Multi-Scale Modeling with CompuCell3D and SBW/SBML

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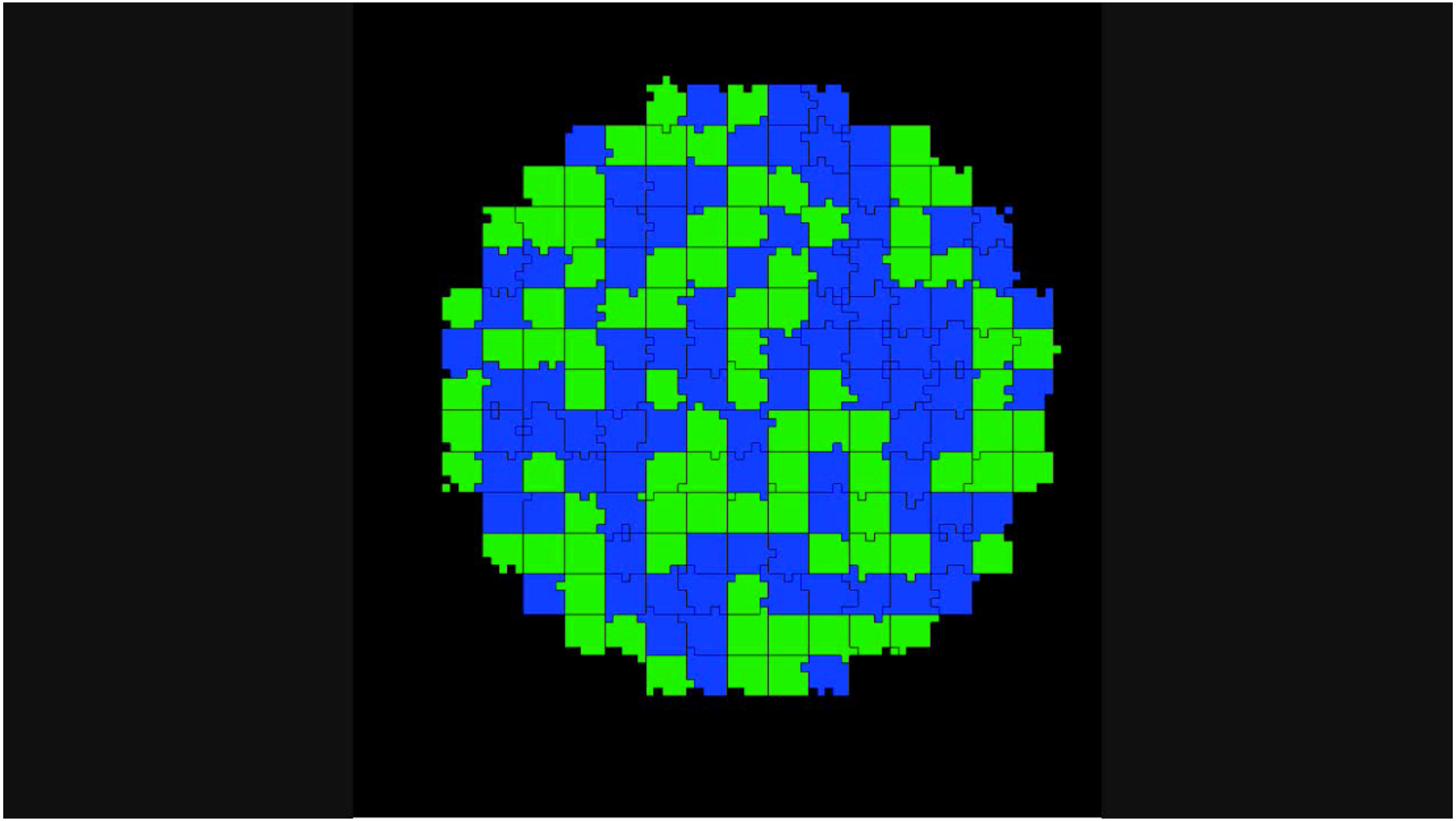
Outline

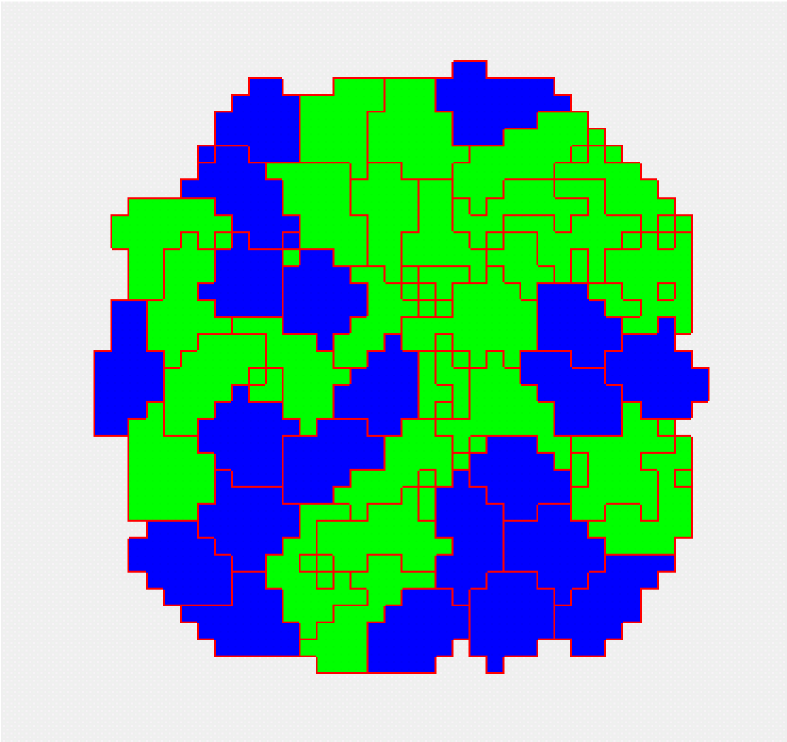
- Multi-scale extensions of the CPM
- Ways to add RK to CC3D
- SBML format
- Integrating with CC3D
  - Delta-Notch example
  - Adding Cell Cycle model from *sbml.org*
- Matching scales
  - Spatial scale
  - Time scale - Diffusion

Typical Cellular Potts Model Simulation

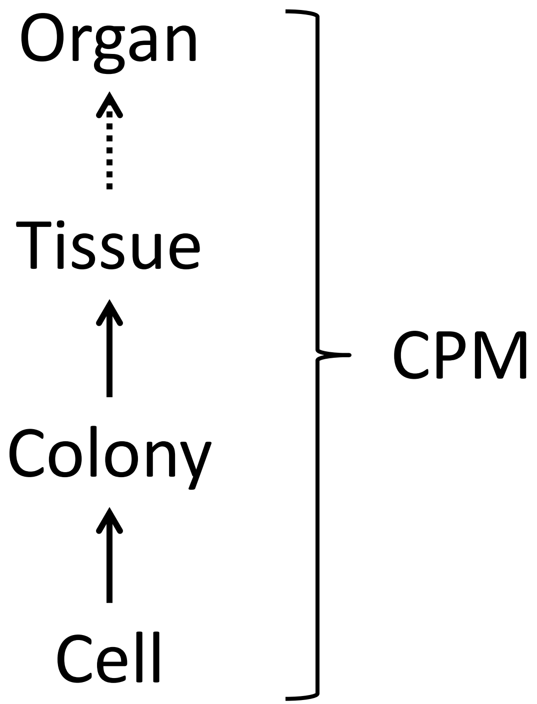


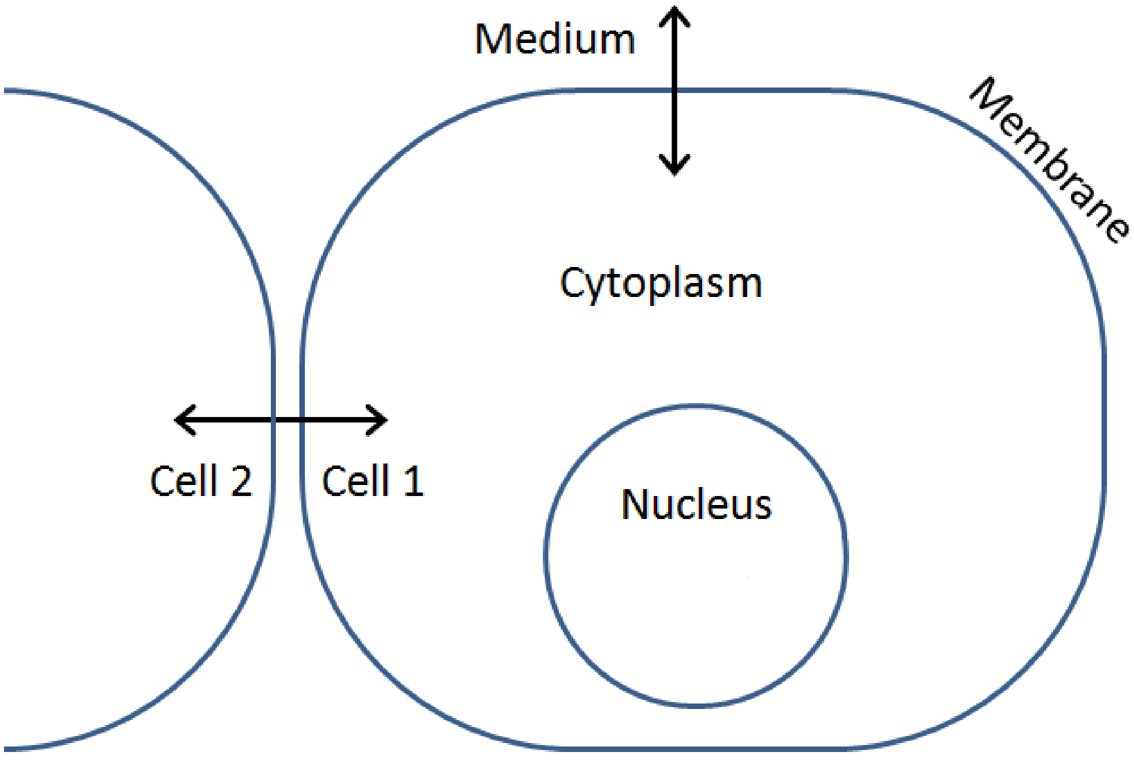
CPM modeling Scope

- Cellular behaviors:
  - Location
  - Volume
  - Shape
  - Movement
  - Adhesion
  - Mitosis
  - Death
  - Differentiation
  - Polarization
  - Etc…

