Supporting Text S1: Influence of cell shape, inhomogeneities and diffusion barriers in cell polarization models

Wolfgang Giese1, Martin Eigel2, Sebastian Westerheide3, Christian Engwer3,4, Edda Klipp1,*

1 Theoretical Biophysics, Humboldt-Universität zu Berlin, Berlin, Germany
2 Weierstrass Institute, Berlin, Germany
3 Institute for Computational and Applied Mathematics, University of Münster, Münster, Germany
4 Cells in Motion (CiM) Cluster of Excellence EXC 1003, University of Münster, Münster, Germany

* Corresponding author: Edda Klipp, e-mail: edda.klipp@rz.hu-berlin.de

1 Modeling framework

In our models, the computational domain comprises the cytosolic volume \( V_{\text{cyt}} \subset \mathbb{R}^2 \), the outer cell membrane \( M_{\text{cell}} \subset \partial V_{\text{cyt}} \) and membranes \( M_{\text{org}} = \partial V_{\text{cyt}} \setminus M_{\text{cell}} \) that separate the organelles from the cytosol. A sketch of the computational domain can be seen in Figure S1. Furthermore, we equip our models with diffusion rates which are not necessarily constant along the cell compartments \( M_{\text{cell}} \) and \( V_{\text{cyt}} \). Given some initial values \( u(\cdot, 0) \) on \( M_{\text{cell}} \) and \( v(\cdot, 0) \) in \( V_{\text{cyt}} \), the model equations incorporating the described cell geometry and inhomogeneous diffusion read

\[
\frac{\partial u}{\partial t} = \nabla \Gamma \cdot \left( D_m \nabla u \right) + f(u, v|_{M_{\text{cell}}}) \quad \text{on} \quad M_{\text{cell}} \times [0, T],
\]

\[
\frac{\partial v}{\partial t} = \nabla \cdot \left( D_c \nabla v \right) \quad \text{in} \quad V_{\text{cyt}} \times [0, T],
\]

with boundary conditions

\[
-D_c \nabla v \cdot n = f(u, v|_{M_{\text{cell}}}) \quad \text{on} \quad M_{\text{cell}} \times [0, T],
\]

\[
-D_c \nabla v \cdot n = 0 \quad \text{on} \quad M_{\text{org}} \times [0, T]
\]

for the cytosolic equation (2). Here, \( n \) denotes the vector field of outer unit normals on \( M_{\text{cell}} \) and \( M_{\text{org}} \), respectively. For this system of equations, we have mass conservation

\[
\int_{M_{\text{cell}}} u \, dA + \int_{V_{\text{cyt}}} v \, dV = K \quad \text{for each} \ t \in [0, T],
\]

where \( K \in \mathbb{R} \). This conservation property directly follows from the model equations’ weak formulation, see Section 2.1.

2 Numerical methods used for simulations

In the following, the numerical approach is described that is used for simulating the class of mathematical models from Section 1. As for all numerical approaches, the fundamental idea is to discretize the mathematical model. This process yields a system of algebraic equations which can be solved using a computer.

To separate discretization in space and time, we use the well-known method of lines, see e.g. [1], and start with a semidiscretization in space using conforming first-order finite element methods based on triangular meshes. Given a triangular mesh which describes the geometrical setup introduced in
Section 1, the equation for the volume species is treated by the standard conforming finite element approach, employing Lagrange basis functions of polynomial degree one. To treat the equation describing the membrane-bound species, we apply a surface finite element method on the boundary of the mesh using a restriction of the same volumetric basis functions. This enables implementing the numerical approach with tools provided by standard software frameworks for scientific computing. The idea of performing spatial discretization by combining the conforming finite element method and surface finite elements on the same mesh is related to the procedure presented in [2], where a similar approach is used for the discretization of a coupled elliptic model problem.

With the method of lines, different schemes can be employed for the discretization in time. In accordance with our spatial discretization, we restrict ourselves to first-order schemes. We use both a fully implicit scheme and a semi-implicit scheme inspired by the implicit-explicit (IMEX) Euler method presented e.g. in [3]. The idea of the IMEX method is to treat the spatially discretized reaction part of the system explicitly. Therefore, on the one hand the membrane equation and the cytosolic equation are decoupled and thus can be treated separately, and on the other hand the non-linearities are treated explicitly which enables using a linear solver. On the downside, an explicit treatment of the reaction part can affect the stability of the scheme in the reaction-dominated case and for a stiff reaction part in general [3]. Our semi-implicit scheme decouples membrane and cytosolic equations while still treating the reaction part of each separate equation and its non-linearities implicitly. For each equation, this is done by treating only the unknowns of the other equation explicitly.

2.1 Weak formulation

First, we derive a weak formulation of model equations (1) – (4) in order to apply finite element methods for semidiscretization in space. Let \( \mathcal{V}_{\text{bulk}} := H^1(\mathcal{V}_{\text{cyt}}) \) denote the usual Sobolev space containing weak solutions of elliptic equations in the bulk domain \( \mathcal{V}_{\text{cyt}} \). A natural counterpart containing weak solutions of elliptic equations on hypersurfaces are surface Sobolev spaces [4–6]. To treat equation (1) on the closed hypersurface \( M_{\text{cell}} \), we therefore define the surface Sobolev space \( \mathcal{V}_{\text{sur}} := H^1(M_{\text{cell}}) \).

Multiplication of model equations (1) and (2) with some test functions \( \varphi_m \in H^1(M_{\text{cell}}) \) respectively \( \varphi_c \in H^1(\mathcal{V}_{\text{cyt}}) \) results in

\[
\frac{d}{dt} \int_{M_{\text{cell}}} u \varphi_m \, dA = \int_{M_{\text{cell}}} \nabla \Gamma \cdot (D_m(x) \nabla \Gamma u) \varphi_m \, dA + \int_{M_{\text{cell}}} f(u, v|_{M_{\text{cell}}}) \varphi_m \, dA, \tag{6}
\]

\[
\frac{d}{dt} \int_{\mathcal{V}_{\text{cyt}}} v \varphi_c \, dV = \int_{\mathcal{V}_{\text{cyt}}} \nabla \cdot (D_c(x) \nabla v) \varphi_c \, dV. \tag{7}
\]

Application of the integration by parts formula for Sobolev spaces in (7), and its analog derivable from the surface divergence theorem (see [6] and references therein) in (6), yields

\[
\frac{d}{dt} \int_{M_{\text{cell}}} u \varphi_m \, dA = - \int_{M_{\text{cell}}} D_m(x) \nabla \Gamma u \cdot \nabla \Gamma \varphi_m \, dA + \int_{M_{\text{cell}}} f(u, v|_{M_{\text{cell}}}) \varphi_m \, dA, \tag{8}
\]

\[
\frac{d}{dt} \int_{\mathcal{V}_{\text{cyt}}} v \varphi_c \, dV = - \int_{\mathcal{V}_{\text{cyt}}} D_c(x) \nabla v \cdot \nabla \varphi_c \, dV + \int_{\partial \mathcal{V}_{\text{cyt}}} (D_c(x) \nabla v \cdot \mathbf{n}) \varphi_c |_{\partial \mathcal{V}_{\text{cyt}}} \, dA. \tag{9}
\]

