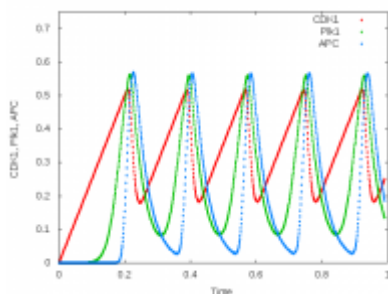


Ordinary differential equation models

ODE model: Cell cycle



Time plots of ODE model of *Xenopus* embryonic cell cycle



Introduction

This model is a simple three-species ODE model of the *Xenopus* embryonic cell cycle (Ferrell et al., 2011). It exhibits sustained limit cycle oscillations.

Model description

One CellType is created that has three variables of Properties representing the concentrations of APC, Plk1, and CDK1. These variables are coupled in a System of DiffEqns.

In the System, a number of Constants are defined whose symbols are used in the DiffEqn. Note that the equations are entered in simple plain text.

The System uses the runga-kutta (4th order) solver for the differential equations and specifies a particular time step (here $ht = 10^{-2}$) which is interpreted in global time steps.

The global time is defined in the Time element and runs from StartTime to StopTime (0 - 25). In this non-spatial model, Space defines a Lattice of size $(x,y,z)=(1,0,0)$.

Results are written to a file using the Analysis plugin Logger. The Logger also visualizes the time plot to screen (in "interactive" mode) or to PNG files (in "local" mode).

Things to try

- Change the dynamics by altering System/time-scaling.

Model

h CellCycle.xml |h

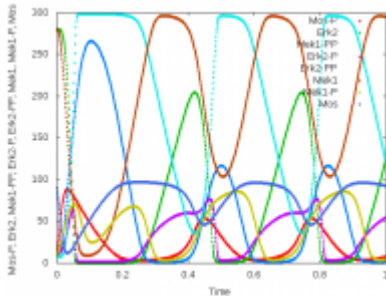
```
extern>http://imc.zih.tu-dresden.de/morpheus/examples/ODE/CellCycle.xml
```

In Morpheus GUI: Examples → ODE → CellCycle.xml.

Reference

Ferrell JE Jr, Tsai TY, Yang Q. [Modeling the cell cycle: why do certain circuits oscillate?](#) *Cell*, 18:144(6), 2011.

SBML import: MAPK signaling



Time plots of oscillations in MAPK signaling (Kholodenko, 2000)



Introduction

This model has been imported and automatically converted from SBML format by Morpheus. It shows oscillations in the MAPK signaling cascade ([Kholodenko, 2000](#)).

Model description

Upon importing an SBML file, a Morpheus model is automatically created. A System of DiffEqns is generated, based on the function and reactions defined in the SBML file and defined as part of a CellType. Additionally, a Logger is generated to record and visualize the output.

Simulation details, such as StartTime and StopTime, as well as the time-step of System, need to be specified manually.

Things to try

- Browse the [Biomodels database](#) and try importing some SBML models.

Model

Original SBML model:

h BIOMD0000000010.xml |h

```
extern>http://imc.zih.tu-dresden.de/morpheus/examples/ODE/BIOMD0000000010.xml
```

Generated Morpheus model:

h MAPK_SBML.xml |h

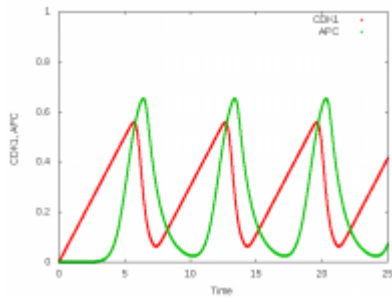
```
extern>http://imc.zih.tu-dresden.de/morpheus/examples/ODE/MAPK_SBML.xml
```

In Morpheus GUI: Examples → ODE → MAPK_SBML.xml.

Reference

Kholodenko BN. [Negative feedback and ultrasensitivity can bring about oscillations in the mitogen-activated protein kinase cascades](#). Eur. J. Biochem. 2000 Mar; 267(6): 1583-1588

Delay differential equations: Cell cycle



Time plots of ODE model of *Xenopus* embryonic cell cycle, modeled with delay differential equations

Introduction

This model is a two-species version of the *Xenopus* embryonic cell cycle shown above that uses delay differential equations (Ferrell et al., 2011). It exhibits sustained limit cycle oscillations.

Model description

This model uses two Properties (CDK1 and APC) and two DelayProperties (CDK1_d and APC_d) with delay τ . The latter are properties that return the value that has been assigned at time $t - \tau$.

The updated values of CDK1 and APC are assigned to (the back of) CDK1_d and APC_d using Equations. When these properties used in the DiffEqn, they return the value assigned in the past.

The two variables are logged and both a time plot and a phase plot are drawn.

Things to try

- Explore the effect of delays by altering the DelayProperty/delay.

Model

`h CellCycleDelay.xml |h`

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

In Morpheus GUI:

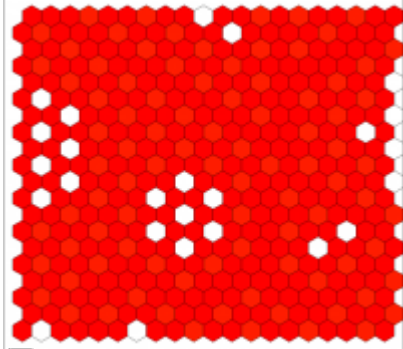
Examples → ODE → CellCycleDelay.xml.

Reference

Ferrell JE Jr, Tsai TY, Yang Q. [Modeling the cell cycle: why do certain circuits oscillate?](#) *Cell*, 18:144(6),

2011.

Coupled ODE lattice: Lateral signaling



Patterning as a result of lateral inhibition and lateral stabilization.



Introduction

This example model cell fate decisions during early patterning of the pancreas (de Back et al., 2012). The simple gene regulatory network of each cell is coupled to adjacent cells by lateral (juxtacrine) signaling.

Model description

The model defines a lattice of cells with a simplified hexagonal epithelial packing. This is specified in Space using a hexagonal lattice structure of size $(x,y,z)=(20,20,0)$ with periodic boundary conditions. The lattice is filled by seeding it with a Population of 400 cells.

Each cell has two basic Properties X and Y representing the expression levels of Ngn3 and Ptf1a that are coupled in a System of DiffEqns.

The NeighborsReporter plugin is used to couple the cells to their directly adjacent neighbors. This plugin checks the values of X in neighboring cells and outputs its mean value in Property Xn.

This model uses a number of Analysis plugins:

- Gnuplotter visualizes the values of Y with a ColorMap that maps values to colors. It outputs to screen (interactive mode) or to PNG (local mode).

- Logger records the values of X and Y expression to file and, at the end of simulation, shows a time plot.
- The first HistogramLogger records and plots the distribution of X and Y expression cells over time.
- The second HistogramLogger records and, after simulation, plots the distribution of τ , the time to cell fate decision (see reference).

Model

h LateralSignaling.xml |h

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

In Morpheus-GUI:

Examples → ODE → LateralSignaling.xml.

Things to try

- Change the lattice structure from hexagonal to square. See Space/Lattice.
- Change the strength of lateral stabilization b and observe the pattern. See CellTypes/CellType/System.
- Change the noise amplitude and observe time to cell fate decision (τ).

Reference

W de Back, J X Zhou, L Brusch, [On the Role of Lateral Stabilization during Early Patterning in the Pancreas](#), *Journal of the Royal Society Interface*, 10:79, 2013.

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