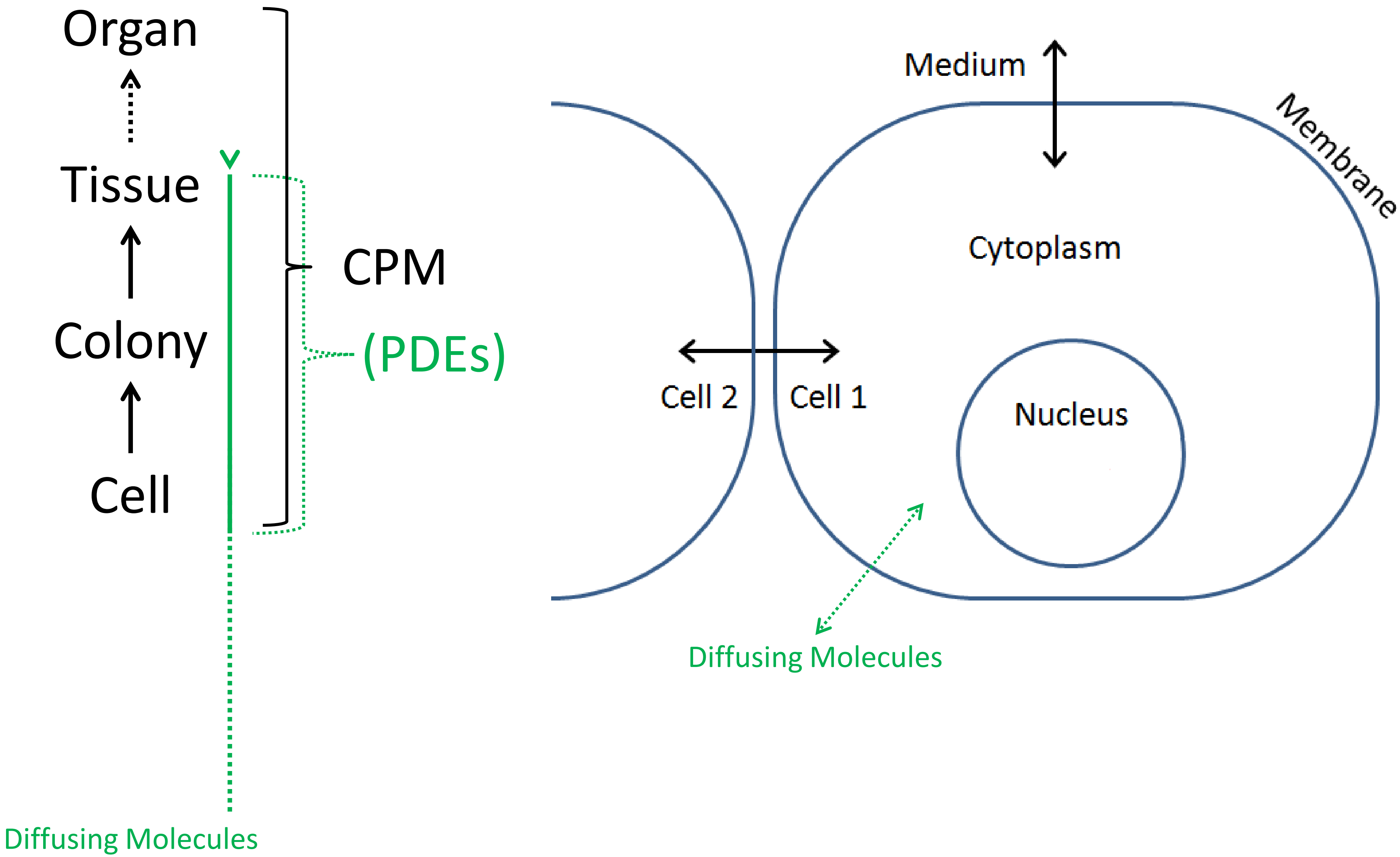


Modelling Scope – CPM

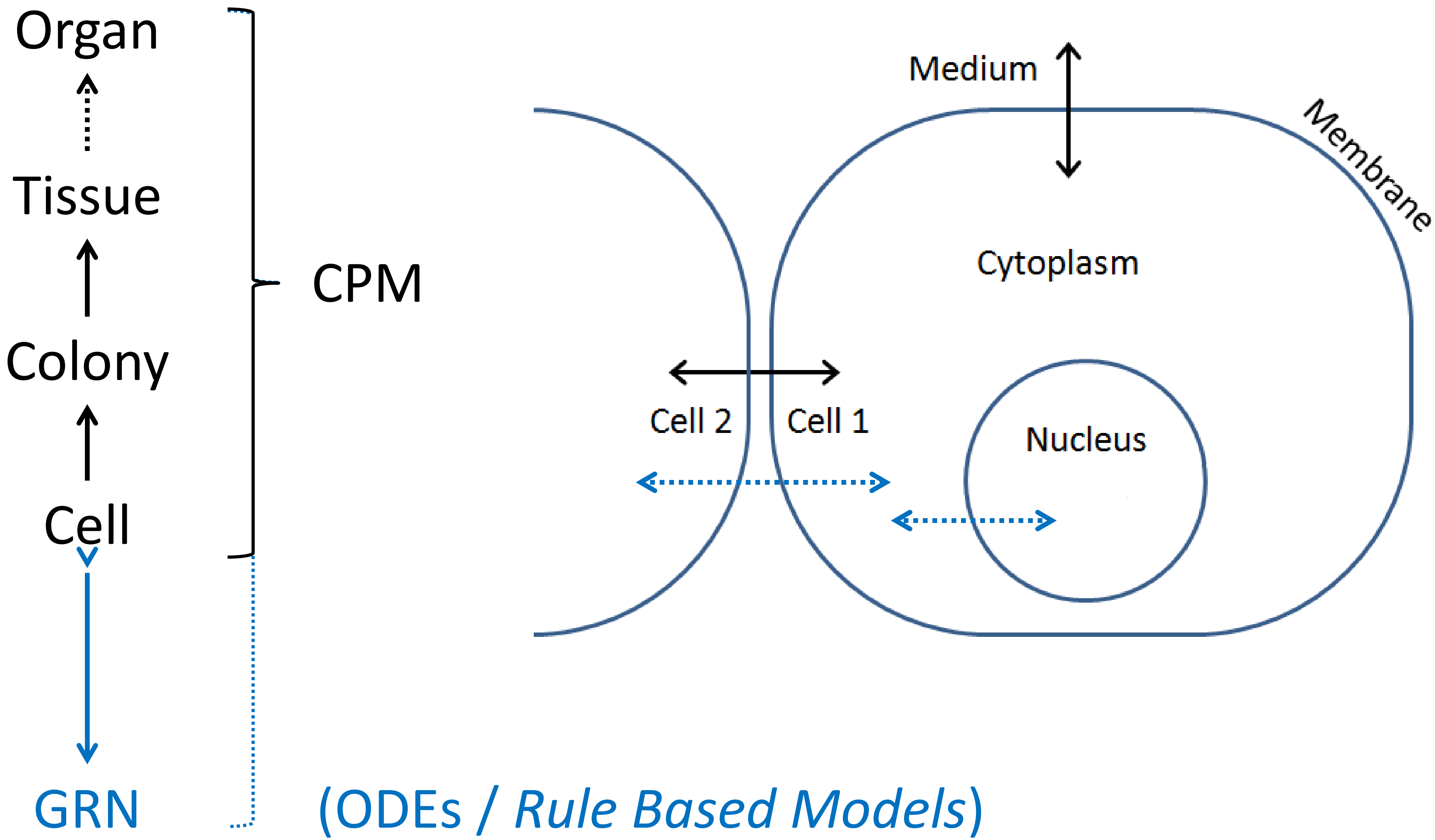




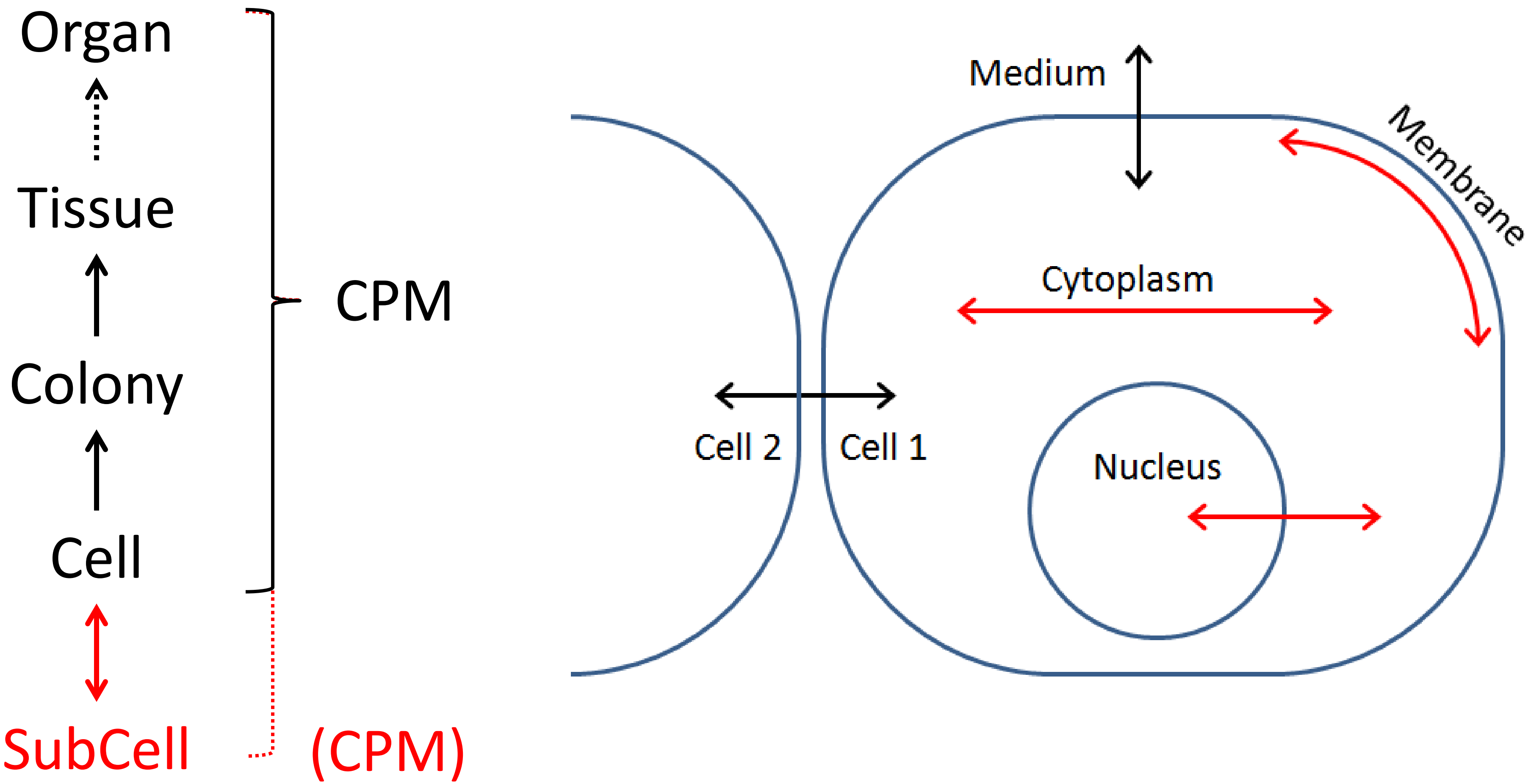
Modelling Scope – CPM + PDEs



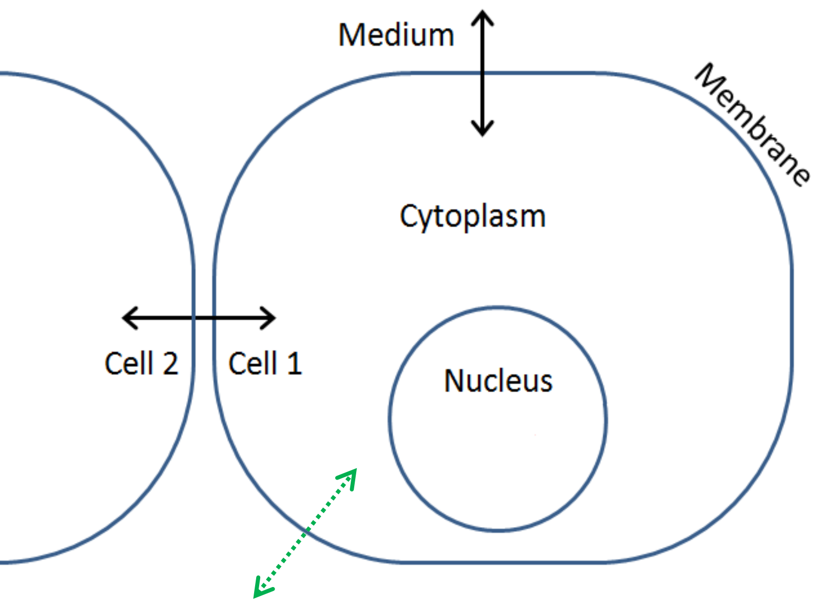
Modelling Scope – CPM + RK

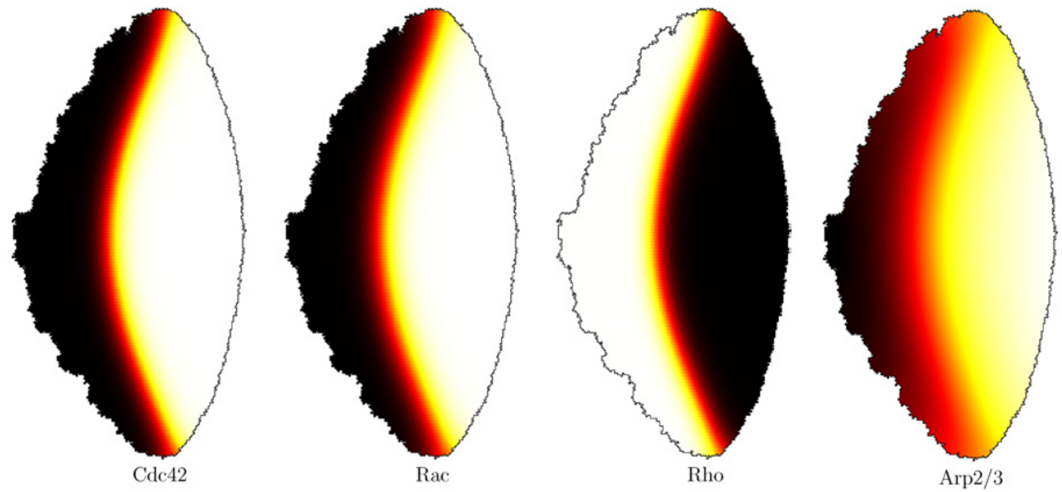


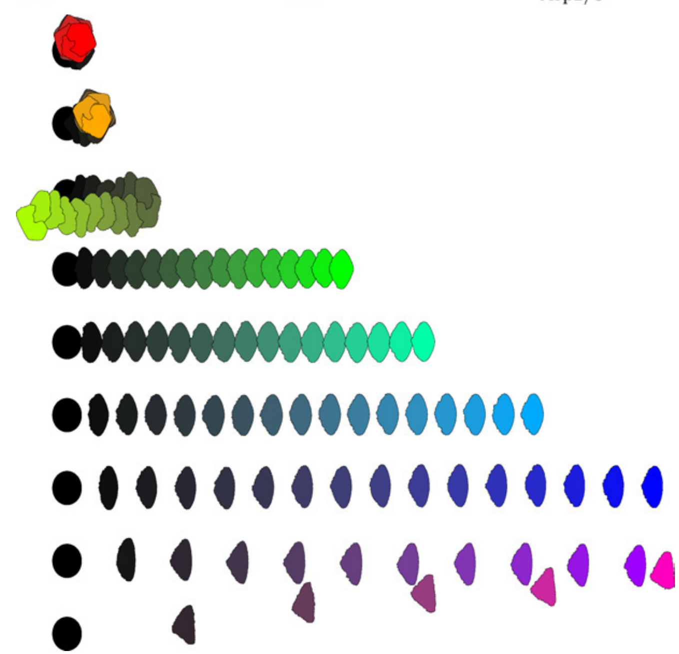
Modelling Scope – *sub*CPM



CPM + PDEs

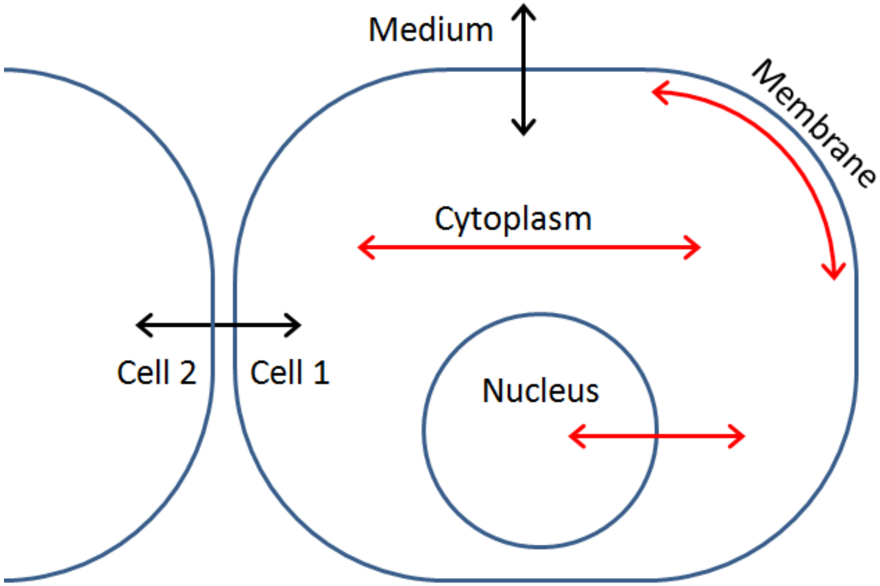


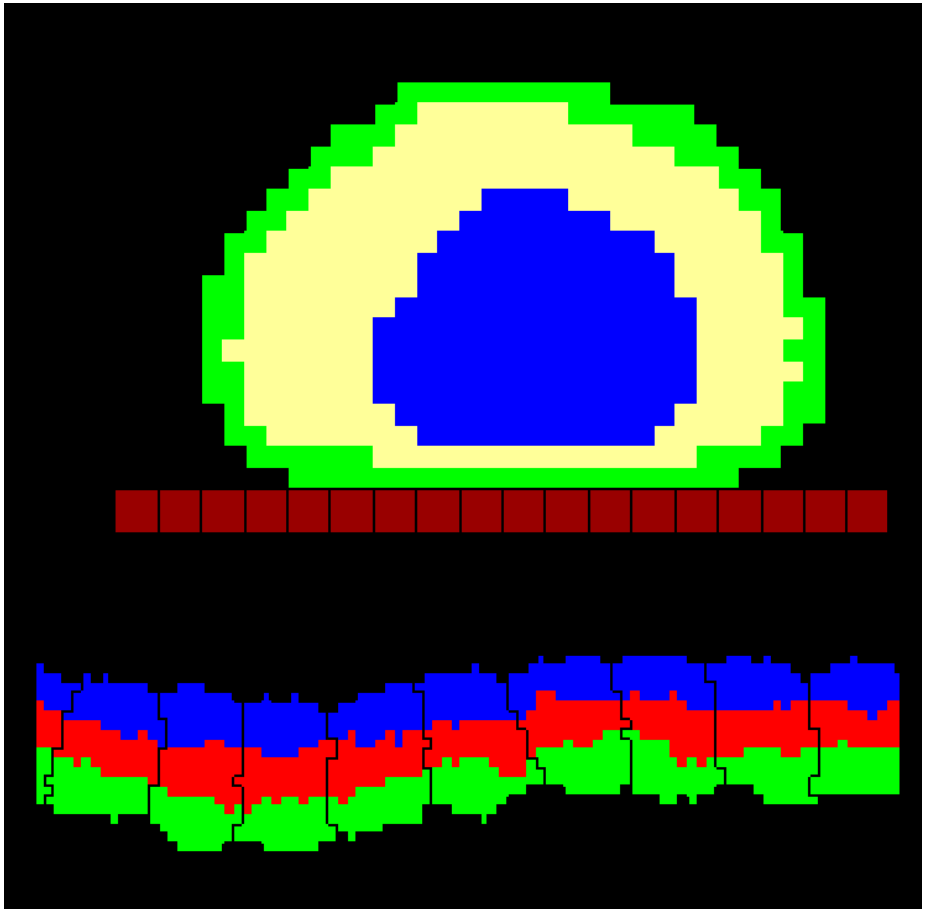




Marée, Jilkineb, Dawesb, Grieneisen, Edelstein-Keshet
Polarization and Movement of Keratocytes (2006)