Due to the boundary conditions (3) and (4), together with \( \partial \mathcal{V}_{\text{cyt}} \) being the disjoint union \( M_{\text{cell}} \cup M_{\text{org}} \),
this is equivalent to

\[
\frac{d}{dt} \int_{M_{cell}} u \varphi_m \, dA = - \int_{M_{cell}} D_m(x) \nabla \Gamma u \cdot \nabla \Gamma \varphi_m \, dA + \int_{M_{cell}} f(u, v|_{M_{cell}}) \varphi_m \, dA, 
\]

(10)

\[
\frac{d}{dt} \int_{V_{cyt}} v \varphi_c \, dV = - \int_{V_{cyt}} D_c(x) \nabla v \cdot \nabla \varphi_c \, dV - \int_{M_{cell}} f(u, v|_{M_{cell}}) \varphi_c \, dA.
\]

(11)

The weak formulation of model equations (1) – (4) now is to look for a solution \((u, v) \in L^2([0, T], V_{sur}) \times L^2([0, T], V_{bulk})\), such that for each \(t \in [0, T]\)

\[
\frac{d}{dt} \int_{M_{cell}} u \varphi_m \, dA = - \int_{M_{cell}} D_m(x) \nabla \Gamma u \cdot \nabla \Gamma \varphi_m \, dA + \int_{M_{cell}} f(u, v|_{M_{cell}}) \varphi_m \, dA \quad \text{for all } \varphi_m \in V_{sur},
\]

(12)

\[
\frac{d}{dt} \int_{V_{cyt}} v \varphi_c \, dV = - \int_{V_{cyt}} D_c(x) \nabla v \cdot \nabla \varphi_c \, dV - \int_{M_{cell}} f(u, v|_{M_{cell}}) \varphi_c \, dA \quad \text{for all } \varphi_c \in V_{bulk}.
\]

(13)

Note that also the constant test functions \(\varphi_m \equiv 1\) respectively \(\varphi_c \equiv 1\) are permitted which yields mass conservation (5).

### 2.2 Semidiscretization in space

To obtain a semidiscretized system, we combine the conforming finite element approach (FEM) and a surface finite element method (SFEM). The FEM is a standard approach which is well-known to literature. See e.g. [7, 8] to gain an insight into the methodology. An SFEM developed in [5] can be seen as a natural generalization, as the idea of FEM is transferred to elliptic equations on hypersurfaces. Its extension [6] to treating parabolic equations, like membrane equation (1), provides the basis for the SFEM that we use.

Both approaches are based on an approximation of the bulk domain \(V_{cyt}\) and the hypersurface \(M_{cell}\), each by a triangulable geometrical object, and corresponding meshes. For simplicity, we assume \(V_{cyt}\) to be a polyhedral domain that can be exactly represented by a triangular mesh \(T_{cur}\). With \(M_{cell}\) being part of the boundary of \(V_{cyt}\), it corresponds to a set of boundary entities of \(T_{cur}\), which make up a surface mesh \(T_{sur} \subset T_{cur}\). Each method uses its corresponding mesh to set up a finite-dimensional function space usable for spatial discretization of the model equations. In particular, we replace the function spaces \(V_{sur}\) and \(V_{bulk}\) by finite-dimensional conforming function spaces \(V_{sur}^h \subset V_{sur}\) respectively \(V_{bulk}^h \subset V_{bulk}\) and seek a semidiscrete solution \((u_h, v_h) \in L^2([0, T], V_{sur}^h) \times L^2([0, T], V_{bulk}^h)\), such that for each \(t \in [0, T]\)

\[
\frac{d}{dt} \int_{M_{cell}} u_h \varphi_{m,h} \, dA = - \int_{M_{cell}} D_m(x) \nabla \Gamma u_h \cdot \nabla \Gamma \varphi_{m,h} \, dA + \int_{M_{cell}} f(u_h, v_h|_{M_{cell}}) \varphi_{m,h} \, dA \quad \text{for all } \varphi_{m,h} \in V_{sur}^h,
\]

(14)

\[
\frac{d}{dt} \int_{V_{cyt}} v_h \varphi_{c,h} \, dV = - \int_{V_{cyt}} D_c(x) \nabla v_h \cdot \nabla \varphi_{c,h} \, dV - \int_{M_{cell}} f(u_h, v_h|_{M_{cell}}) \varphi_{c,h} \, dA \quad \text{for all } \varphi_{c,h} \in V_{bulk}^h.
\]

(15)

As discrete function spaces, we employ the node-based Lagrange spaces of polynomial degree one on \(T_{cur}\) and \(T_{bulk}\). With the basis functions \(\{\varphi_{m,h}^{x_h}\}_{x_h \in X_{cur}^h}^V\) of \(V_{sur}^h\) and the basis functions \(\{\varphi_{c,h}^{x_h}\}_{x_h \in X_{bulk}^h}\) of
\(
\begin{align}
\frac{d}{dt} \int_{M_{\text{cell}}} u_h \varphi_{m,h}^x \, dA &= - \int_{M_{\text{cell}}} D_m(x) \nabla u_h \cdot \nabla \varphi_{m,h}^x \, dA + \int_{M_{\text{cell}}} f(u_h, v_h | M_{\text{cell}}) \varphi_{m,h}^x \, dA \quad \text{for all } x_h \in \mathcal{X}_h^{\text{sur}}, \quad (16) \\
\frac{d}{dt} \int_{V_{\text{cyt}}} v_h \varphi_{c,h}^x \, dV &= - \int_{V_{\text{cyt}}} D_c(x) \nabla v_h \cdot \nabla \varphi_{c,h}^x \, dV - \int_{M_{\text{cell}}} f(u_h, v_h | M_{\text{cell}}) \varphi_{c,h}^x \, dA \quad \text{for all } x_h \in \mathcal{X}_h^{\text{bulk}}. \quad (17)
\end{align}
\)

