

# Multiscale models

## Coupling spatial models: Autocrine chemotaxis



Cell cluster due to chemotaxis towards self-produced chemoattractant



### Introduction

This example models a cellular Potts model for autocrine chemotaxis by coupling a CPM to a diffusive chemoattractant.

### Model description

It exemplifies the combination of a CPM with a PDE through the chemotaxis towards a diffusive chemoattractant produced by cells. The `CellType` has a Property `p` (production rate) which is positive within biological cells, and is zero in the medium 'cell type'. The symbol `p` can then be used in the PDE as the production term for species or Layer `U`. In this way, `U` is produced in each lattice node that is occupied by a cell, and is not produced outside of cells. At the same time, cells perform Chemotaxis towards the chemoattractant `U`.

The simulation is visualized using some advances Gnuplotter feature. Cells are superimposed on the PDE and appear as transparent domains (see `opacity`). Moreover, the concentration gradient of the PDE is emphasized by the use of `isoline` that draws contours as positions with equal concentration.

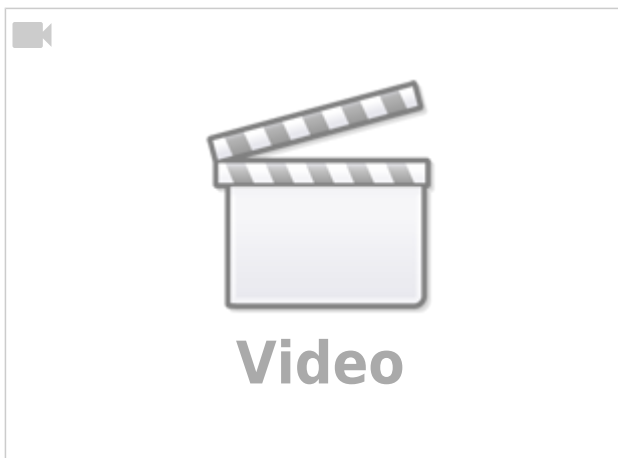
## Model

[h AutocrineChemotaxis.xml |h](#)

```
extern>  
http://imc.zih.tu-dresden.de/morpheus/examples/Multiscale/AutocrineChemotaxis.xml
```

In Morpheus GUI: Examples → Multiscale → AutocrineChemotaxis.xml

## Coupling CPM and PDE: Vascular patterning



Cells organize into networks due to matrix-anchorage of chemoattractant

## Introduction

This example shows a model of vascular network formation by paracrine signaling ([Köhn-Luque et al., 2011](#)) and employs a coupled CPM and reaction-diffusion model.

## Model description

The model defines a CPM as well as a PDE. These models are coupled by two processes:

1. Cells, specified in `CellTypes`, respond chemotactically to a `Layer` (or species) in the PDE
2. Conversely, the production term of one PDE `Layer` is coupled to the presence/absence of cell.

## Model

[h VascularPatterning.xml |h](#)

```
extern>http://imc.zih.tu-dresden.de/morpheus/examples/Multiscale/VascularPat
```

terning.xml

In Morpheus GUI: Examples → Multiscale → VascularPatterning.xml

## Reference

Köhn-Luque A, de Back W, Starruß J, Mattiotti A, Deutsch A, et al. [Early Embryonic Vascular Patterning by Matrix-Mediated Paracrine Signalling: A Mathematical Model Study](#). *PLoS ONE* 6(9): e24175, 2011

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## ODEs in CPM cells: Cell cycle and proliferation



Cells divide according to an oscillatory ODE model representing the early cell cycle in Xenopus.

## Introduction

This multiscale model example shows

1. how to define a coupled system of continuous ODEs in discrete CPM cells
2. how to specify and change time scales between these model formalisms

## Model description

This model specifies an oscillatory ODE model representing the cell cycle in Xenopus oocytes using three components (CDK1, Plk1, APK) (Ferrell et al., *Cell*, 2011) (see `CellTypes→CellType→System`). This ODE model is coupled to 2D shaped CPM cells that perform divide based on the concentration of these components (see `CellTypes→CellType→Proliferation→Condition`). As in the early Xenopus cell cleavage, this leads to exponential growth of the number of cells, without increase of total cell volume.

## Time scales

Time scales are defined in the following fashion:

- The so-called global time scheme is defined in `Time` and here runs from 0 to 1 arbitrary time units. All models and plugins specify their updating scheme in terms this global time scheme (e.g. `Analysis→Gnuplotter→interval`).

