)

a) Study the interface width of the PAR domains as a function of the diffusivities, and the strengths of the mutually inhibitory interactions.

b) Does the interface move during the polarity-establishment phase? Plot the position of the interface as a function of time. Does the interface stop after some time? Can you think of why it should stop? Can it continue moving indefinitely?

c) Globally reduce the flow magnitude for all space-time points by a factor ϵ, i.e., $v(x,t) \to \epsilon v(x,t)$. A measure of the strength of the contractile forces is the parameter ϵ. What is the minimum value of ϵ for which the system still polarizes? Interpret this result in terms of the contractile forces needed to generate flows that will establish cell polarity.

Question 5: Play a designer: pattern formation (optional).

In a two-dimensional simulation, study the steady-state patterns shown by your model when neglecting the flow. Try different initial conditions like a circular domain at the center, a striped domain, or a homogeneous initial condition perturbed with noise. Do all these initial conditions relax to the same steady state? Note that, you need not stick to the parameter values given.

Question 6: Play a referee: uncover and evaluate assumptions (optional).

We encourage you to question important statements in the challenge description and your model derivation. Which assumptions are listed and which are hidden? Is each assumption justified,

either only for this particular situation or possibly even for single cells in general? How could you experimentally test the validity of each assumption? Suggest control experiments. For cell biological mechanisms that are neglected in the model, can you estimate their potential impact? Some of the simplifications may cause your model to overestimate, others to underestimate the true values of the modeled quantities or parameter values - discuss such cases. You can analyze further simplified toy models to explore effects of neglected mechanisms and estimate the magnitude of such effects. Does the optimization of the parameter set let your model mimic or subsume also additional mechanisms that are not modeled explicitly?

Question 7: Play a statistician: Infer the unknown parameters (optional).

So far you formulated a quantitative model and you probably found a parameter set that could explain the data. But how confident are you that these are the true parameters. Could there be a better parameter set? To answer this question you have to infer your model parameters by comparing your prediction to the data. But you have a lot of spatio-temporal data. Maybe it's a good idea to first think about which observables you actually would like to fit.

There's different paradigms to infer the model parameters (check Wikipedia: Least squares, Maximum likelihood, Bayesian inference,...). What would be the best for your case? Now that you have chosen observables and a paradigm you can actually start fitting your model. Or maybe first think about how much computational time this would need. Can you still make it this week?