The semidiscrete solution \((u_h, v_h)\) can be represented as
\[
\begin{align}
    u_h &= \sum_{\tilde{x}_h \in \mathcal{X}_h^{\text{sur}}} b_{m}^{\tilde{x}_h}(t) \varphi_{m,h}^{\tilde{x}_h} \quad \text{and} \quad v_h = \sum_{\tilde{x}_h \in \mathcal{X}_h^{\text{bulk}}} b_{c}^{\tilde{x}_h}(t) \varphi_{c,h}^{\tilde{x}_h} \quad (18)
\end{align}
\]
by time-dependent coefficient vectors \(b_{m}(t) = (b_{m}^{\tilde{x}_h}(t))_{\tilde{x}_h \in \mathcal{X}_h^{\text{sur}}}\) and \(b_{c}(t) = (b_{c}^{\tilde{x}_h}(t))_{\tilde{x}_h \in \mathcal{X}_h^{\text{bulk}}}\). Therefore, we get a system of ordinary differential equations
\[
\begin{align}
    M_{c} \cdot b_{c}'(t) + S_{c} \cdot b_{c}(t) &= f_{c}(b_{m}(t), b_{c}(t)) \quad \text{on } [0,T], \quad \text{(19)}
\end{align}
\]
with mass and stiffness matrices
\[
\begin{align}
    M_{m} := \left( \int_{M_{\text{cell}}} \varphi_{m,h}^{\tilde{x}_h} \varphi_{m,h}^{\tilde{x}_h} \, dA \right)_{\tilde{x}_h \in \mathcal{X}_h^{\text{sur}}, \tilde{x}_h \in \mathcal{X}_h^{\text{sur}}}, \quad S_{m} := \left( \int_{M_{\text{cell}}} D_m(x) \nabla \varphi_{m,h}^{\tilde{x}_h} \cdot \nabla \varphi_{m,h}^{\tilde{x}_h} \, dA \right)_{\tilde{x}_h \in \mathcal{X}_h^{\text{sur}}, \tilde{x}_h \in \mathcal{X}_h^{\text{sur}}}, \\
    M_{c} := \left( \int_{V_{\text{cyt}}} \varphi_{c,h}^{\tilde{x}_h} \varphi_{c,h}^{\tilde{x}_h} \, dA \right)_{\tilde{x}_h \in \mathcal{X}_h^{\text{bulk}}, \tilde{x}_h \in \mathcal{X}_h^{\text{bulk}}}, \quad S_{c} := \left( \int_{V_{\text{cyt}}} D_c(x) \nabla \varphi_{c,h}^{\tilde{x}_h} \cdot \nabla \varphi_{c,h}^{\tilde{x}_h} \, dA \right)_{\tilde{x}_h \in \mathcal{X}_h^{\text{bulk}}, \tilde{x}_h \in \mathcal{X}_h^{\text{bulk}}} \quad (20)
\end{align}
\]
and vector valued right hand side functions \(f_{m}, f_{c}\),
\[
\begin{align}
    f_{m}(b_{m}(t), b_{c}(t)) := \left( \int_{M_{\text{cell}}} f \left( \sum_{\tilde{x}_h \in \mathcal{X}_h^{\text{sur}}} b_{m}^{\tilde{x}_h}(t) \varphi_{m,h}^{\tilde{x}_h}, \sum_{\tilde{x}_h \in \mathcal{X}_h^{\text{bulk}}} b_{c}^{\tilde{x}_h}(t) \varphi_{c,h}^{\tilde{x}_h} \right) \varphi_{m,h}^{\tilde{x}_h} \, dA \right)_{\tilde{x}_h \in \mathcal{X}_h^{\text{sur}}}, \\
    f_{c}(b_{m}(t), b_{c}(t)) := \left( \int_{M_{\text{cell}}} f \left( \sum_{\tilde{x}_h \in \mathcal{X}_h^{\text{sur}}} b_{m}^{\tilde{x}_h}(t) \varphi_{m,h}^{\tilde{x}_h}, \sum_{\tilde{x}_h \in \mathcal{X}_h^{\text{bulk}}} b_{c}^{\tilde{x}_h}(t) \varphi_{c,h}^{\tilde{x}_h} \right) \varphi_{c,h}^{\tilde{x}_h} \, dA \right)_{\tilde{x}_h \in \mathcal{X}_h^{\text{bulk}}}. \quad (22)
\end{align}
\)

### 2.2.1 SFEM matrix/vector assembly via volumetric FEM basis functions

As we use node-based Lagrange spaces of the same polynomial degree based on the same triangular mesh, the set of Lagrange nodes of \(\mathcal{V}_h^{\text{sur}}\) can be described as \(\mathcal{X}_h^{\text{sur}} = \{ x_h \in \mathcal{X}_h^{\text{bulk}} \mid x_h \in M_{\text{cell}} \} \subset \mathcal{X}_h^{\text{bulk}}\). Moreover, the employed Lagrange basis functions have the property, that
\[
\varphi_{m,h}^{x_h} = \varphi_{c,h}^{x_h} \mid M_{\text{cell}} \forall x_h \in \mathcal{X}_h^{\text{sur}}. \quad (24)
\]

Thus, instead of directly implementing the SFEM ansatz space \(\mathcal{V}_h^{\text{sur}}\), the constrained function space
\[
\partial \mathcal{V}_h^{\text{bulk}} := \{ v \in \mathcal{V}_h^{\text{bulk}} \mid v(x_h) = 0 \text{ for } x_h \in \mathcal{X}_h^{\text{bulk}} \setminus \mathcal{X}_h^{\text{sur}} \} \subset \mathcal{V}_h^{\text{bulk}} 
\]
\[
\text{(25)}
\]
can be utilized to perform the assembly of \(M_{m}, S_{m}, f_{m} \) and \(f_{c}\). In particular, the restriction of its basis \(\{ \varphi_{x,h} \}_{x_h \in \mathcal{X}_h^{\text{sur}}} \) to the set \(M_{\text{cell}}\) equals the Lagrange basis \(\{ \varphi_{x,h} \}_{x_h \in \mathcal{X}_h^{\text{sur}}} \) of \(\mathcal{V}_h^{\text{sur}}\).

Note that \(\partial \mathcal{V}_h^{\text{bulk}} \not\subset \mathcal{V}_h^{\text{sur}}\). Hence, the surface component of the numerical solution can not be directly represented in the space \(\partial \mathcal{V}_h^{\text{bulk}}\). Nevertheless, using the identity \(\partial \mathcal{V}_h^{\text{bulk}} | M_{\text{cell}} = \mathcal{V}_h^{\text{sur}}\), the semidiscrete solution \((u_h, v_h) \in L^2([0,T], \mathcal{V}_h^{\text{sur}}) \times L^2([0,T], \mathcal{V}_h^{\text{bulk}})\) can be calculated as
\[
\begin{align}
    u_h &= \sum_{\tilde{x}_h \in \mathcal{X}_h^{\text{sur}}} b_{m}^{\tilde{x}_h}(t) \varphi_{m,h}^{\tilde{x}_h} \mid M_{\text{cell}} \quad \text{and} \quad v_h = \sum_{\tilde{x}_h \in \mathcal{X}_h^{\text{bulk}}} b_{c}^{\tilde{x}_h}(t) \varphi_{c,h}^{\tilde{x}_h}.
\end{align}
\]
\[
\text{(26)}
\]
2.3 Fully discretized systems