Cell Compartments





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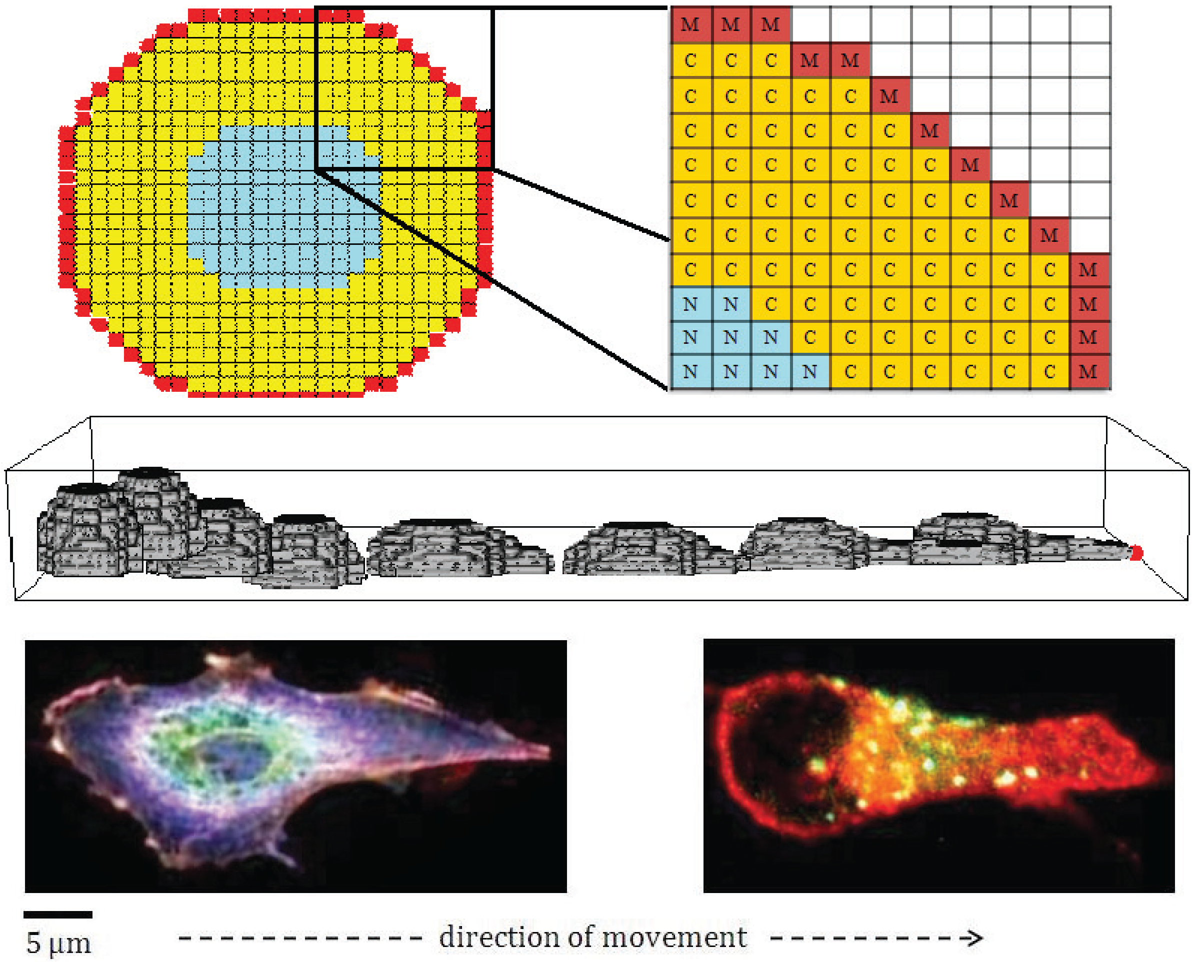
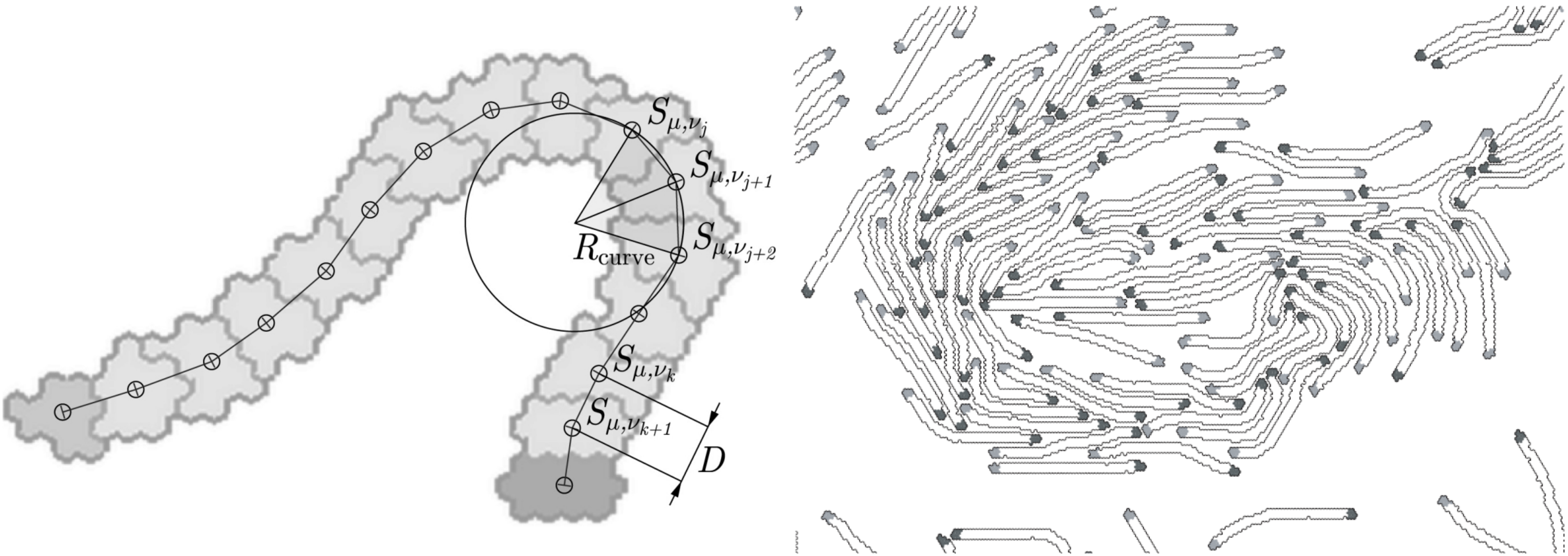


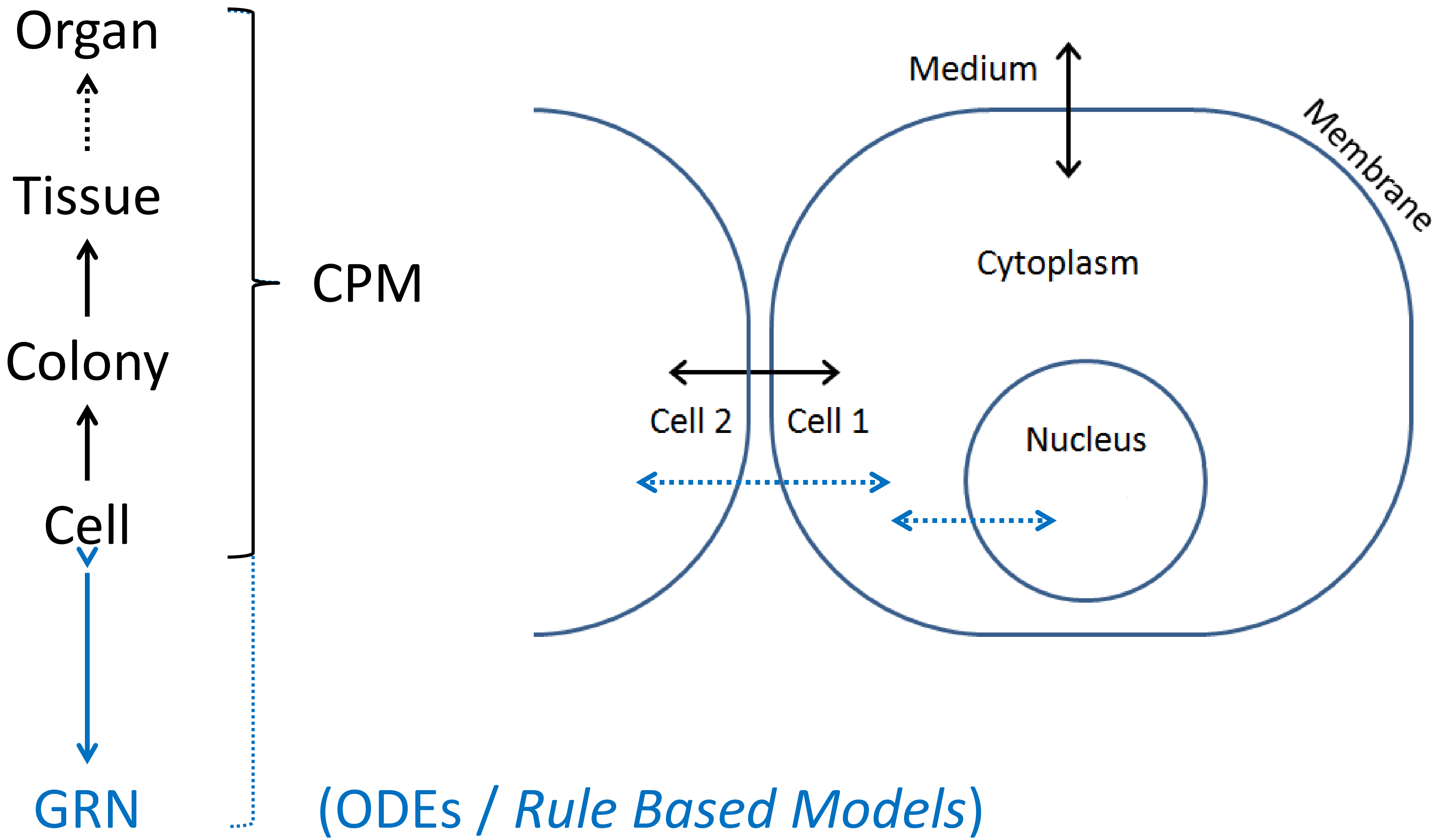
Scianna, Preziosi *Multiscale Developments of the CPM* (2012)

Cell Compartments



Starruss, Peruani, Bär, Deutsch *Bacterial swarming driven by rod shape* (2007)

Modelling Scope – CPM + RK



(ODEs / *Rule Based Models*)

Cell-based modeling

- Cellular behaviors:
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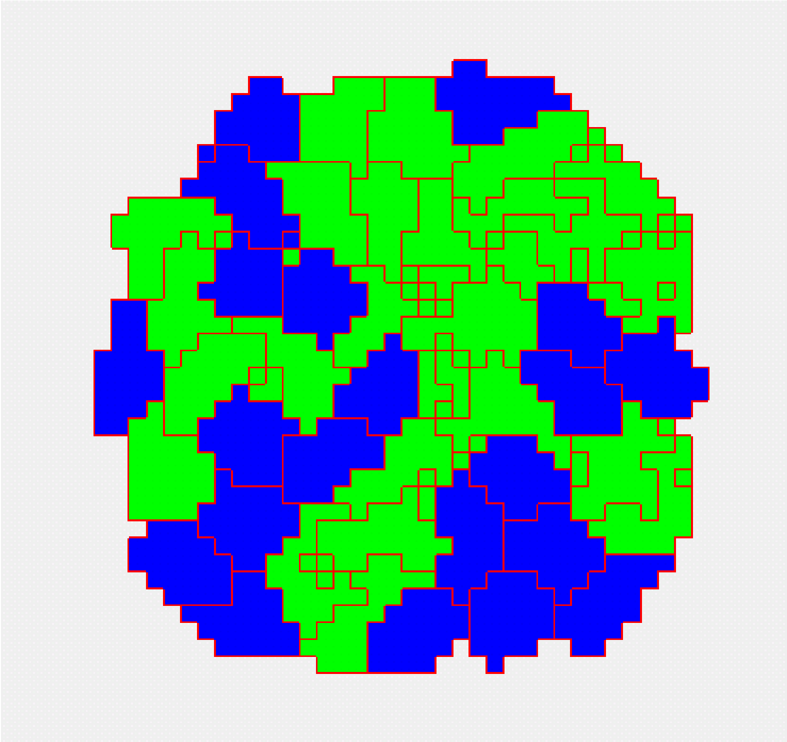

Subcellular modelling

- Biochemical Kinetics:
  - Cell-Cycle
  - Circadian rhythms
  - Cardiac rhythms
  - cAMP oscillations
  - Delta-Notch patterning
  - WNT pathway
  - FGF pathway
  - Etc…

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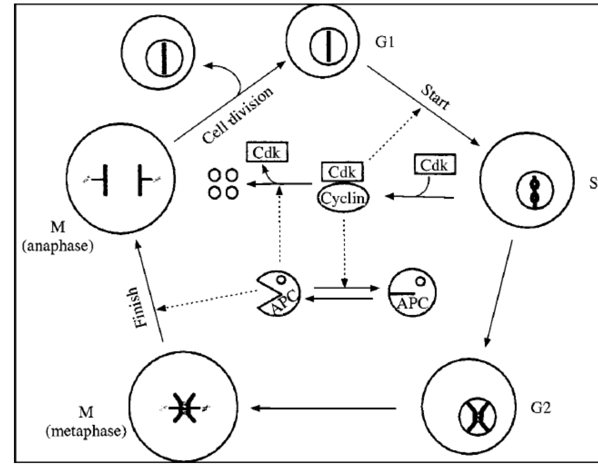