- The CPM time scale for cell motility and behaviors is defined in `CPM→MCSDuration`. This specifies the time that a single Monte Carlo step in the CPM lasts, in terms of the 'global time'. Here, the `MCSDuration` is  $1.0 \cdot 10^{-4}$  which means the CPM is executed 10.000 times during this simulation.
- For setting time of ODEs, one has to distinguish the (1) how often the ODEs are evaluated from (2) controlling the time scale of the ODE dynamics:
  1. The time scale of the ODE dynamics can be changed using `System→time-scaling`. When larger or smaller than  $1.0$ , this speeds up or slows down make the dynamics, without influencing the accuracy of the approximation.
  2. The accuracy of the numerical approximation (and is equal to the  $\Delta t$  of the numerical solver) is controlled using `System→time-step` (and is automatically rescaled according to the time scale).

## Things to try

- Change the CPM time scale, relative to the ODE dynamics: Change `CPM→MCSDuration` to  $1.0 \cdot 10^{-3}$  or decrease to  $1.0 \cdot 10^{-5}$ . This makes cells to have less resp. more motility/relaxation in between cell divisions.
- Change the time scale of the ODE dynamics, relative to the CPM by altering `System→time-scaling`.

## Model

h `CellCycle.xml` |h

```
extern>  
http://imc.zih.tu-dresden.de/morpheus/examples/Multiscale/CellCycle.xml
```

In Morpheus GUI: Examples → Multiscale → `CellCycle.xml`

## Dictyostelium



Aggregation of amoebas through chemotaxis towards waves of cAMP.



## Introduction

This model show chemotactic aggregation of Dictyostelium. It was constructed by students attending the [ECMI modeling week 2012](#) in Dresden.

## Model description

This model shows an interesting coupling between CPM cells and reaction-diffusion PDE. Cell state depends on the perceived concentration of cAMP, and determines whether a cell produces cAMP and whether it performs chemotaxis. The PDE is governed by a Fitzhugh-Nagumo-like model of an excitable medium, which causes traveling waves upon excitation. Chemotaxis through those waves causes cell aggregation.

Background colors indicate the cAMP concentration. Cells are color-coded according to their phase: excitable/resting (yellow), excited/chemotactic (green), refractory/resting (red).

## Model

h Dictyostelium.xml |h

```
extern>  
http://imc.zih.tu-dresden.de/morpheus/examples/Multiscale/Dictyostelium.xml
```

In Morpheus GUI: Examples → Multiscale → Dictyostelium.xml

## References

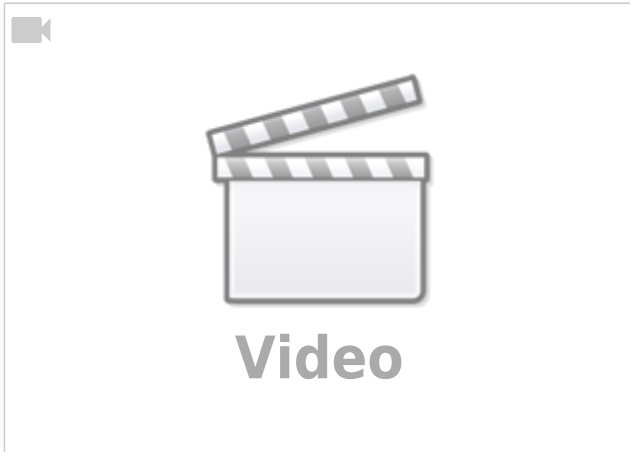
- Rost F, Quintero A, Myllykoski M, Igolkina A, Rohde O'Sullivan Freltoft A, Dixit N, [Morphogenesis and Dynamics of Multicellular Systems](#). *ECMI Newsletter*, 52, 2012.
- Savill N and Hogeweg P. [Modelling morphogenesis: from single cells to crawling slugs](#). *J. Theor. Biol*, 184:229-235, 1997.

## MembraneProperties: Cell polarization and chemotaxis

*Note: MembraneProperties are not available in public version of Morpheus.*



Cell dynamically re-polarizes in response to switching external gradient



### Introduction

This model of cell polarity shows the coupling of three model formalisms:

- A cellular Potts model
- A PDE model, solved on the membrane of the cell
- And an external gradient.

The cell membrane polarizes in response to the external gradient. Chemotactic cell motility depends on the polarity of the cell and the external gradient.

### Description

This example implements two models of cell polarity: Meinhardt's substrate-depletion model and Edelstein-Keshet's wave-pinning model. The user can switch polarity model by **Disabling/Enabling** the relevant System.

The model defines a one-dimensional reaction-diffusion system (**MembraneProperty**) representing

membrane-bound molecules, and is mapped to a cellular Potts model defining a discrete shaped cell. An external gradient, specified in a PDE, provides a signal for the polarization of the cell. In turn, the polarity of the cell influences its chemotactic behavior.

After a switch in direction of the gradient, the cell re-polarizes in the new direction and starts to move up the gradient, iff the wave pinning model has been selected.

## Model

h CellPolarity.xml |h

```
extern>  
http://imc.zih.tu-dresden.de/morpheus/examples/Multiscale/CellPolarity.xml
```

*Note: This model is not available in Morpheus GUI.*

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