System (19) can be equivalently written as

\[ b_m'(t) = -\mathcal{M}_m^{-1} S_m \cdot b_m(t) + \mathcal{M}_m^{-1} \cdot f_m(b_m(t), b_c(t)), \]

\[ b_c'(t) = -\mathcal{M}_c^{-1} S_c \cdot b_c(t) - \mathcal{M}_c^{-1} \cdot f_c(b_m(t), b_c(t)), \]

or as

\[ \mathbf{b}'(t) = -\mathbf{M}^{-1} \mathbf{S} \cdot \mathbf{b}(t) + \mathbf{M}^{-1} \cdot \mathbf{f}(\mathbf{b}(t)) \quad \text{on } [0,T], \]

using the notation

\[ \mathbf{M} := \begin{pmatrix} \mathcal{M}_m & 0 \\ 0 & \mathcal{M}_c \end{pmatrix}, \quad \mathbf{S} := \begin{pmatrix} S_m & 0 \\ 0 & S_c \end{pmatrix}, \quad \mathbf{b}(t) := \begin{pmatrix} \mathbf{b}_m(t) \\ \mathbf{b}_c(t) \end{pmatrix} \quad \text{and} \quad \mathbf{f}(\mathbf{b}(t)) := \begin{pmatrix} \mathbf{f}_m(\mathbf{b}(t)) \\ \mathbf{f}_c(\mathbf{b}(t)) \end{pmatrix}. \]

For discretization in time, the interval \([0,T]\) is split into sub-intervals \([t_k, t_{k-1}]\) of length \(\tau_k := t_k - t_{k-1}\), \(k = 1, \ldots, K\), with \(0 = t_0 < t_1 < \cdots < t_k < \cdots < t_{K-1} < t_K = T\). By \(\mathbf{b}^k\) we denote a time-dependent coefficient vector \(\mathbf{b}\) evaluated at \(t_k\). Employing the backward Euler method in (29), we end up with a system of nonlinear algebraic equations

\[ \mathbf{b}^k = \mathbf{b}^{k-1} - \tau \mathbf{M}_m^{-1} S_m \cdot \mathbf{b}^k + \tau \mathbf{M}_m^{-1} \cdot \mathbf{f}(\mathbf{b}^k), \quad k \in \{1, \ldots, K\}, \]

which can be solved e.g. using a multidimensional Newton’s method. However, solving this fully discretized system can get very time-consuming, especially when a fine finite element mesh is used, as this results in high-dimensional coefficient vectors. For this reason, we employ a semi-implicit scheme for temporal discretization which decouples equations (27) and (28). In particular, we use the backward Euler method separately for each equation, while treating the unknowns of the other equation explicitly. In contrast to the IMEX Euler method (see e.g. [3]), the unknowns of each separate equation are thus treated fully implicit. The fully discretized system then reads

\[
\begin{align*}
\mathbf{b}_m^k &= \mathbf{b}_m^{k-1} - \tau \mathcal{M}_m^{-1} S_m \cdot \mathbf{b}_m^k + \tau \mathcal{M}_m^{-1} \cdot f_m(\mathbf{b}_m^k, \mathbf{b}_c^{k-1}) \\
\mathbf{b}_c^k &= \mathbf{b}_c^{k-1} - \tau \mathcal{M}_c^{-1} S_c \cdot \mathbf{b}_c^k + \tau \mathcal{M}_c^{-1} \cdot f_c(\mathbf{b}_m^{k-1}, \mathbf{b}_c^k)
\end{align*}
\]

\(k \in \{1, \ldots, K\}\)

and can be solved e.g. using a multidimensional Newton’s method for both equations in parallel.

Our experiments have shown no obvious qualitative differences between the solutions computed with both schemes (31) and (32).

2.4 Simulation framework

The presented numerical approach can be implemented with tools provided by standard PDE software frameworks. For the assembly of the required matrices, the framework has to provide the space of simplicial Lagrange finite elements of order one on a triangular mesh. Furthermore, it either has to provide the space of simplicial Lagrange finite elements of order one on the boundary of the same mesh or a mechanism for constraining the degrees of freedom of the volumetric Lagrange space which do not lie on the boundary of the mesh. The latter mechanism usually is available in those frameworks, since constrained degrees of freedom are frequently used to implement Dirichlet boundary conditions.

All of our simulations were performed using the Distributed and Unified Numerics Environment (DUNE) [9, 10]. The numerical discretization schemes were implemented using the discretization module DUNE-PDELab which is based on DUNE. It provides the volumetric finite element space \(V_h^{\text{bulk}}\) which in addition can be constrained for SFEM matrix/vector assembly using the space \(\partial V_h^{\text{bulk}}\). Furthermore, it features an easy to use assembly infrastructure, as well as the linear solver, nonlinear solver and time-stepping schemes that were used.
The finite element meshes were generated with Gmsh [11], examples of which are depicted in Figure S4. All of these meshes comprise several thousand elements to guarantee a high precision of the method. Additionally, meshes are refined near the outer cell membrane $M_{cell}$ in our simulations to enable an accurate computation of the coupling process on the surface. All code and meshes used in this work are freely available from the authors on request.

2.5 Alternative approaches

An alternative approach usable for simulating the mathematical models is presented in [12]. It uses an implicit description of the cellular geometry via level set functions and seems to be promising especially in the context of geometrical setups that are more complex than those investigated in this work, like those arising from real microscopy data. Particularly, it might be useful for coping with a cellular geometry that even evolves in time. Furthermore, already for simple geometries it can be advantageous as there is no need for a customized mesh generation. This can ease the simulation workflow. A similar approach can be found in [13], which also has the advantage of using an implicit geometry description, but uses a diffuse-interface representation via a phase-field function.

Another alternative approach is presented in [14] and implemented in the cell modeling and simulation software Virtual Cell [15]. Though employing a cell-centered finite volume scheme on a regular mesh and approximating the membrane $M_{cell}$ in a staircase manner, convergence results for static spherical geometries are presented in [14] that render the method well-suited in the considered case.

3 Linear stability analysis

We used linear stability analysis as in [16] to capture the essential behavior and parameter dependencies of the GOR and WP model. For the analysis we consider the following simplifications. First, we assume the computational domain to have a circular shape with radius $R$ and computational domain $\Omega$. For the analysis we consider the following simplifications. First, we assume the computational domain to have a circular shape with radius $R$ and computational domain $\Omega$. For the analysis we consider the following simplifications. First, we assume the computational domain to have a circular shape with radius $R$ and computational domain $\Omega$.