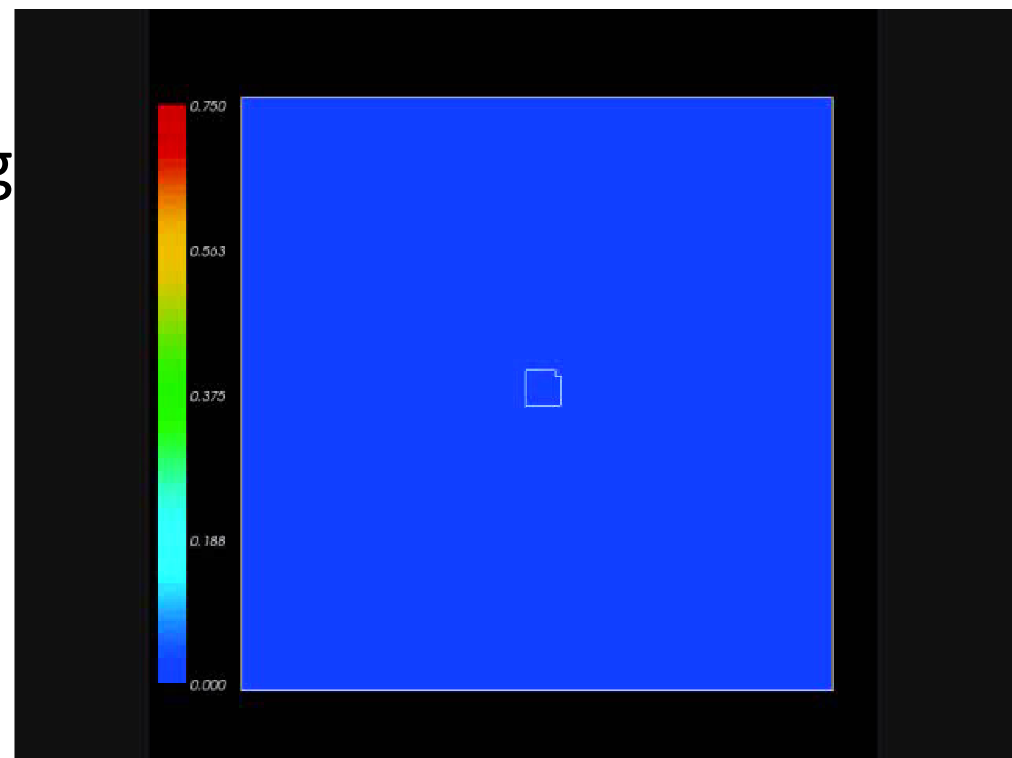

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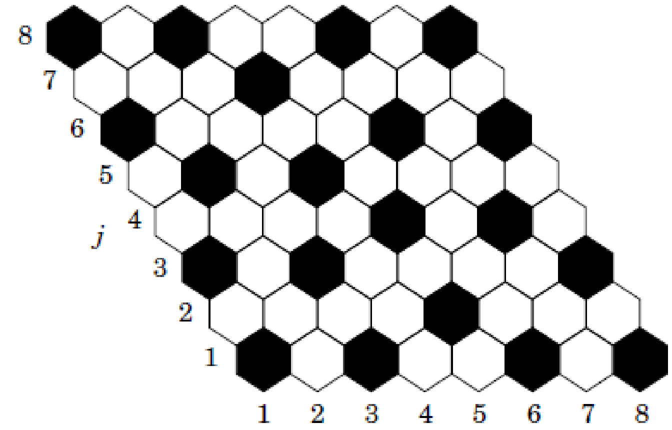

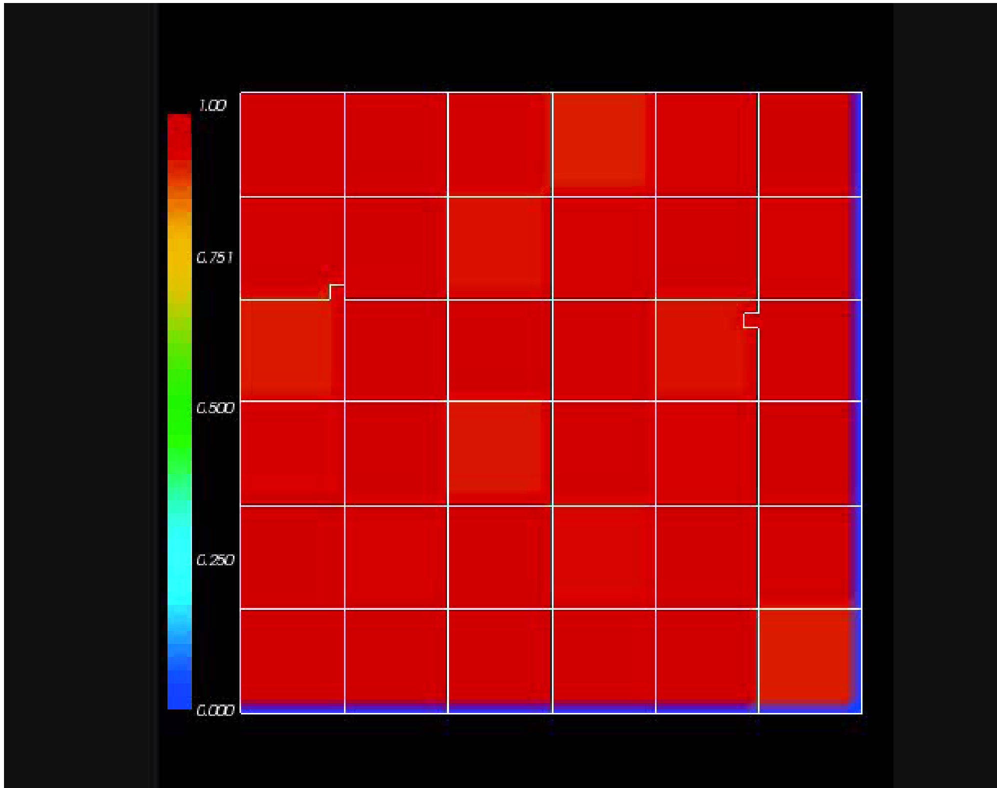

Multiscale model - Somitogenesis

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2) C++ file to be wrapped into Python
   - Too complicated

3) Import SBML

SBML – Systems Biology Markup Language

- Not a software!
- Machine-readable format for representing subcellular models
- Standard for storage and exchange of models
- Implementation agnostic

SBML

- How does it work?

Developer software (SBW/Jarnac)

SBML

Simulation software (CompuCell3D)

SBML

$$S_1 \xrightarrow{k} 2 \cdot S_2$$

- Initial conditions:

$$S_1 = 5 \text{ nM}$$

$$S_2 = 0 \text{ nM}$$

- Parameters:

$$k = 0.1 \text{ min}^{-1}$$

SBML

```xml
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns = "http://www.sbml.org/sbml/level2" level = "2" version = "1">
  <model id = "cell">
    <listOfCompartments>
      <compartment id = "compartment" size = "1"/>
    </listOfCompartments>
    <listOfSpecies>
        <species id = "S1" boundaryCondition = "false" initialConcentration = “5.0" compartment = "compartment"/>
        <species id = "S2" boundaryCondition = "false" initialConcentration = “0.0" compartment = "compartment"/>
    </listOfSpecies>
    <listOfParameters>
      <parameter id = "k1" value = "0.1"/>
    </listOfParameters>
    <listOfReactions>
      <reaction id = "_J1" reversible = "false">
        <listOfReactants>
          <speciesReference species = "S1" stoichiometry = "1"/>
        </listOfReactants>
        <listOfProducts>
          <speciesReference species = "S2" stoichiometry = “2"/>
        </listOfProducts>
        <kineticLaw>
          <math xmlns = "http://www.w3.org/1998/Math/MathML">
            <apply>
              <times/>
              <ci>
                  k1
              </ci>
              <ci>
                  S1
              </ci>
            </apply>
          </math>
        </kineticLaw>
      </reaction>
    </listOfReactions>
  </model>
</sbml>
```

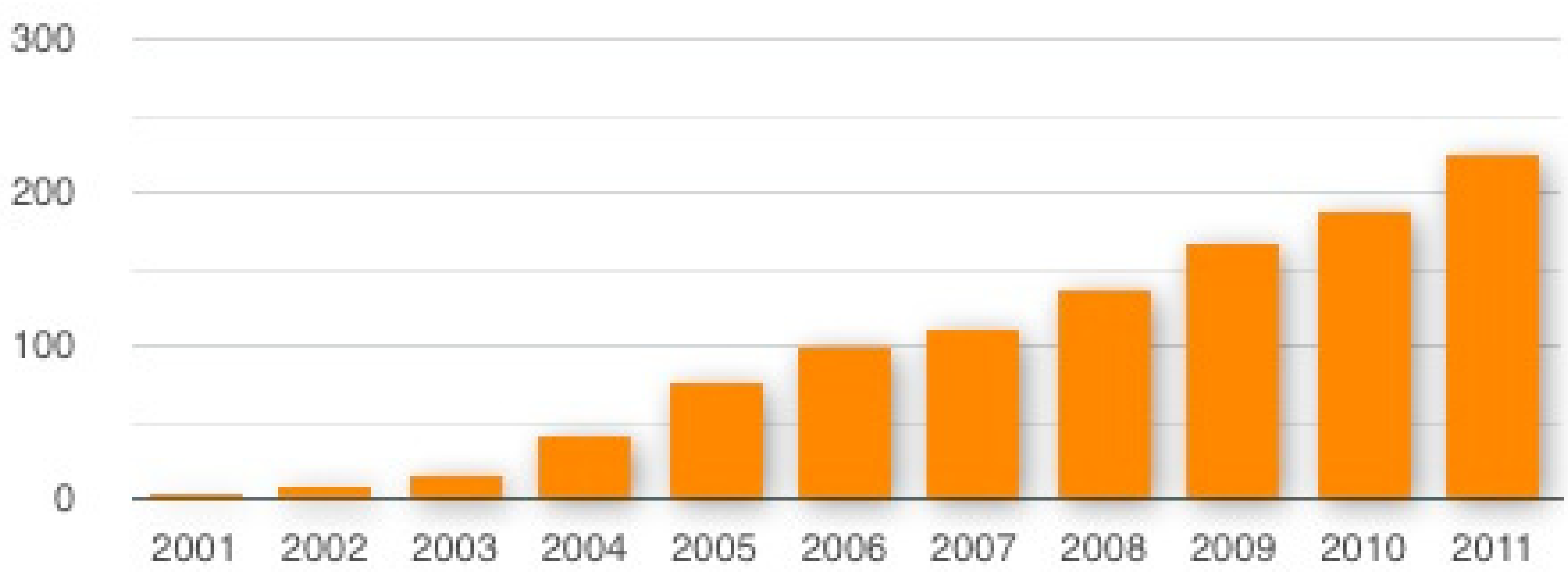
$$S_1 = 5\ \text{nM}$$
$$S_2 = 0\ \text{nM}$$

$$k = 0.1\ \text{min}^{-1}$$

$$S_1 \xrightarrow{k} 2 \cdot S_2$$

SBML

- Total number of known SBML-compatible software packages each year :



How to write SBML?

- Bio-Spice
  - Large collection of tools, integrated via a "Dashboard." Free download (BSD), various platforms.
- Teranode
  - Suite of tools for model management, design, and simulation. (Linux/Mac/Windows) Commercial (30-day trial available).
- SBW
  - Systems Biology Workbench.

- Check http://sbml.org/SBML_Software_Guide

Integration with CC3D – cell

```
class <someClass>(SteppableBasePy):
  def __init__(self,_simulator,_frequency):
    SteppableBasePy.__init__(self,_simulator,_frequency)

  def start(self):
    # Define a SBML model
    Path = <ModelPath>    # Path where the model is stored
    Name = <ModelName>    # Name of the model
    Step = <timeStep>     # Time step of integration

    # Add SBML model to a cell
    for cell in self.cellList:
       self.addSBMLToCell(_modelFile=Path, _modelName=Name, _cell=cell, _stepSize=Step)

  def step(self,mcs):
    # Iterate the model (run it for the time step specified on the load command)
    self.timeStepSBML()

    # Get the parameter value or molecular concentration from a cell
    for cell in self.cellList:
       <var> = self.getSBMLValue(_modelName=<Name>, _valueName=<param/molecule>, _cell=cell)

       # Set a new parameter value or molecular concentration value for a cell
       self.setSBMLValue(_modelName=<Name>,_valueName=<param/molecule>,_value=<val>,_cell=cell)

       # Change integration step of a cell
       self.setStepSizeForCell(_modelName=<Name>, _cell=cell, _stepSize=<newStep>)

    # Copy a SBML model from one cell to another
    self.copySBMLs(_fromCell=cell1, _toCell=cell2, _sbmlNames=[<ModelName1>,<ModelName2>,…])

    # Delete a SBML model from a cell
    self.deleteSBMLFromCell(_modelName=<Name>, _cell=cell)
```

Integration with CC3D – cell id

```
class <someClass>(SteppableBasePy):
  def __init__(self,_simulator,_frequency):
    SteppableBasePy.__init__(self,_simulator,_frequency)

  def start(self):
    # Define a SBML model
    Path = <ModelPath>    # Path where the model is stored
    Name = <ModelName>    # Name of the model
    Step = <timeStep>     # Time step of integration

    # Add SBML model to a cell
    for cell in self.cellList:
       self.addSBMLToCellIds(_modelFile=Path, _modelName=Name, _ids=[cell.id], _stepSize=Step)

  def step(self,mcs):
    # Iterate the model (run it for the time step specified on the load command)
    self.timeStepSBML()

    # Get the parameter value or molecular concentration from a cell
    for cell in self.cellList:
       <var> = self.getSBMLValue(_modelName=<Name>, _valueName=<param/molecule>, _cell=cell)

       # Set a new parameter value or molecular concentration value for a cell
       self.setSBMLValue(_modelName=<Name>,_valueName=<param/molecule>,_value=<val>,_cell=cell)

       # Change integration step of a cell (overwrites the initial step value)
       self. setStepSizeForCellIds(_modelName=<Name>, _ids=[cell.id], _stepSize=<newStep>)

    # Copy a SBML model from one cell to another
    self.copySBMLs(_fromCell=cell1, _toCell=cell2, _sbmlNames=[<ModelName1>,<ModelName2>,…])

    # Delete a SBML model from a cell
    self.deleteSBMLFromCellIds(_modelName=<Name>, _ids=[id1,id2,…])
```

Integration with CC3D – cell types

```
class <someClass>(SteppableBasePy):
  def __init__(self,_simulator,_frequency):
    SteppableBasePy.__init__(self,_simulator,_frequency)

  def start(self):
    # Define a SBML model
    Path = <ModelPath>    # Path where the model is stored
    Name = <ModelName>    # Name of the model
    Step = <timeStep>     # Time step of integration

    # Add SBML model to a cell type (all cells of that cell type will have it)
    self.addSBMLToCellTypes(_modelFile=Path,_modelName=Name,_types=[self.TYPE1…],_stepSize=Step)

  def step(self,mcs):
    # Iterate the model (run it for the time step specified on the load command)
    self.timeStepSBML()

    # Get the parameter value or molecular concentration from a cell
    for cell in self.cellList:
       <var> = self.getSBMLValue(_modelName=<Name>, _valueName=<param/molecule>, _cell=cell)

       # Set a new parameter value or molecular concentration value for a cell
       self.setSBMLValue(_modelName=<Name>,_valueName=<param/molecule>,_value=<val>,_cell=cell)

    # Change integration step of a cell type (overwrites the initial step value)
    self.setStepSizeForCellTypes(_modelName=<Name>, _types=[self.TYPE1,…], _stepSize=<newStep>)

    # Copy a SBML model from one cell to another
    self.copySBMLs(_fromCell=cell1, _toCell=cell2, _sbmlNames=[<ModelName1>,<ModelName2>,…])

    # Delete a SBML model from a cell type (all cells of that type will loose the model)
    self.deleteSBMLFromCellTypes(_modelName=<ModelName>, _types=[self.TYPE1,…])
```