In polar coordinates $(r, \phi)$, the Laplace-Beltrami operator on the boundary can then be expressed as $\Delta_r = \frac{\partial^2}{\partial r^2} + \frac{1}{r} \frac{\partial}{\partial r} + \frac{1}{r^2} \frac{\partial^2}{\partial \phi^2}$, where we define $\Delta_\phi := \frac{1}{r^2} \frac{\partial^2}{\partial \phi^2}$. Note that $\Delta = \Delta_r + \Delta_\phi$ in polar coordinates, with $\Delta_r := \frac{\partial^2}{\partial r^2} + \frac{1}{r} \frac{\partial}{\partial r}$. Second, we assume that there are no inhomogeneities on the membrane as well as in the cytosol. Expressed in polar coordinates, the equations from Section 1 then read

$$\frac{\partial u(\phi, t)}{\partial t} = D_m \Delta_\phi u(\phi, t) + f(u(\phi, t), v(R, \phi, t)) \quad \text{on} \quad \{R\} \times [0, 2\pi) \times [0, T],$$

$$\frac{\partial v(r, \phi, t)}{\partial t} = D_c [\Delta_r + \Delta_\phi] v(r, \phi, t) \quad \text{in} \quad [0, R] \times [0, 2\pi) \times [0, T],$$

with only one boundary condition

$$-D_c \frac{\partial}{\partial r} v(r, \phi, t) \bigg|_{r=R} = f(u(\phi, t), v(R, \phi, t)) \quad \text{on} \quad \{R\} \times [0, 2\pi) \times [0, T]$$

for the cytosolic equation (34). Let $(\tilde{u}_0, \tilde{v}_0)$ be a steady state of our system such that $f(\tilde{u}_0, \tilde{v}_0) = 0$. We consider small perturbations from this steady state which are described by functions $\xi_m = u - \tilde{u}_0$ and $\xi_c = v - \tilde{v}_0$. For these perturbations, we have

$$\frac{\partial \xi_m}{\partial t}(\phi, t) = D_m \Delta_\phi \xi_m(\phi, t) + f_u(\tilde{u}_0, \tilde{v}_0|_{R=R}) \xi_m(\phi, t) + f_v(\tilde{u}_0, \tilde{v}_0|_{R=R}) \xi_c(\phi, t),$$

$$\frac{\partial \xi_c}{\partial t}(r, \phi, t) = D_c [\Delta_r + \Delta_\phi] \xi_c(r, \phi, t)$$

in the linear regime, and boundary condition

$$-D_c \frac{\partial}{\partial r} \xi_c(r, \phi, t) \bigg|_{r=R} = f_u(\tilde{u}_0, \tilde{v}_0|_{R=R}) \xi_m(\phi, t) + f_v(\tilde{u}_0, \tilde{v}_0|_{R=R}) \xi_c(R, \phi, t).$$
3.1 Power series expansion using two-dimensional polar harmonics as ansatz

Since \( R^2 \Delta_r h = \frac{\partial^2}{\partial r^2} = -k^2 h \) for \( h(\phi) = \cos(k \phi) \) and \( h(\phi) = \sin(k \phi) \), the eigenfunctions of \( \Delta \phi \mid_{r=R} \) are the sine and cosine functions. Therefore, we expand the functions \( \xi_m \) and \( \xi_c \) as follows:

\[
\xi_m(\phi, t) = \sum_{k=0}^{\infty} \xi_m^k(\phi, t), \quad \xi_m^k(\phi, t) := \left[ a_m^k \cos(k \phi) + b_m^k \sin(k \phi) \right] \exp(\lambda_k t),
\]

\[
\xi_c(r, \phi, t) = \sum_{k=0}^{\infty} \xi_c^k(r, \phi, t), \quad \xi_c^k(r, \phi, t) := A_k(r) \left[ a_c^k \cos(k \phi) + b_c^k \sin(k \phi) \right] \exp(\lambda_k t).
\]

Due to linearity of the linearized system (36) – (38) with respect to solutions \( (\xi_m, \xi_c) \), it is sufficient to identify solutions \( (\xi_m^k, \xi_c^k) \), as defined in equations (39) – (40), via their corresponding parameters first. We thus determine the parameters \( a_m^k, b_m^k, a_c^k, b_c^k \) and \( \lambda_k \) separately for each \( k = 0, 1, 2, \ldots \). Inserting the ansatz for \( \xi_c^k \) into cytosolic equation (37), we get

\[
r^2 \lambda_k A_k(r) \left[ a_c^k \cos(k \phi) + b_c^k \sin(k \phi) \right] \exp(\lambda_k t) = -D_c k^2 A_k(r) \left[ a_c^k \cos(k \phi) + b_c^k \sin(k \phi) \right] \exp(\lambda_k t) + D_c r^2 (\Delta_r A_k(r)) \left[ a_c^k \cos(k \phi) + b_c^k \sin(k \phi) \right] \exp(\lambda_k t).
\]

After canceling, this takes the form

\[
r^2 \lambda_k A_k(r) = -D_c k^2 A_k(r) + D_c r^2 (\Delta_r A_k(r)),
\]

which leads to

\[
0 = \left[ r^2 \frac{\partial^2}{\partial r^2} + r \frac{\partial}{\partial r} - k^2 \frac{\lambda_k}{D_c} \right] A_k(r).
\]

Mathematical solutions of this equation are modified Bessel functions of the first kind. We thus obtain \( A_k(r) = I_k(r \sqrt{\lambda_k/D_c}) \). Inserting \( \xi_m^k \) and \( \xi_c^k \) into cytosolic boundary condition (38), we get

\[
-D_c \frac{\partial}{\partial r} I_k(r \sqrt{\lambda_k/D_c}) \mid_{r=R} \left[ a_c^k \cos(k \phi) + b_c^k \sin(k \phi) \right] \exp(\lambda_k t) =
\]

\[
f_u(\vec{u}_0, \vec{v}_0 \mid_{r=R}) \left[ a_m^k \cos(k \phi) + b_m^k \sin(k \phi) \right] \exp(\lambda_k t) + f_c(\vec{u}_0, \vec{v}_0 \mid_{r=R}) I_k(R \sqrt{\lambda_k/D_c}) \left[ a_c^k \cos(k \phi) + b_c^k \sin(k \phi) \right] \exp(\lambda_k t),
\]

Since the choice of \( \phi \) is arbitrary, this leads to

\[
a_c^k = -\frac{f_u(\vec{u}_0, \vec{v}_0 \mid_{r=R}) a_m^k}{D_c \frac{\partial}{\partial r} I_k(r \sqrt{\lambda_k/D_c}) \mid_{r=R} + f_c(\vec{u}_0, \vec{v}_0 \mid_{r=R}) I_k(R \sqrt{\lambda_k/D_c})},
\]

\[
b_c^k = -\frac{f_u(\vec{u}_0, \vec{v}_0 \mid_{r=R}) b_m^k}{D_c \frac{\partial}{\partial r} I_k(r \sqrt{\lambda_k/D_c}) \mid_{r=R} + f_c(\vec{u}_0, \vec{v}_0 \mid_{r=R}) I_k(R \sqrt{\lambda_k/D_c})}.
\]