Integration with CC3D – outside cells

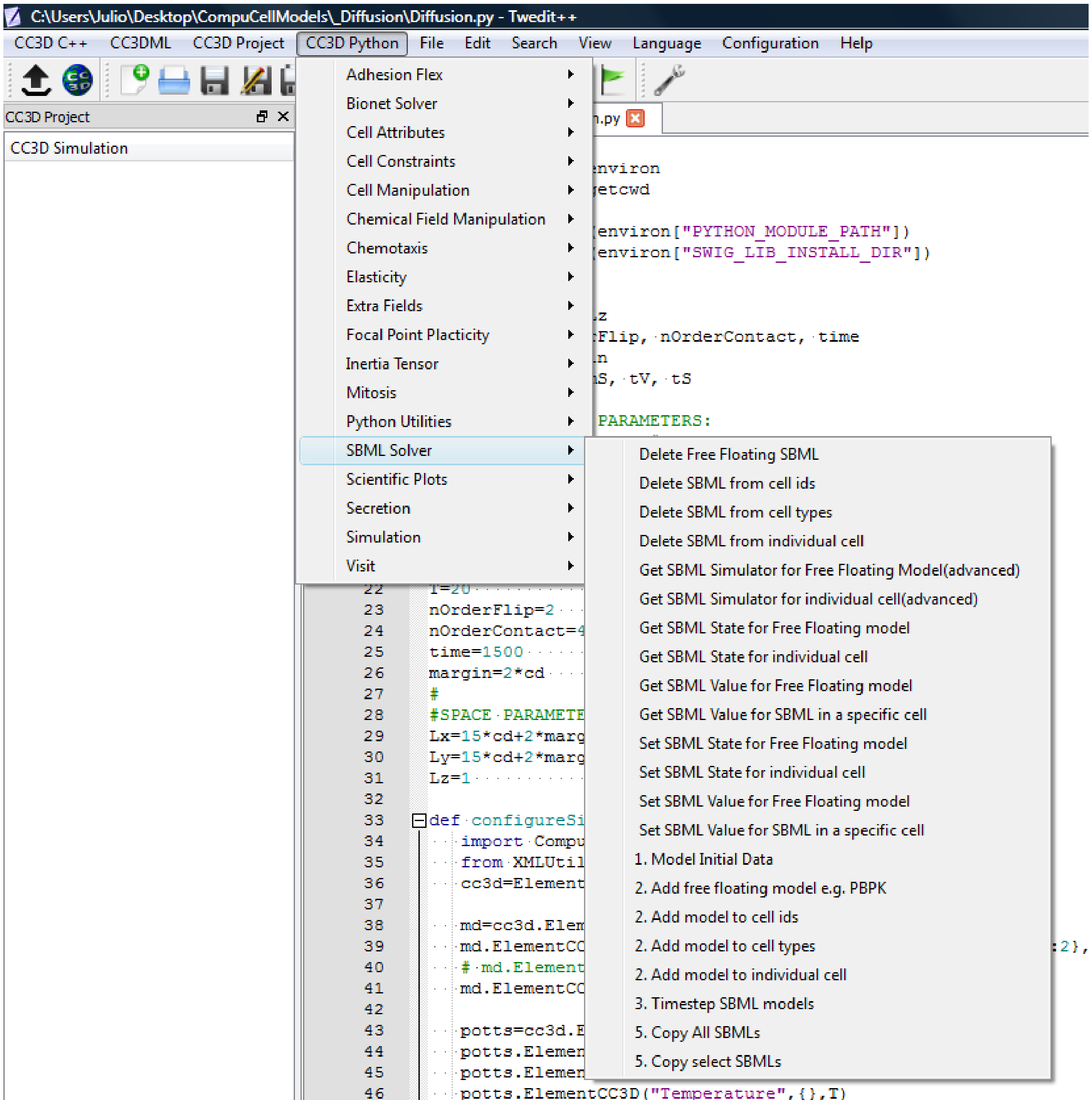
```
class <someClass>(SteppableBasePy):
  def __init__(self,_simulator,_frequency):
    SteppableBasePy.__init__(self,_simulator,_frequency)

  def start(self):
    # Define a SBML model
    Path = <ModelPath>    # Path where the model is stored
    Name = <ModelName>    # Name of the model
    Step = <timeStep>     # Time step of integration

    # Add a free floating SBML
    self.addFreeFloatingSBML(_modelFile=Path, _modelName=Name, _stepSize=Step)

  def step(self,mcs):
    # Iterate the model (run it for the time step specified on the load command)
    self.timeStepSBML()

    # Get the parameter value or molecular concentration from a free floating SBML
    <var> = self.getSBMLValue(_modelName=<Name>, _valueName=<param/molecule>)

    # Set a new parameter value or molecular concentration value for a free floating SBML
    self.setSBMLValue(_modelName=<Name>, _valueName=<param/molecule>, _value=<val>)

    # Change integration step of a free floating SBML (overwrites the initial step value)
    self.setStepSizeForFreeFloatingSBML(_modelName=<Name>, _stepSize=<newStep>)

    # Delete a SBML model from a free floating SBML
    self.deleteFreeFloatingSBML(_modelName=<ModelName>)
```

Integration with CC3D

- Other commands:

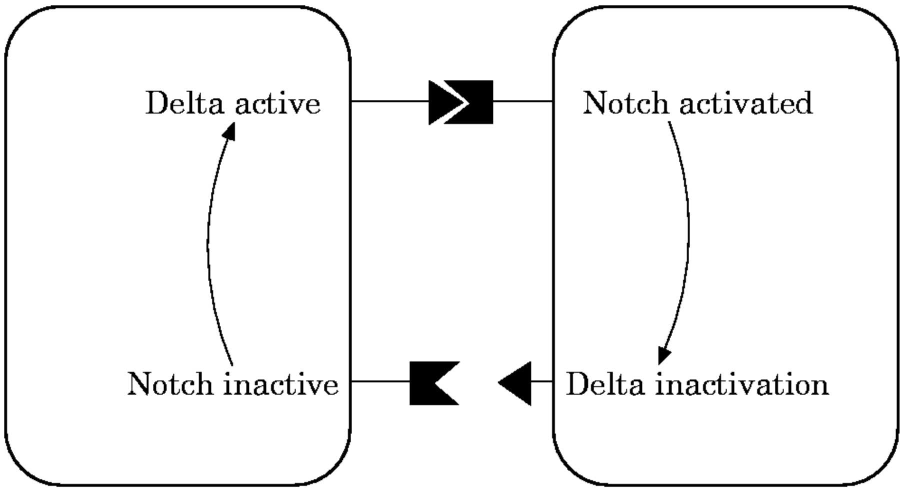
```
self.timestepSBML() # time step all models

self.timestepCellSBML() # time step all models associated with cells

self.timestepFreeFloatingSBML() # time step all free floating models

# check if a model is loaded into a cell
self.getSBMLSimulator(_modelName='',_cell=)

# check if a free floating model is defined
self.getSBMLSimulator(_modelName='')

# returns dictionary with all parameters and concentration values
state = self.getSBMLState(_modelName='',_cell=)

     state = self.getSBMLState(_modelName='myModel',_cell=cell)
     state >> {'S1':1.0, 'S2':0.0, 'k':0.1}

# sets new values for all parameters and concentrations defined in the dictionary
self.setSBMLState(_modelName='',_cell=,_state={})

     newState = {'S1':2.0, 'S2':0.5}
     self.setSBMLState(_modelName='myModel',_cell=cell,_state=newState)
```

Integration with CC3D



Example – Delta-Notch Patterning

- We will use the model published by Collier *et al.* in 1996:



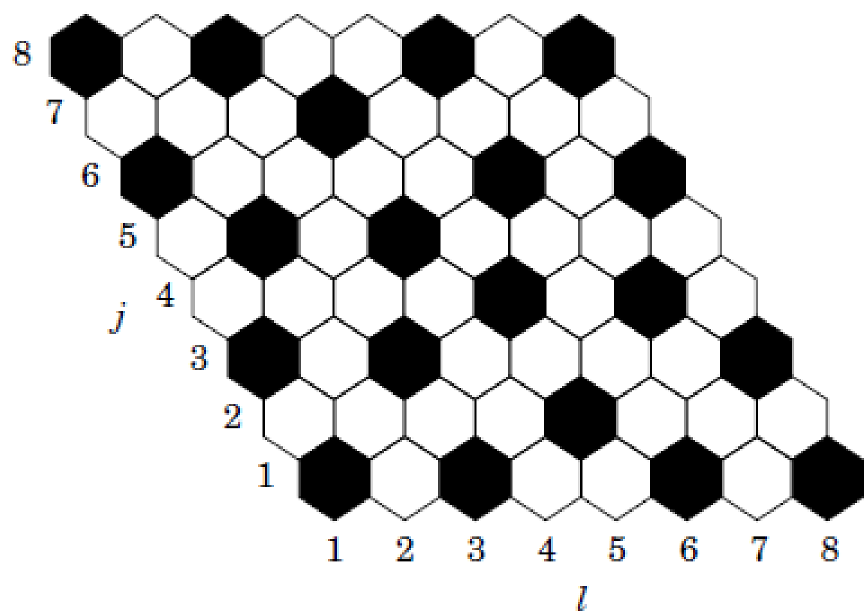
$$\frac{dD}{dt} = v \cdot \left(\frac{1}{1 + b \cdot N^h} - D \right)$$

$$\frac{dN}{dt} = \frac{\overline{D}^k}{a + \overline{D}^k} - N$$

  - N : Notch
  - D : Delta
  - D̄: average Delta from neighbors

Example – Delta-Notch Patterning

- In this model, when a cell receives high levels of Delta from neighbors its Notch level becomes downregulated.
- This leads to the high/low Notch patterning shown by their simulations on an hexagonal lattice:



Example – Delta-Notch Patterning

- CC3D comes with this model as one of its examples:

CompuCell3D\Demos\BoolChapterDemos_ComputationalMethodsInCellBiology\DeltaNotch

- As an initial condition all cells start with random values of Delta and Notch between 0.9 and 1.0:

```
class DeltaNotchClass(SteppableBasePy):
  def __init__(self,_simulator,_frequency):
      SteppableBasePy.__init__(self,_simulator,_frequency)

  def start(self):
    modelFile='Simulation/DN_Collier.sbml'
    self.addSBMLToCellTypes(_modelFile=modelFile,_modelName='DN',_types=[self.TYPEA],_stepSize=0.2)

    #Initial conditions
    import random
    state={} #dictionary to store state variables of the SBML model
    for cell in self.cellList:
        state['D'] = random.uniform(0.9,1.0)
        state['N'] = random.uniform(0.9,1.0)
        self.setSBMLState(_modelName='DN',_cell=cell,_state=state)

        cellDict=self.getDictionaryAttribute(cell)
        cellDict['D']=state['D']
        cellDict['N']=state['N']

  def step(self,mcs):
```

Example – Delta-Notch Patterning

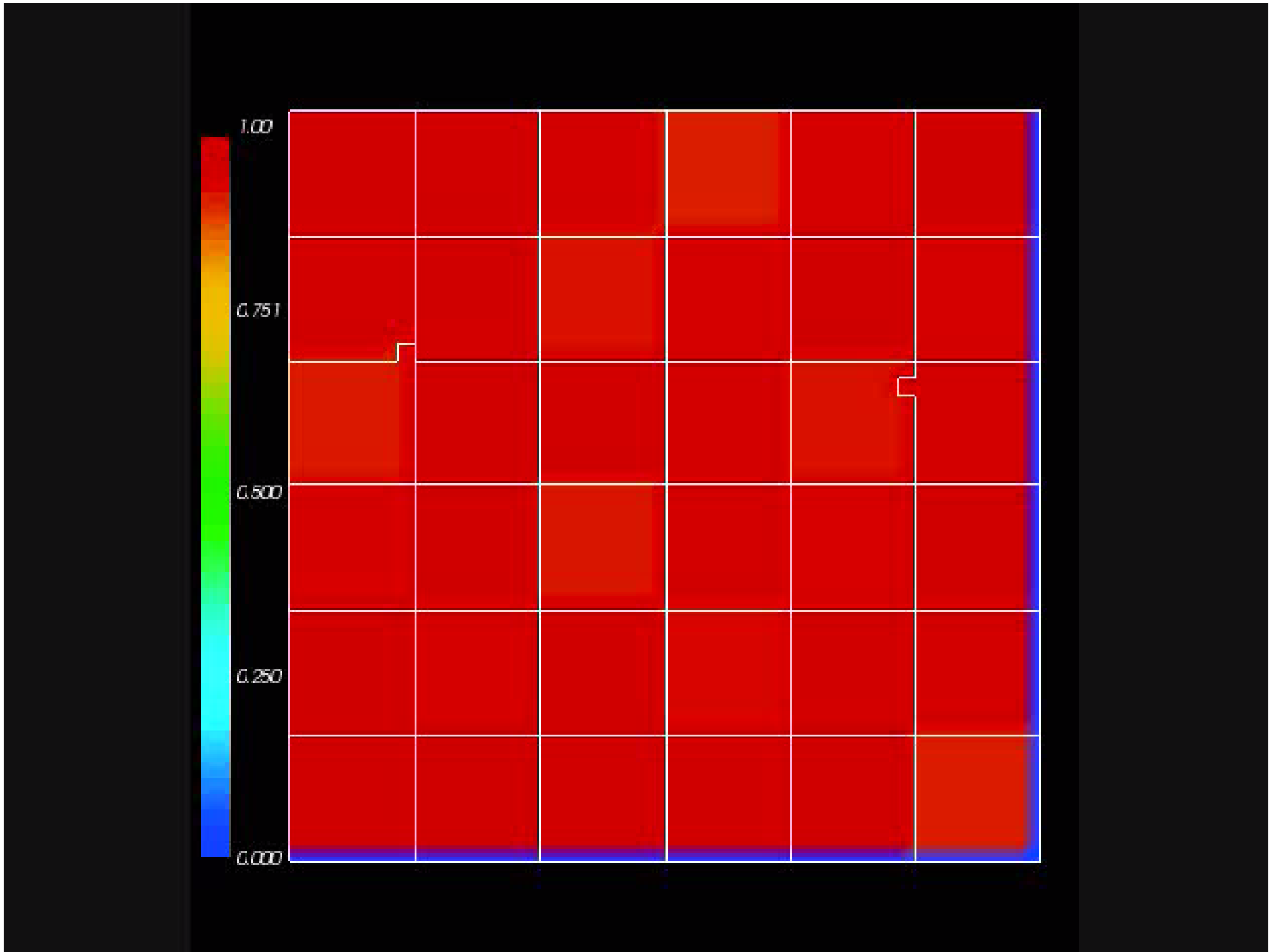
- At every MCS we loop over all cells' neighbors and store their Delta:

```
    def step(self,mcs):
        for cell in self.cellList:

            D=0.0; nn=0
            for neighbor , commonSurfaceArea in self.getCellNeighborDataList(cell):
                if neighbor:
                    nn+=1
                    state=self.getSBMLState(_modelName='DN',_cell=neighbor)
                    D+=state['D']

            if (nn>0):
                D=D/nn
            state={}
            state['Davg']=D
            self.setSBMLState(_modelName='DN',_cell=cell,_state=state)

            state=self.getSBMLState(_modelName='DN',_cell=cell)
            cellDict=self.getDictionaryAttribute(cell)
            cellDict['D']=D
            cellDict['N']=state['N']
        self.timestepSBML()

```

- Then we average it and use it as the new <u>D</u> parameter of that cell:

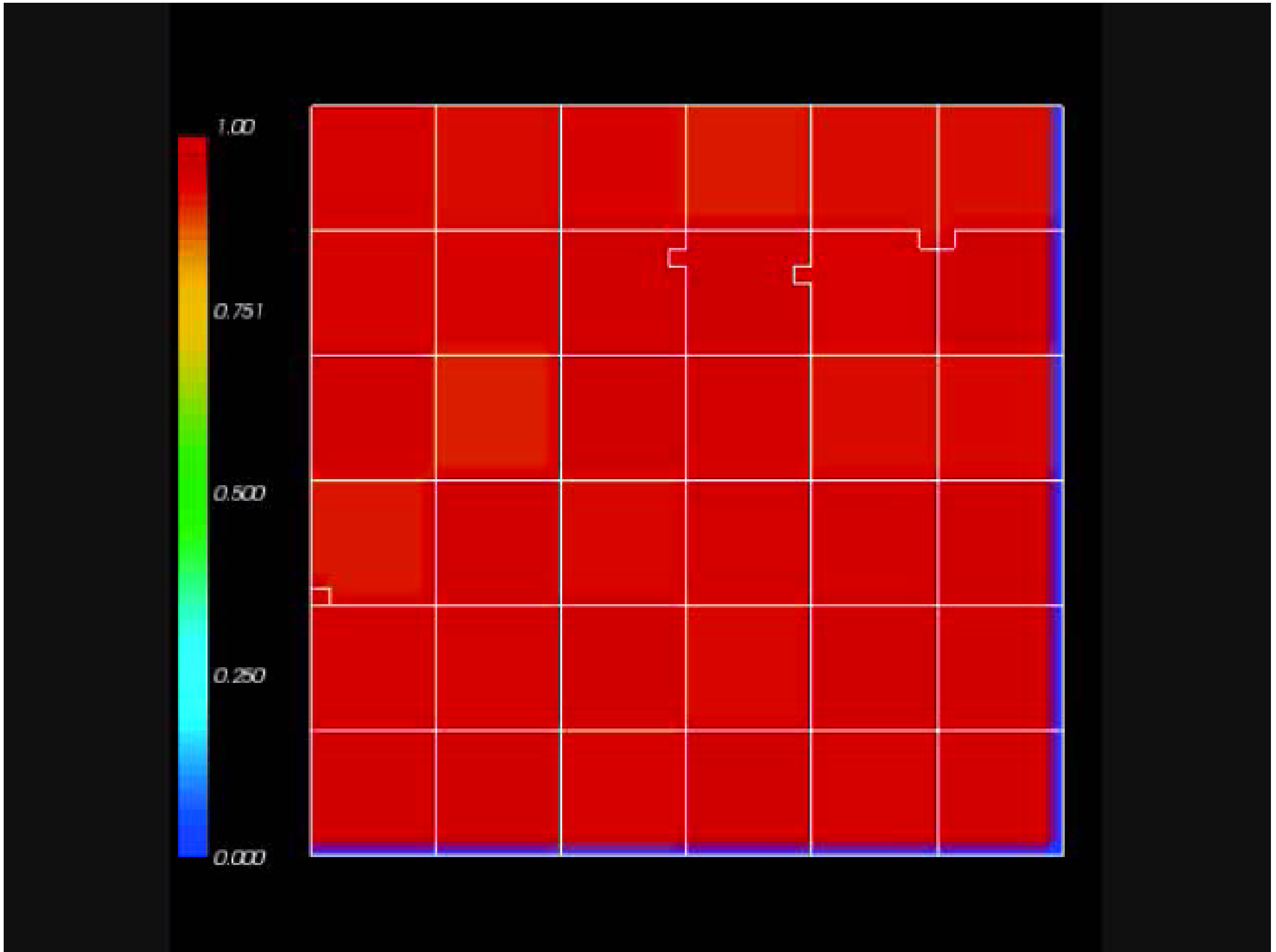
Example – Delta-Notch Patterning

- When we run this model we can see that first the Notch values go down before the pattern emerges:



Example – Delta-Notch Patterning

- If we increase the level of membrane fluctuations the pattern will be disrupted :



Exercise 1

- Open the Delta-Notch example and run it
- Make sure you understand the code
- Check that the pattern is lost when the motility of the cells is high

Second Example – Cell Cycle from web

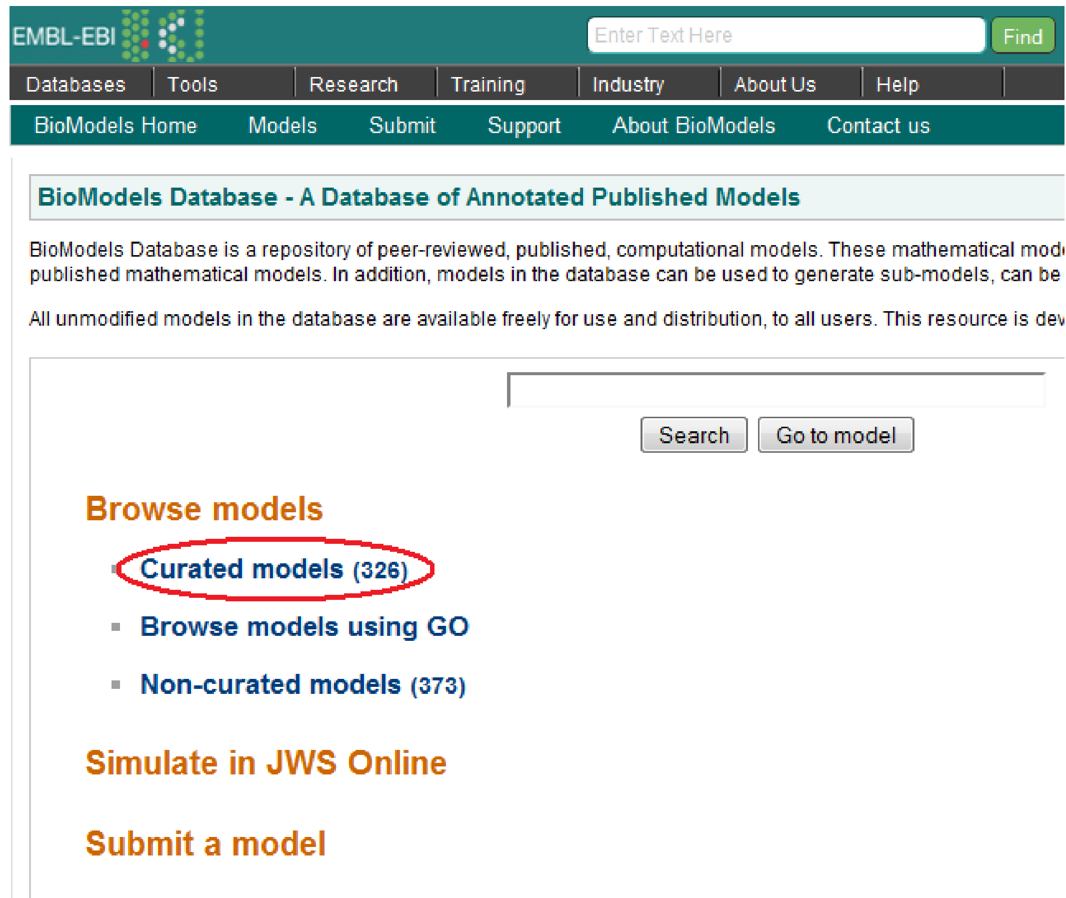
- In our second example we will use a published model for the cell cycle.

- The website www.sbml.org contains a repository of published models in SBML format.

- If you wish to submit your own SBML to the repository, follow the instructions at: www.ebi.ac.uk/biomodels-main/submit

Second Example – Cell Cycle Model

- On www.sbml.org, click on the link "*BioModels Database*" and then on "*Curated models*":



Second Example – Cell Cycle from web

- From the model list select the third one by clicking on the link under the column “BioModels ID”

BioModels Home   Models   Submit   Support   About BioModels   Contact us

Browse - Curated models

⊟ The following fields are used to describe a model:

- *BioModels ID* → A unique string of characters associated with the model, which will never be re-used even if the model is deleted from the BioModels Database.
- *Name* → The name of the model, as written in the model itself by its creator(s).
- *Publication ID* → The unique identifier of the reference publication describing the model, specified either as a PubMed identifier (linked to the EBI Medline database), or as a DOI (linked to the original must have one publication identifier, and the same identifier can be shared amongst several models if they have been described in the same publication.
- *Last Modified* → The date when the model was last modified.

To view a model, simply click on the correspondant BioModels ID provided within the leftmost column of the row corresponding to the model.

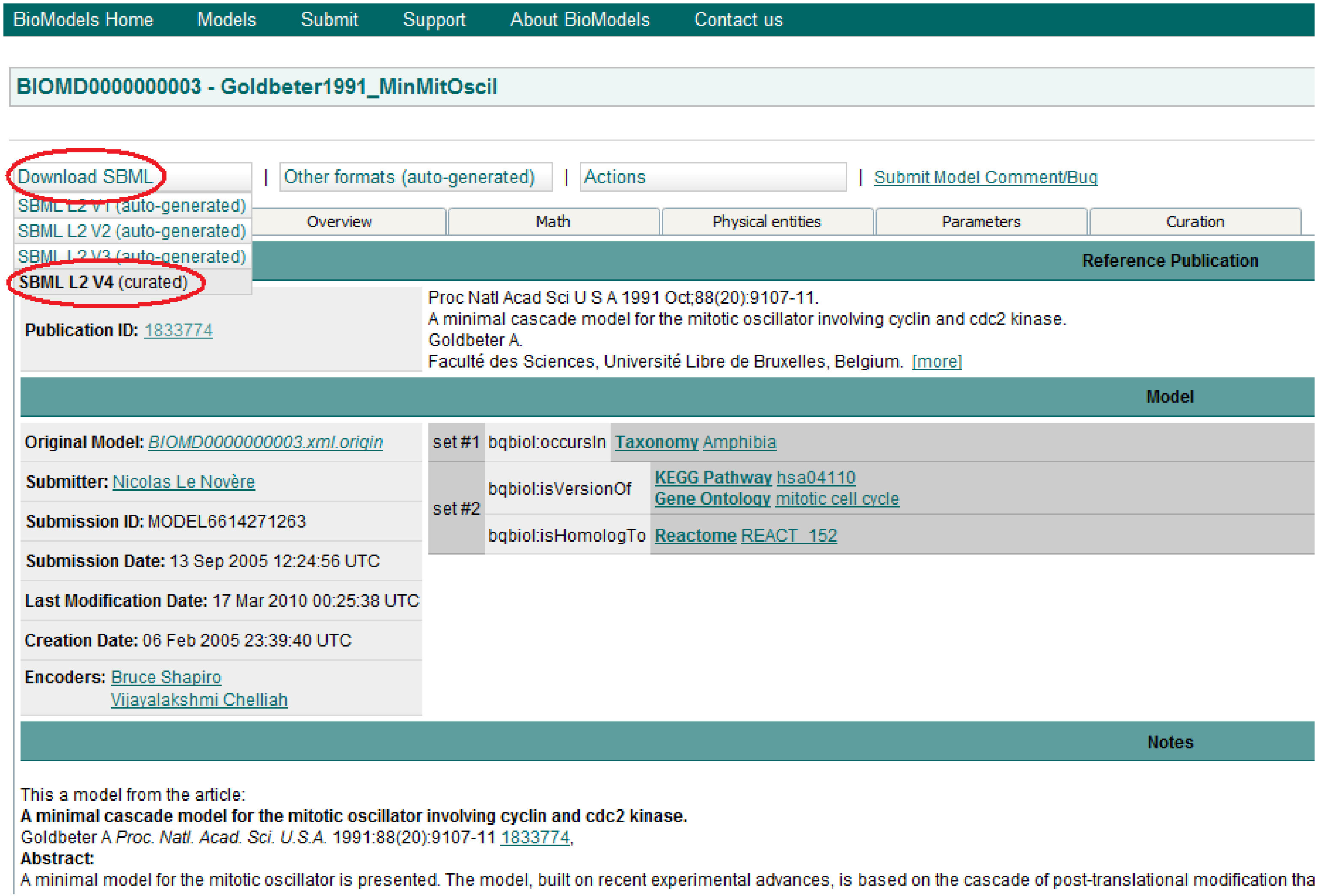
⇦ 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 ⇨

BioModels ID	Name	Publication ID
BIOMD0000000001	Edelstein1996_EPSP_AChEvent	8983160
BIOMD0000000002	Edelstein1996_EPSP_AChSpecies	8983160
BIOMD0000000003	Goldbeter1991_MinMitOscil	1833774
BIOMD0000000004	Goldbeter1991_MinMitOscil_ExplInact	1833774
BIOMD0000000005	Tyson1991_CellCycle_6var	1831270
BIOMD0000000006	Tyson1991_CellCycle_2var	1831270
BIOMD0000000007	Novak1997_CellCycle	9256450
BIOMD0000000008	Gardner1998_CellCycle_Goldbeter	9826676
BIOMD0000000009	Huang1996_MAPK_ultrasens	8816754
BIOMD0000000010	Kholodenko2000_MAPK_feedback	10712587

Computational Systems Neurobiology Group, European Bioinformatics Institute. : Terms of Use : Contact Us : Developed by the BioModels.net Team

Second Example – Cell Cycle from web

- To download the model click on “Download SBML” and select “SBML L2 V4 (curated)”