Therefore, \( a_c^k \) as well as \( b_c^k \) can be expressed in terms of the coefficients \( a_m^k \) and \( b_m^k \), respectively. This yields

\[
\xi_c^k(r, \phi, t) = -\frac{f_u(\vec{u}_0, \vec{v}_0 \mid_{r=R}) I_k(r \sqrt{\lambda_k/D_c}) [a_m^k \cos(k \phi) + b_m^k \sin(k \phi)] \exp(\lambda_k t)}{D_c \frac{\partial}{\partial r} I_k(r \sqrt{\lambda_k/D_c}) \mid_{r=R} + f_c(\vec{u}_0, \vec{v}_0 \mid_{r=R}) I_k(R \sqrt{\lambda_k/D_c})}.
\]
Putting $\xi_m^k$ and $\xi_m^i$ into equation (36) for processes on the membrane, we can deduce

$$
\lambda_k [a_m^k \cos(k\phi) + b_m^k \sin(k\phi)] \exp(\lambda_k t) = 
- \frac{D_m k^2}{R^2} [a_m^k \cos(k\phi) + b_m^k \sin(k\phi)] \exp(\lambda_k t) + f_u(\bar{u}_0, \bar{v}_0 |_{r=R}) \frac{I_k(R \sqrt{\lambda_k / D_c}) [a_m^k \cos(k\phi) + b_m^k \sin(k\phi)] \exp(\lambda_k t)}{D_c \frac{\partial}{\partial r} I_k(r \sqrt{\lambda_k / D_c}) |_{r=R} + f_v(\bar{u}_0, \bar{v}_0 |_{r=R}) I_k(R \sqrt{\lambda_k / D_c})}.
$$

After canceling the nonzero terms, we finally get

$$
\lambda_k = f_u(\bar{u}_0, \bar{v}_0 |_{r=R}) - \frac{D_m k^2}{R^2} 
- f_u(\bar{u}_0, \bar{v}_0 |_{r=R}) f_v(\bar{u}_0, \bar{v}_0 |_{r=R}) \frac{I_k(R \sqrt{\lambda_k / D_c})}{D_c \frac{\partial}{\partial r} I_k(r \sqrt{\lambda_k / D_c}) |_{r=R} + f_v(\bar{u}_0, \bar{v}_0 |_{r=R}) I_k(R \sqrt{\lambda_k / D_c})}.
$$

(43)

Note that initial conditions for system (36) – (38) would be required in order to determine the free parameters $a_m^k$ and $b_m^k$.

Having an equation for the parameters $\lambda_k$, we now want to identify conditions which lead to growing eigenmodes. Following [17], the derivative of $I_k$ can be expressed as

$$
\frac{\partial}{\partial r} I_k(r \sqrt{\lambda_k / D_c}) |_{r=R} = I_{k+1}(R \sqrt{\lambda_k / D_c}) \sqrt{\lambda_k / D_c} + \frac{k}{R} I_k(R \sqrt{\lambda_k / D_c}).
$$

Since $I_k(x) > 0$ for $x > 0$ and for all $k = 0, 1, 2, \ldots$, we have the inequality

$$
\frac{\partial}{\partial r} I_k(r \sqrt{\lambda_k / D_c}) |_{r=R} \geq \frac{k}{R} I_k(R \sqrt{\lambda_k / D_c}).
$$

We use this inequality for the derivative $\frac{\partial}{\partial r} I_k$ and furthermore assume $f_u(\bar{u}_0, \bar{v}_0 |_{r=R}), f_v(\bar{u}_0, \bar{v}_0 |_{r=R}) \geq 0$. This holds true for the GOR model in the stable steady state and for their WP model in the transient steady state ($\bar{v}_0, \bar{u}_0^R$), where phase separation occurs. Therfore, we obtain:

$$
\lambda_k = f_u(\bar{u}_0, \bar{v}_0 |_{r=R}) - \frac{D_m k^2}{R^2} 
- f_u(\bar{u}_0, \bar{v}_0 |_{r=R}) f_v(\bar{u}_0, \bar{v}_0 |_{r=R}) \frac{I_k(R \sqrt{\lambda_k / D_c})}{D_c \frac{\partial}{\partial r} I_k(r \sqrt{\lambda_k / D_c}) |_{r=R} + f_v(\bar{u}_0, \bar{v}_0 |_{r=R}) I_k(R \sqrt{\lambda_k / D_c})} 
\geq \frac{f_u(\bar{u}_0, \bar{v}_0 |_{r=R})}{D_c \frac{\partial}{\partial r} I_k(r \sqrt{\lambda_k / D_c}) |_{r=R} + f_v(\bar{u}_0, \bar{v}_0 |_{r=R}) I_k(R \sqrt{\lambda_k / D_c})}.
$$

This finally yields the following inequality for $\lambda_k$:

$$
f_u(\bar{u}_0, \bar{v}_0 |_{r=R}) - \frac{D_m k^2}{R^2} \geq \frac{f_u(\bar{u}_0, \bar{v}_0 |_{r=R}) f_v(\bar{u}_0, \bar{v}_0 |_{r=R})}{D_c \frac{\partial}{\partial r} I_k(r \sqrt{\lambda_k / D_c}) |_{r=R} + f_v(\bar{u}_0, \bar{v}_0 |_{r=R}) I_k(R \sqrt{\lambda_k / D_c})} \leq \lambda_k \leq f_u(\bar{u}_0, \bar{v}_0 |_{r=R}) - \frac{D_m k^2}{R^2}.
$$

(44)

In a physiological range, the term $\frac{f_u(\bar{u}_0, \bar{v}_0 |_{r=R}) f_v(\bar{u}_0, \bar{v}_0 |_{r=R})}{D_c \frac{\partial}{\partial r} I_k(r \sqrt{\lambda_k / D_c}) |_{r=R} + f_v(\bar{u}_0, \bar{v}_0 |_{r=R}) I_k(R \sqrt{\lambda_k / D_c})}$ is very small and we get

$$
\lambda_k \approx f_u(\bar{u}_0, \bar{v}_0 |_{r=R}) - \frac{D_m k^2}{R^2}.
$$
For $k = 0$, the fundamental solutions $\xi^0_m(\phi, t) = \phi_m^0 \exp(\lambda_0 t)$ and $\xi^0(r, \phi, t) = A_0(r) \phi_m^0 \exp(\lambda_0 t)$ do not depend on the polar angle $\phi$ and, therefore, do not contribute to cellular asymmetry. Hence, we only consider wave numbers $k = 1, 2, 3, \ldots$ in the following. For cell sizes $R_{\text{small}}$ with

$$
\lambda_1 \approx f_u(\bar{u}_0, \bar{v}_0) - \frac{D_m 1^2}{R_{\text{small}}^2} < 0 \quad \Leftrightarrow \quad R_{\text{small}} < \sqrt{\frac{D_m}{f_u(\bar{u}_0, \bar{v}_0)}}
$$

we have no growing eigenmodes since $\lambda_1 \gtrsim \lambda_2 \gtrsim \ldots$. For cell sizes $R_{\text{large}}$ with

$$
\lambda_2 \approx f_u(\bar{u}_0, \bar{v}_0) - \frac{D_m 2^2}{R_{\text{large}}^2} > 0 \quad \Leftrightarrow \quad R_{\text{large}} > 2 \sqrt{\frac{D_m}{f_u(\bar{u}_0, \bar{v}_0)}}
$$

we have more than one growing eigenmode and therefore several clusters.

\section{Cluster width approximation for the WP model}

In the following, we want to examine the size of the cluster for the WP model analytically. Stimulation of the system, as performed in the simulations in the main text, causes a traveling wave on the cell surface that is pinned due to mass conservation. The cluster grows mainly in width but only slightly in height. In addition to the POL measure from the main text which describes the relative height of the cluster, we therefore introduce a new measure for the relative cluster width as follows:

$$
\text{POL}^W := \frac{|M^+|}{|M^{cell}|}
$$

where $M^+$ is the excited region of the cell surface. The excited region of the cell surface is defined as that part of the surface, where the surface concentration $u$ is higher than the average surface concentration $\bar{u}$:

$$
M^+ := \{x \in M^{cell} : u(x) > \bar{u}\},
$$

$$
\bar{u} := \frac{1}{|M^{cell}|} \int_{M^{cell}} u \, dA.
$$

Therefore, the $\text{POL}^W$ measure compares the size of the excited part and the total surface area of the cell.

Due to the structure of the reaction kinetics of the WP model, the concentration level of active molecules $u$ on the cell surface separates the cell surface into two parts. The excited part $M^+ \subset M^{cell}$ of the cell surface is at concentration level $u_+$ and the part $M^- = M^{cell} \setminus M^+$ which is not excited is at concentration level $u_-$. At steady state, the concentration in the volume is almost equally distributed and takes the value $v_c$. The cytosolic concentration $v_c$ is in the range of parameters where $f(\cdot, v_c)$ has three roots $u_-, u_T$ and $u_+$, with $u_- < u_T < u_+$. The critical steady state concentration $v_c$ can be calculated solving the Maxwell condition \cite{18}:

$$
0 = \int_{u_-}^{u_+} f(u, v_c) \, du, \quad \text{with respect to } f(u_-, v_c) = f(u_+, v_c) = 0.
$$

Note that the value for $v_c$ is independent of the cell size. We obtained the values $v_c \approx 0.179 \mu M$, $u_- \approx 0.017 \mu M$ and $u_+ \approx 0.11 \mu M$.

Due to mass conservation, in steady state the approximation

$$
|M^+| u_+ + (|M^{cell}| - |M^+|) u_- + |V^{cell}| v_c \approx |M^{cell}| u(0) + |V^{cell}| v(0)
$$

For $k = 0$, the fundamental solutions $\xi^0_m(\phi, t) = \phi_m^0 \exp(\lambda_0 t)$ and $\xi^0(r, \phi, t) = A_0(r) \phi_m^0 \exp(\lambda_0 t)$ do not depend on the polar angle $\phi$ and, therefore, do not contribute to cellular asymmetry. Hence, we only consider wave numbers $k = 1, 2, 3, \ldots$ in the following. For cell sizes $R_{\text{small}}$ with

$$
\lambda_1 \approx f_u(\bar{u}_0, \bar{v}_0) - \frac{D_m 1^2}{R_{\text{small}}^2} < 0 \quad \Leftrightarrow \quad R_{\text{small}} < \sqrt{\frac{D_m}{f_u(\bar{u}_0, \bar{v}_0)}}
$$

we have no growing eigenmodes since $\lambda_1 \gtrsim \lambda_2 \gtrsim \ldots$. For cell sizes $R_{\text{large}}$ with

$$
\lambda_2 \approx f_u(\bar{u}_0, \bar{v}_0) - \frac{D_m 2^2}{R_{\text{large}}^2} > 0 \quad \Leftrightarrow \quad R_{\text{large}} > 2 \sqrt{\frac{D_m}{f_u(\bar{u}_0, \bar{v}_0)}}
$$

we have more than one growing eigenmode and therefore several clusters.

\section{Cluster width approximation for the WP model}

In the following, we want to examine the size of the cluster for the WP model analytically. Stimulation of the system, as performed in the simulations in the main text, causes a traveling wave on the cell surface that is pinned due to mass conservation. The cluster grows mainly in width but only slightly in height. In addition to the POL measure from the main text which describes the relative height of the cluster, we therefore introduce a new measure for the relative cluster width as follows:

$$
\text{POL}^W := \frac{|M^+|}{|M^{cell}|},
$$

(45)

where $M^+$ is the excited region of the cell surface. The excited region of the cell surface is defined as that part of the surface, where the surface concentration $u$ is higher than the average surface concentration $\bar{u}$:

$$
M^+ := \{x \in M^{cell} : u(x) > \bar{u}\},
$$

$$
\bar{u} := \frac{1}{|M^{cell}|} \int_{M^{cell}} u \, dA.
$$

Therefore, the $\text{POL}^W$ measure compares the size of the excited part and the total surface area of the cell.

Due to the structure of the reaction kinetics of the WP model, the concentration level of active molecules $u$ on the cell surface separates the cell surface into two parts. The excited part $M^+ \subset M^{cell}$ of the cell surface is at concentration level $u_+$ and the part $M^- = M^{cell} \setminus M^+$ which is not excited is at concentration level $u_-$. At steady state, the concentration in the volume is almost equally distributed and takes the value $v_c$. The cytosolic concentration $v_c$ is in the range of parameters where $f(\cdot, v_c)$ has three roots $u_-, u_T$ and $u_+$, with $u_- < u_T < u_+$. The critical steady state concentration $v_c$ can be calculated solving the Maxwell condition \cite{18}:

$$
0 = \int_{u_-}^{u_+} f(u, v_c) \, du, \quad \text{with respect to } f(u_-, v_c) = f(u_+, v_c) = 0.
$$

Note that the value for $v_c$ is independent of the cell size. We obtained the values $v_c \approx 0.179 \mu M$, $u_- \approx 0.017 \mu M$ and $u_+ \approx 0.11 \mu M$.

Due to mass conservation, in steady state the approximation

$$
|M^+| u_+ + (|M^{cell}| - |M^+|) u_- + |V^{cell}| v_c \approx |M^{cell}| u(0) + |V^{cell}| v(0)
$$
holds. Solving this equation for the excited area of the cell surface $|M^+|$, we get

$$|M^+| \approx \frac{|M^{cell}|(u(0) - u_{-}) + |V^{cell}|(v(0) - v_{c})}{u_{+} - u_{-}}.$$  

Using this relation, we can easily approximate the $POL^W$ measure:

$$POL^W \approx \frac{1}{u_{+} - u_{-}} \left( (u(0) - u_{-}) + \frac{|V^{cell}|}{|M^{cell}|}(v(0) - v_{c}) \right). \quad (46)$$

In the case of a circular cell, this becomes

$$POL^W \approx \frac{1}{u_{+} - u_{-}} \left( (u(0) - u_{-}) + \frac{R}{d}(v(0) - v_{c}) \right), \quad (47)$$

where $d = 2$ is the dimension of the computational representation of the cell. Therefore, the relative cluster width grows linearly with the cell size. Note that for the corresponding 1D model, the ratio $\frac{|V^{cell}|}{|M^{cell}|}$ is constant and the approximated relative cluster width in (46) becomes independent of the cell size. A comparison of the simulated and the approximated relative cluster width is presented in Figure S6.