Second Example – Cell Cycle from web

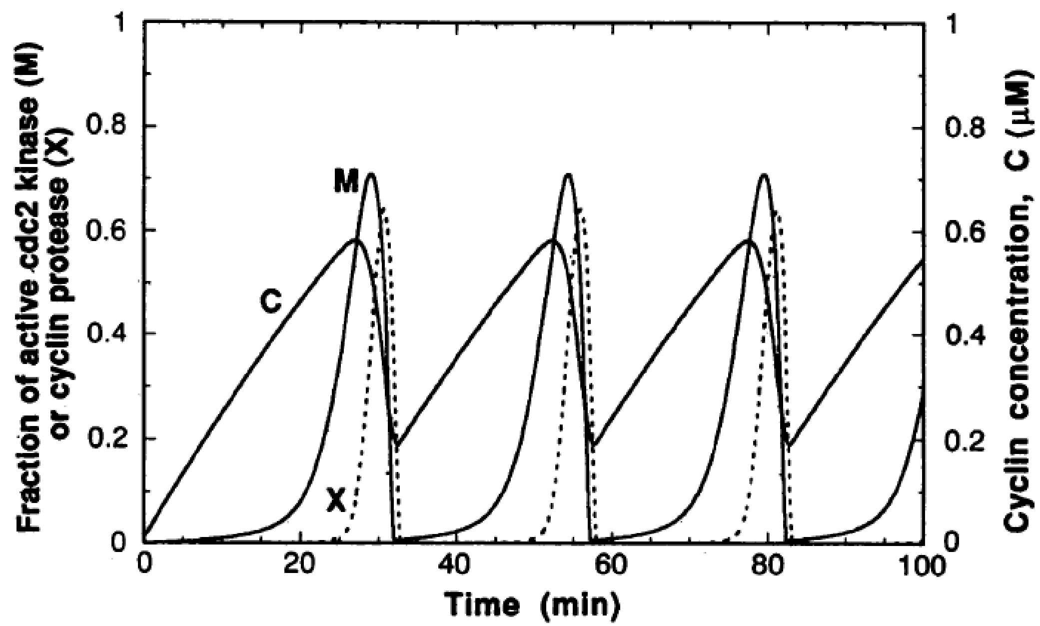
- This model is composed of 3 ODEs that forms an oscillating system:

$$\frac{dC}{dt} = v_i - v_d X \frac{C}{K_d + C} - k_d C,$$

$$\frac{dM}{dt} = V_1 \frac{(1-M)}{K_1 + (1-M)} - V_2 \frac{M}{K_2 + M},$$

$$\frac{dX}{dt} = V_3 \frac{(1-X)}{K_3 + (1-X)} - V_4 \frac{X}{K_4 + X}$$

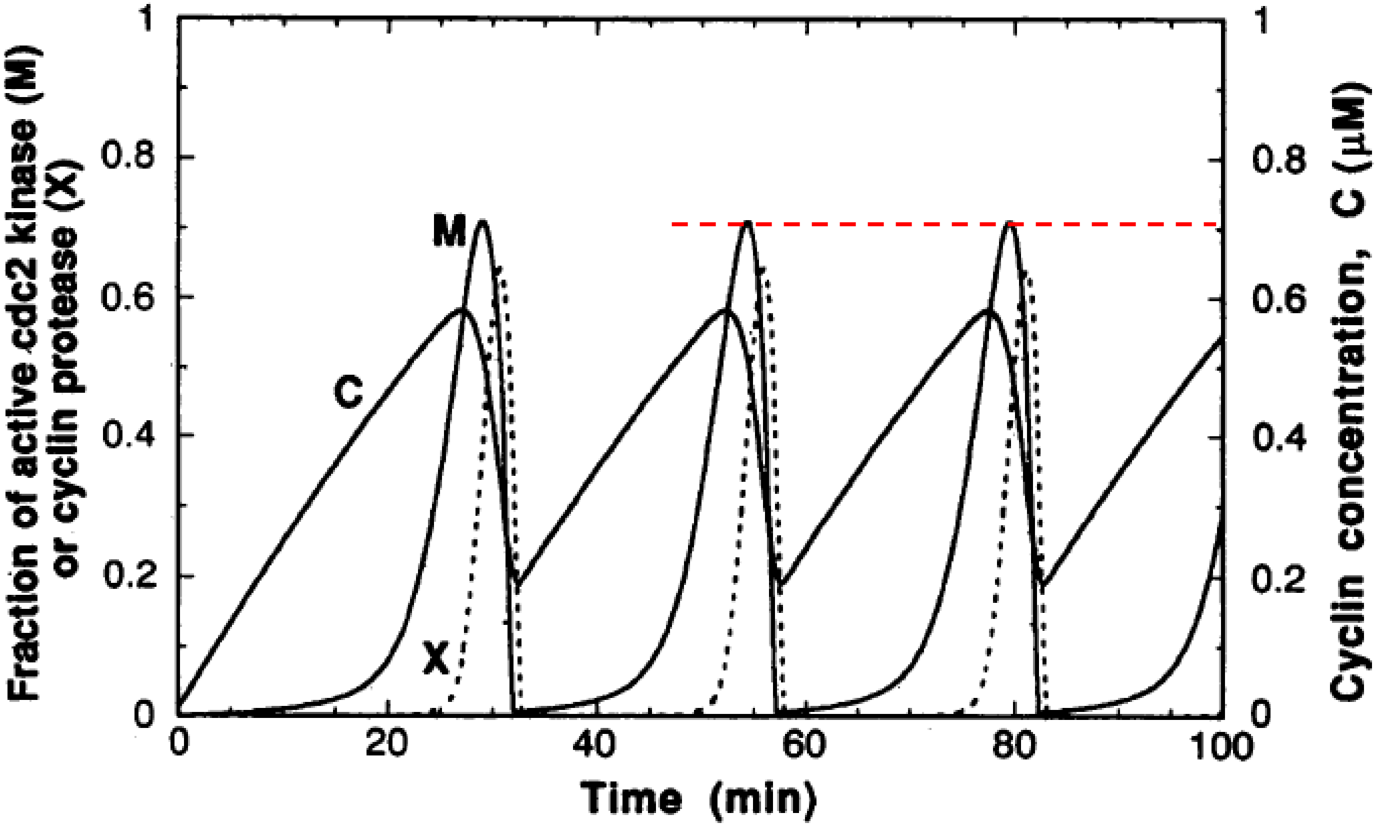
$$V_1 = \frac{C}{K_c + C} V_{M1}, \; V_3 = M V_{M3}.$$



  - C : cyclin concentration
  - M : fraction of active cdc2 kinase
  - X : fraction of active cyclin protease

Second Example – Cell Cycle from web

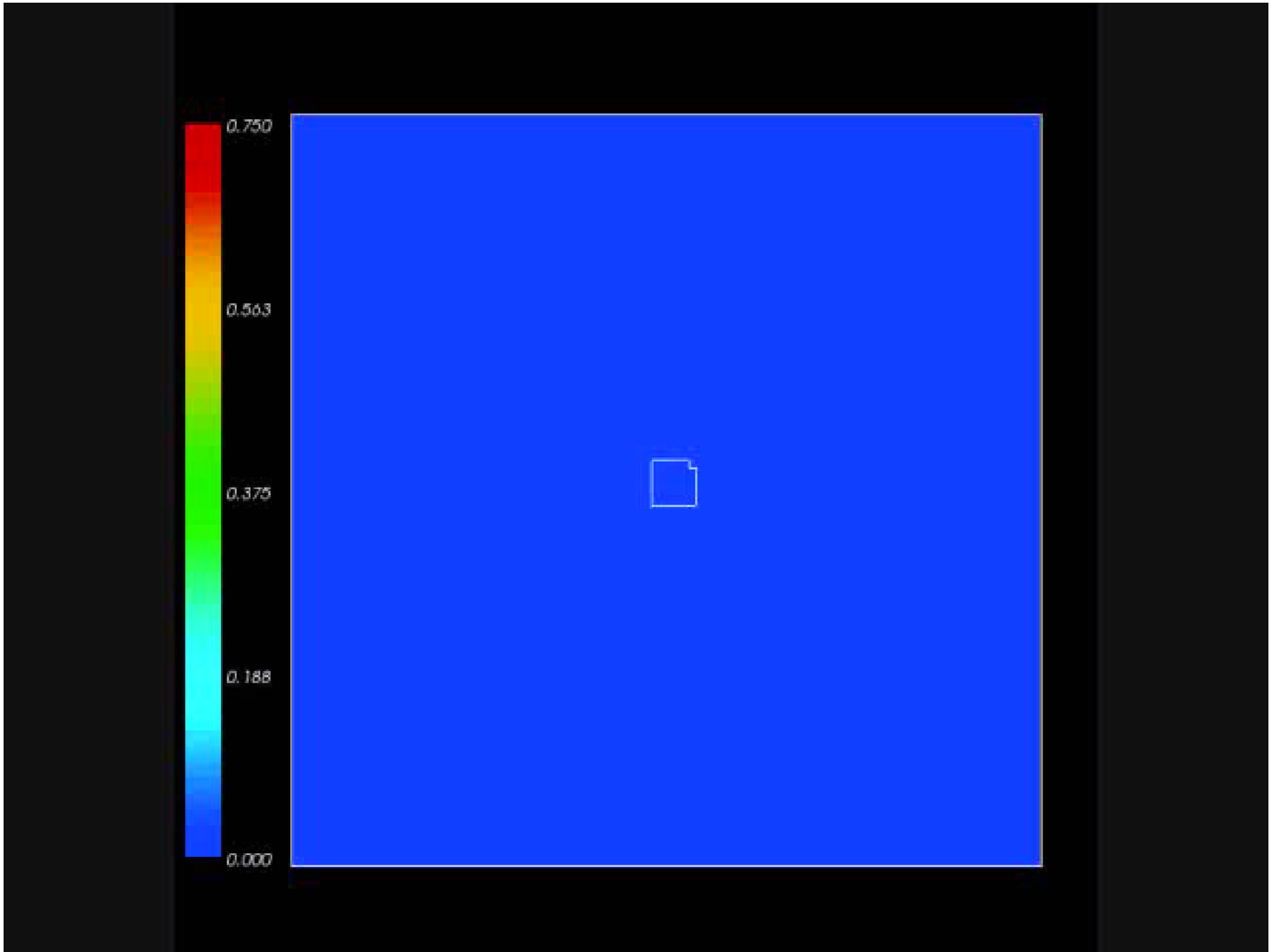
- Mitosis occur when fraction of active Cdc2 kinase (M) reaches 0.7.



- .

Second Example – Cell Cycle from web

- Open the model in CC3D, set the maximum concentration of the “M” field to 0.75, and run the simulation:

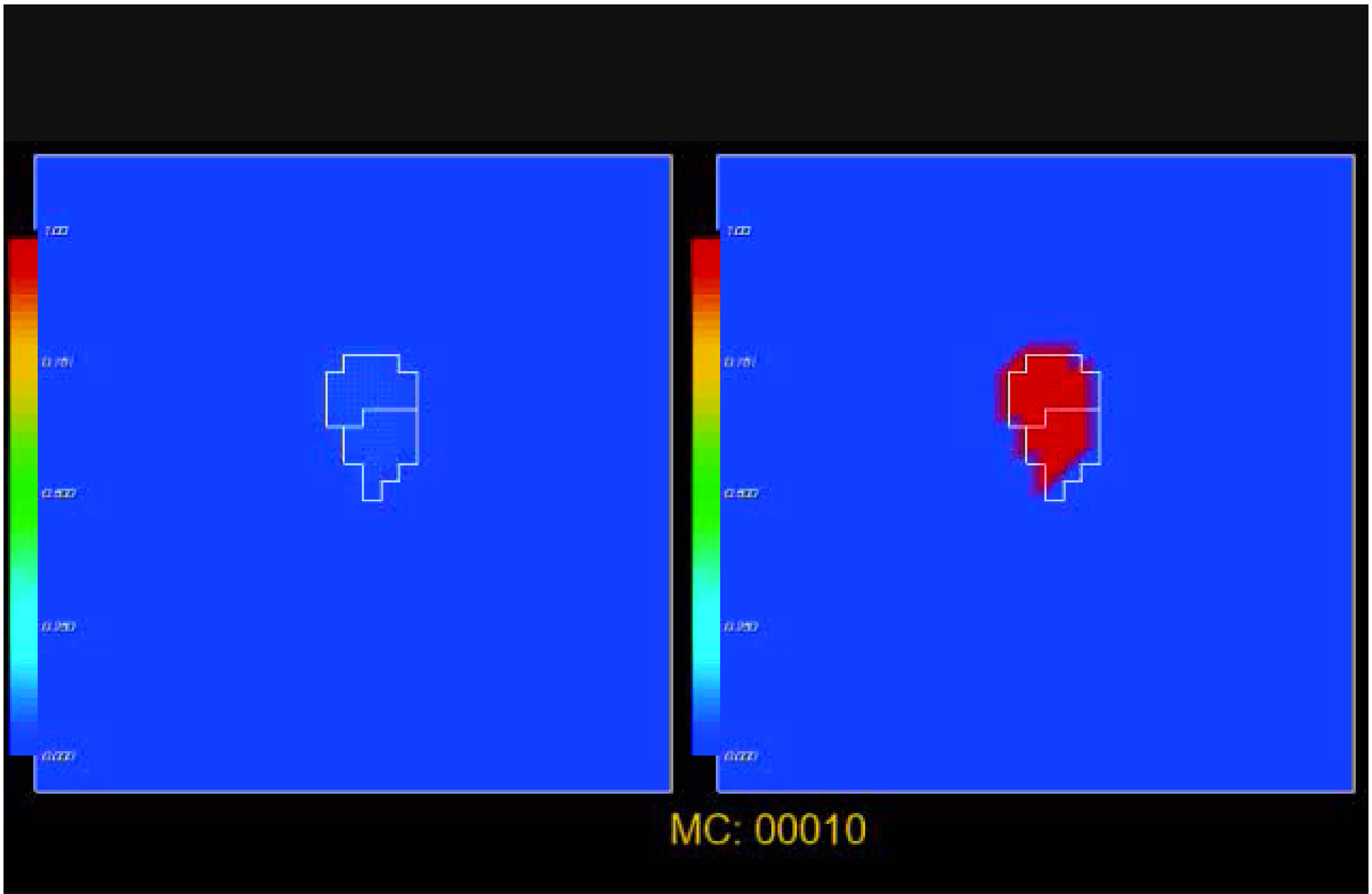


Exercise 2

- Download the SBML model from the web
- Run it on SBW
- Create a CC3D simulation with mitosis and just one cell as the initial condition
- Add the SBML model to the cell, make the integration step size to be 0.1
- Set the growth rate to zero and change the mitosis condition to be [M] > 0.7. Change the frequency of the mitosis steppable to 10 MCS.

2 SBML models

- Below is a simulation with Cell Cycle and Collier's Delta Notch models:

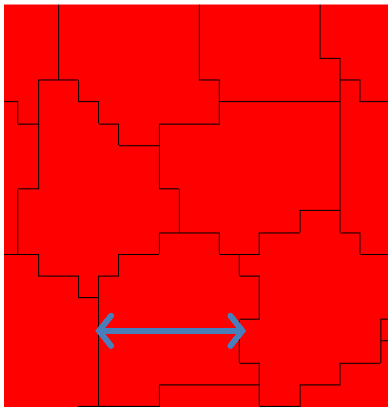


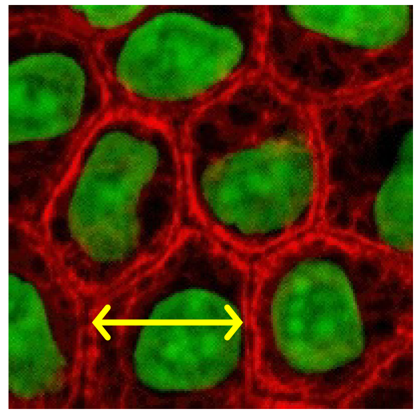
Exercise 3

- Using the codes from the Delta-Notch example and the cell cycle exercise make a simulation with the two models

Matching Scales

- Spatial scale:
  - Pixel-to-micrometer correspondence set by target volume of cells