References

1. Schiesser W 1991 *The numerical method of lines* (Academic Press Inc.) ISBN 0-12-624130-9 integration of partial differential equations

2. Elliott C M and Ranner T 2012 *IMA Journal of Numerical Analysis* (Preprint http://imajna.oxfordjournals.org/content/early/2012/09/21/imanum.drs022.full.pdf+html) URL http://imajna.oxfordjournals.org/content/early/2012/09/21/imanum.drs022.abstract

3. Koto T 2008 *Journal of Computational and Applied Mathematics* 215 182–195 ISSN 0377-0427 URL http://www.sciencedirect.com/science/article/pii/S0377042707001951

4. Wloka J 1987 *Partial Differential Equations* (Cambridge University Press) ISBN 9780521277594

5. Dziuk G 1988 Finite Elements for the Beltrami operator on arbitrary surfaces *Partial Differential Equations and Calculus of Variations* (Lecture Notes in Mathematics vol 1357) (Springer) pp 142–155 ISBN 978-3-540-50508-2

6. Dziuk G and Elliott C 2007 *Journal of Computational Mathematics* 25 385–407

7. Ciarlet P G 2002 *Finite Element Method for Elliptic Problems* (Philadelphia, PA, USA: Society for Industrial and Applied Mathematics) ISBN 0898715148

8. Braess D 2007 *Finite Elements: Theory, Fast Solvers, and Applications in Solid Mechanics, Third edition* (Cambridge University Press)

9. Bastian P, Blatt M, Dedner A, Engwer C, Klöfkorn R, Ohlberger M and Sander O 2008 *Computing* 82 103–119 ISSN 0010-485X URL http://dx.doi.org/10.1007/s00607-008-0003-x

10. Bastian P, Blatt M, Dedner A, Engwer C, Klöfkorn R, Kornhuber R, Ohlberger M and Sander O 2008 *Computing* 82 121–138 ISSN 0010-485X URL http://dx.doi.org/10.1007/s00607-008-0004-9
11. Geuzaine C and Remacle J F 2009 *International Journal for Numerical Methods in Engineering* 79(11) 1309 – 1331

12. Engwer C and Westerheide S 2013 Heterogeneous coupling for implicitly described domains *Proceedings of the Domain Decomposition 21* in press

13. Teigen K E, Li X, Lowengrub J, Wang F and Voigt A 2009 *Communications in mathematical sciences* 4 1009–1037 ISSN 1945-0796 URL http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3046400

14. Novak I L, Gao F, Choi Y S, Resasco D, Schaff J C and Slepchenko B M 2007 *J. Comput. Phys.* 226 1271–1290 ISSN 0021-9991 URL http://dx.doi.org/10.1016/j.jcp.2007.05.025

15. Cowan A E, Moraru I I, Schaff J C, Slepchenko B M and Loew L M 2012 *Methods Cell Biol* 110 195–221 ISSN 0091-679X URL http://www.ncbi.nlm.nih.gov/pubmed/22482950

16. Levine H and Rappel W J 2005 *Physical Review E (Statistical, Nonlinear, and Soft Matter Physics)* 72 URL http://dx.doi.org/10.1103/physreve.72.061912

17. Abramowitz M and Stegun I A 1972 *Handbook of Mathematical Functions with Formulas, Graphs, and Mathematical Tables* (Wiley) chap Modified Bessel Functions I and K, pp 374–377 10th ed

18. Mori Y, Jilkine A and Edelstein-Keshet L 2008 *Biophysical Journal* 94 3684–3697 ISSN 00063495 URL http://dx.doi.org/10.1529/biophysj.107.120824
5 Figures

**Figure S1** The schematic cell polarization process is shown next to the computational domain. The cytosolic volume is represented as a two-dimensional bulk domain $V_{cyt}$. Its boundary $\partial V_{cyt}$ consists of closed hypersurfaces $M^{cell}$ and $M^{org}$ which describe the outer cell membrane and the organelles’ membranes.
**Figure S2** The right hand side of both models, plotted for a fixed volume concentration $v$. In case of the GOR model, we obtain two homogeneous steady states. The first steady state at $u_1 = 0$ is stable while the second at $u_2 > 0$ is transient; e.g. we have a membrane/cytosolic flux on the membrane for $u > u_2$ (region II in the plots) and a dissociation to the cytosol for $u < u_2$ (region I in the plots). In case of the WP model, we observe a bimodal behavior. For the shown range of values for $v$, we can either have one, two or three steady states. If there are three steady states, say $u_1$, $u_2$ and $u_3$ with $u_1 < u_2 < u_3$, the steady states $u_1$ and $u_3$ are stable while $u_2$ is transient. If the membrane concentration $u$ is in the regions I or III of the plots, there is a flux from the cytosol to the membrane. If the membrane concentration $u$ is in the regions II or IV, there is a dissociation from the membrane to the cytosol.
Figure S3 Comparison of a simulation performed in 2D (left) and in 1D (right). The results essentially look the same, especially the steady state profile in the end. Slight differences are expected since the volume/surface ratio is different in the 1D case and in the 2D case.
**Figure S4** The influence of cytosolic diffusion barriers on the GOR and the WP model is investigated, see results section (D). Organelles (represented by circles or ellipses) which serve as diffusion barriers are placed at different positions. Two stimuli S1 and S2 of different strengths are applied. Stimulus S1 at the top prevails only if the organelle is sufficiently far away, i.e., if it has a bottom position. With the organelles placed close to the stronger stimulus S1, S1 is suppressed and S2 dominates.
Figure S5 Triangular Meshes for different cell geometries. Coarse triangular meshes [left column] and fine triangular mesh used for the computations in this paper [right column]. The fine meshes contain (A) 7832, (B) 9005 and (C) 6758 elements, respectively.
Figure S6 (A) Comparison of simulations for different cell sizes and the approximation formula for the cluster width for the WP model. (B) The relative cluster width and the polarization measure POL for different cell sizes for the GOR model.
Figure S7 Excitation of the system with one weakly graded and one strongly graded signal. Both signals are persistent and defined by $k_S(x, t) = c \cdot (x_2 - (x_{\text{min}})_2)$, where $x_{\text{min}}$ is the lowest point along the $x_2$-direction of the two dimensional cell (opposite side of the protrusion). For the weak gradient, we choose $c = 1.0 \cdot 10^{-4}$ and for the strong gradient, we choose the ten-fold higher value $c = 1.0 \cdot 10^{-3}$. The signals are plotted along the surface of each cell shape (see top figures of A and B). In case of the WP model, the simulations show that the system is strongly shape-dependend. The circular cell polarizes toward the gradient as expected. On the contrary, for the cell with a protrusion, polarization is either strongly delayed (strong gradient) or occurs on the opposite side of the protrusion (weak gradient).