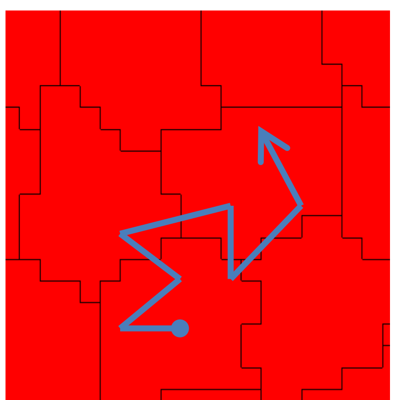


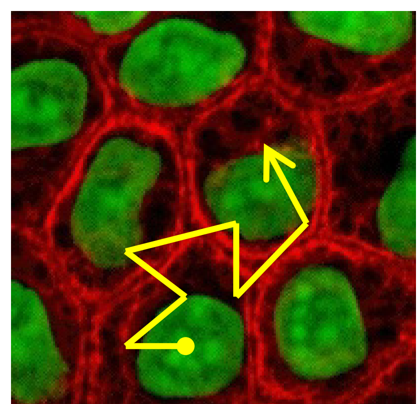


7 pixel ⇔ 10 µm

1 pixel = 1.43 µm

- Time scale:
  - MCS-to-second/minutes/hours set by diffusion constant of cells

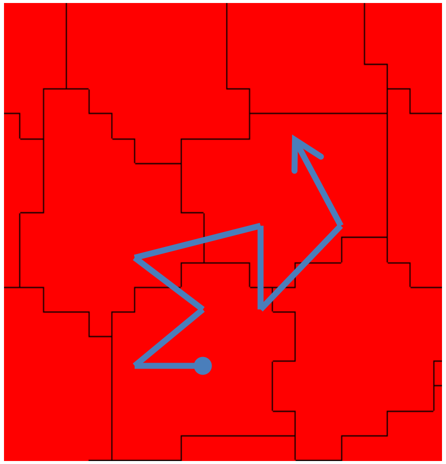


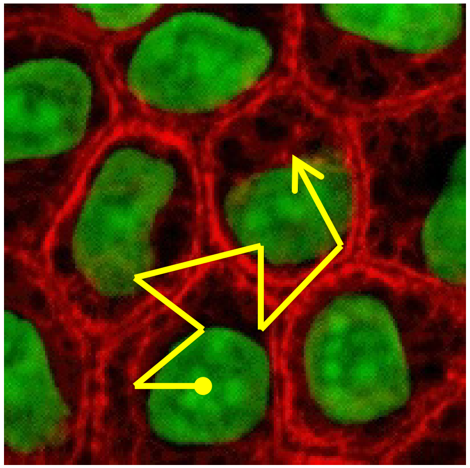


Matching Scales

- Diffusion:

$$D = \frac{\left\langle \Delta x^2 \right\rangle}{2 \cdot d \cdot t}$$



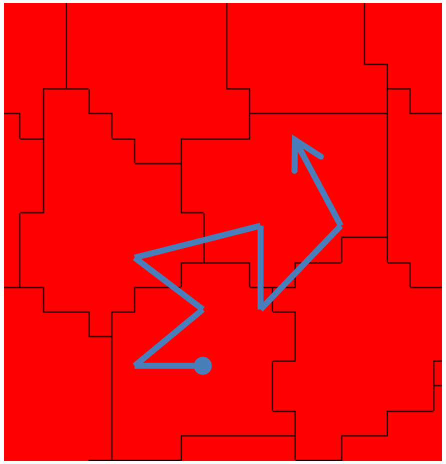


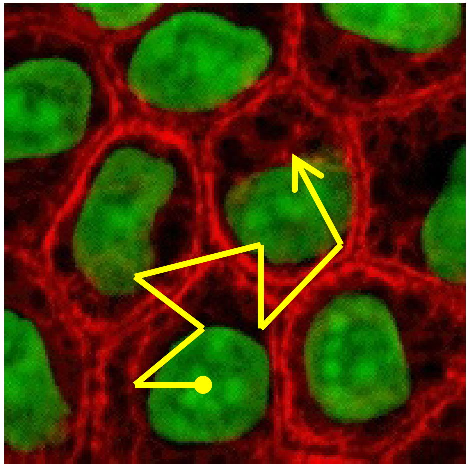
Matching Scales

- Diffusion:

$$D = \frac{\langle \Delta x^2 \rangle}{2 \cdot d \cdot t}$$

$$|\Delta x| \propto \sqrt{t}$$





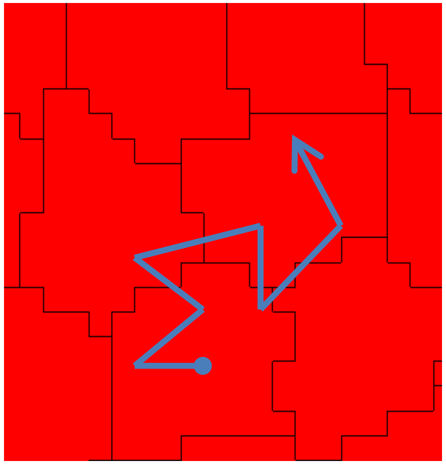
Matching Scales

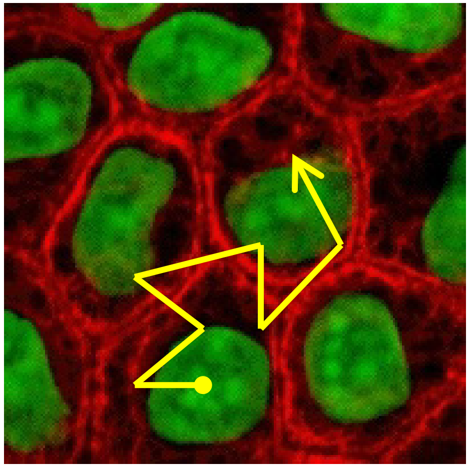
- Diffusion:

$$D = \frac{\left\langle \Delta x^2 \right\rangle}{2 \cdot d \cdot t}$$

$$\left| \Delta x \right| \propto \sqrt{t}$$

Only true if cells behave like a random walk





Matching Scales

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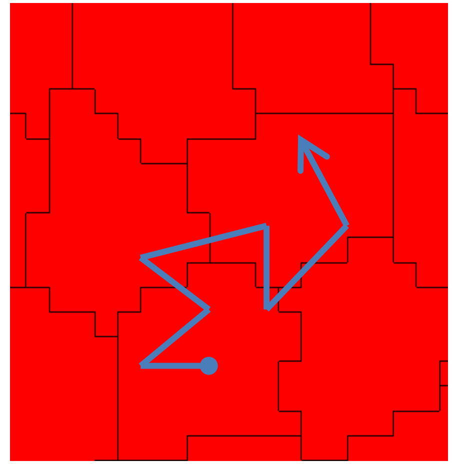
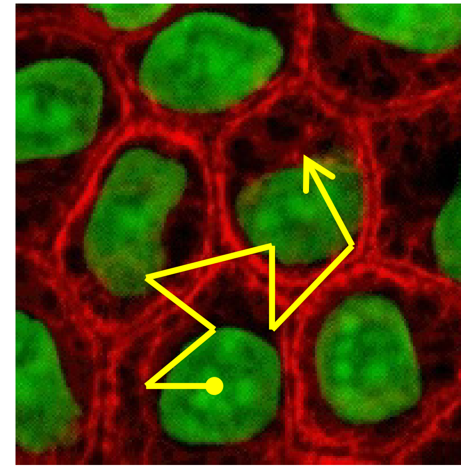




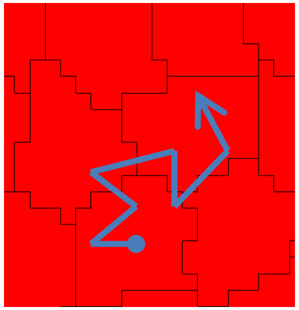
- Diffusion as a relation between displacement and time

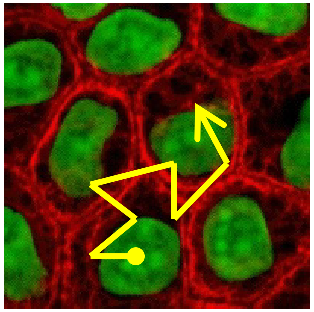
$$\boxed{\langle \Delta x^2 \rangle = f(\langle \Delta t \rangle)}$$

Matching Scales

- Diffusion:

$$\left\langle \Delta x^2 \right\rangle = D \cdot \left\langle \Delta t \right\rangle^{\alpha}$$

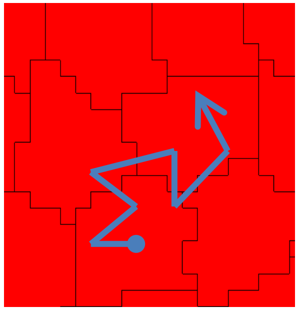


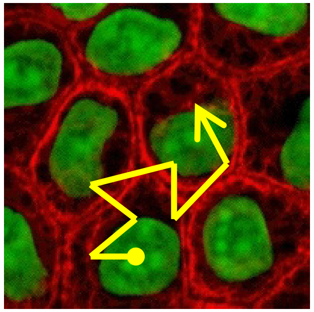


Matching Scales

- Diffusion:

$$\left\langle \Delta x^2 \right\rangle = D \cdot \left\langle \Delta t \right\rangle^{\alpha} \begin{cases} \alpha < 1 & subdiffusion & \\ \alpha = 1 & random\ \ walk & \left|\Delta x\right| \propto \sqrt{\Delta t} \\ 1 < \alpha < 2 & superdiffusion & \\ \alpha = 2 & ballistic & \Delta x = D \cdot \Delta t \\ \alpha > 2 & acceleration & \end{cases}$$





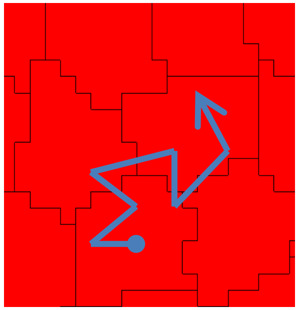
Matching Scales

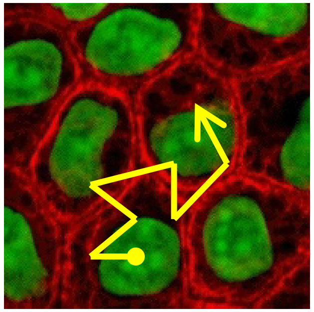
- How to calculate:

$$\left\langle \Delta x^2 \right\rangle = D \cdot \left\langle \Delta t \right\rangle^{\alpha}$$

- Keep a record of all the positions of your cells (x) at each time (t).
- Change the time window (Δt) and average the mean square displacement (Δx^2) of all cells from all time points.
- Plot $< \Delta x^2 >$ vs. $< \Delta t >$ on a log-log scale and use a linear fit.

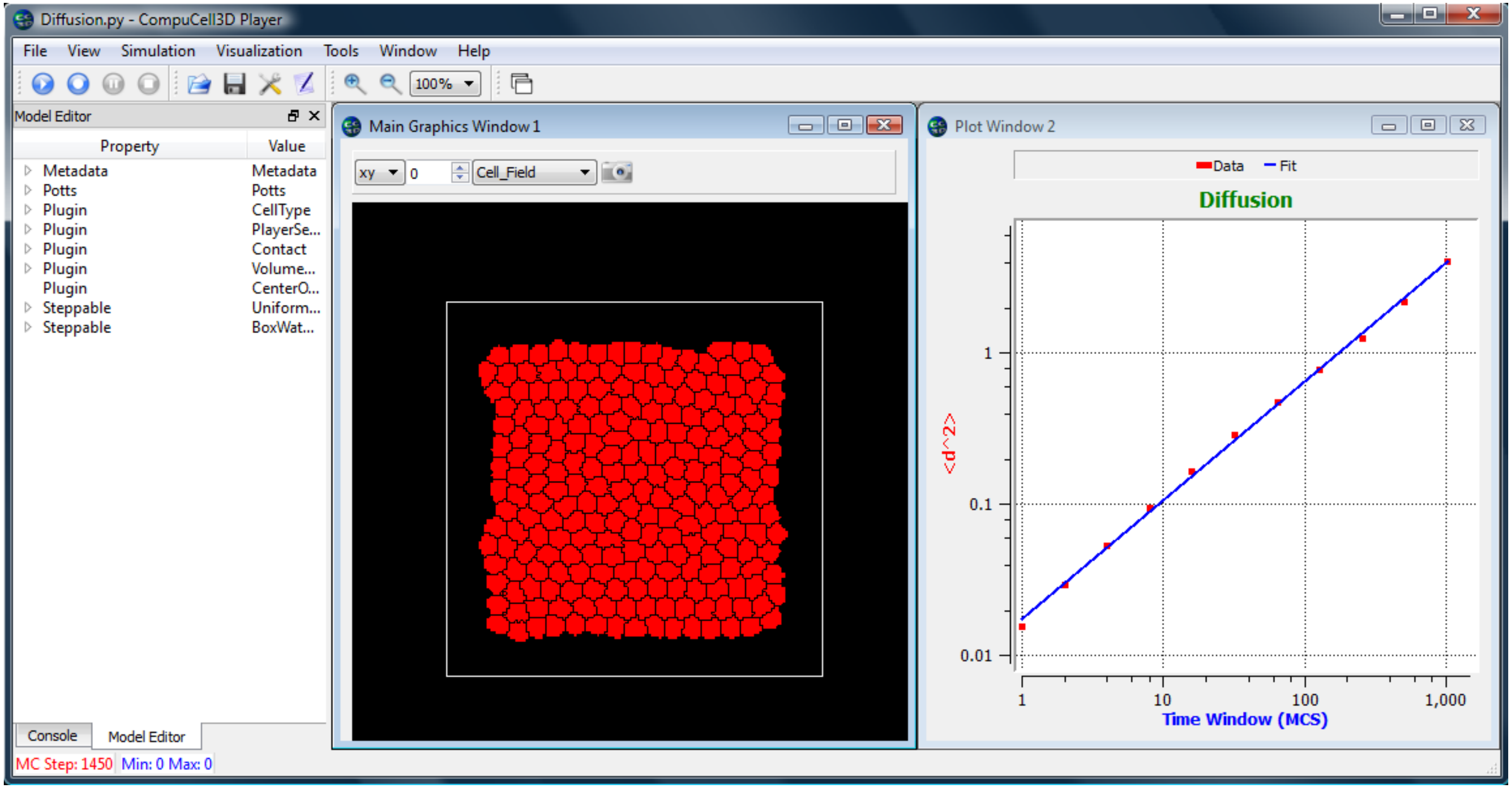
$$\log\left\langle \Delta x^2 \right\rangle = \log\left(D \cdot \left\langle \Delta t \right\rangle^{\alpha}\right) = \log D + \alpha \cdot \log\left\langle \Delta t \right\rangle$$

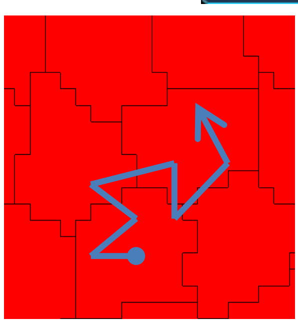


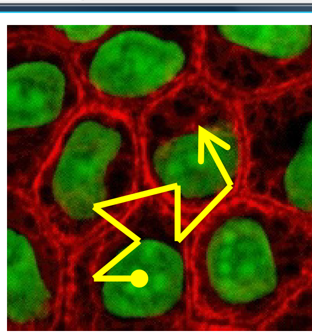


Matching Scales

- Diffusion calculator (CC3D-PASI webpage):







Exercise 4

- Download and run the diffusion calculator for CC3D
- Check if you understand the code
- Which type of diffusion does the simulated cells have?
- Is that what you expect?
- Change the parameters to check how does the diffusion coefficient change.

Exercises

- Exercise 1:
  - Open the Delta-Notch example, understand it and run it
  - Check that the pattern is lost when the motility of the cells is high
- Exercise 2:
  - Download the SBML model from the web and run it on SBW
  - Build a simulation with mitosis and just one cell as the initial condition
  - Add the SBML model, make the integration step size to be 0.1
  - Set the growth rate to zero and change the mitosis condition to [M]>0.7. Change the frequency of the mitosis steppable to 10 MCS.
- Exercise 3:
  - Using the codes from the Delta-Notch example and the cell cycle exercise make a simulation with the two models
- Exercise 4:
  - Use the diffusion calculator and check how do the cells move