Merging CompuCell3D and SBW/SBML

Julio M. Belmonte

Indiana University, Bloomington

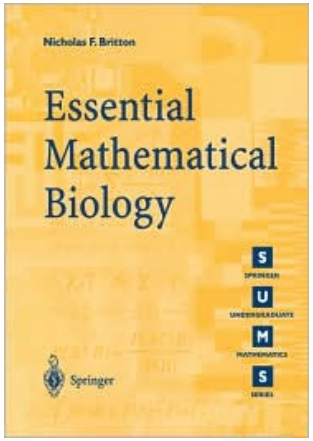
Outline

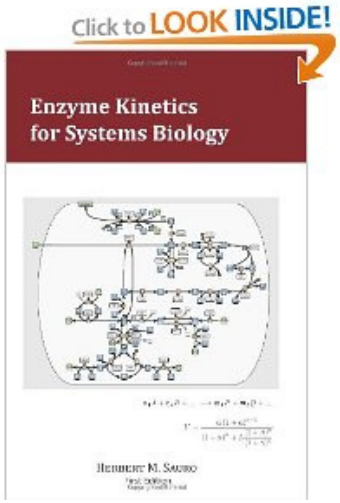
- Objectives
- Ways to add RK to CC3D
- SBML format
- Generating SBML using Jarnac
    - Simple Oscillator
- Integrating with CC3D
    - Adding Simple Oscillator to CC3D
    - Adding Cell Cycle model from *sbml.org*
    - John Tyson's Cell Cycle model
    - Collier *et al.* Delta-Notch patterning model

More on Reaction Kinetics Modeling

Essential Mathematical Biology

Nicholas Britton





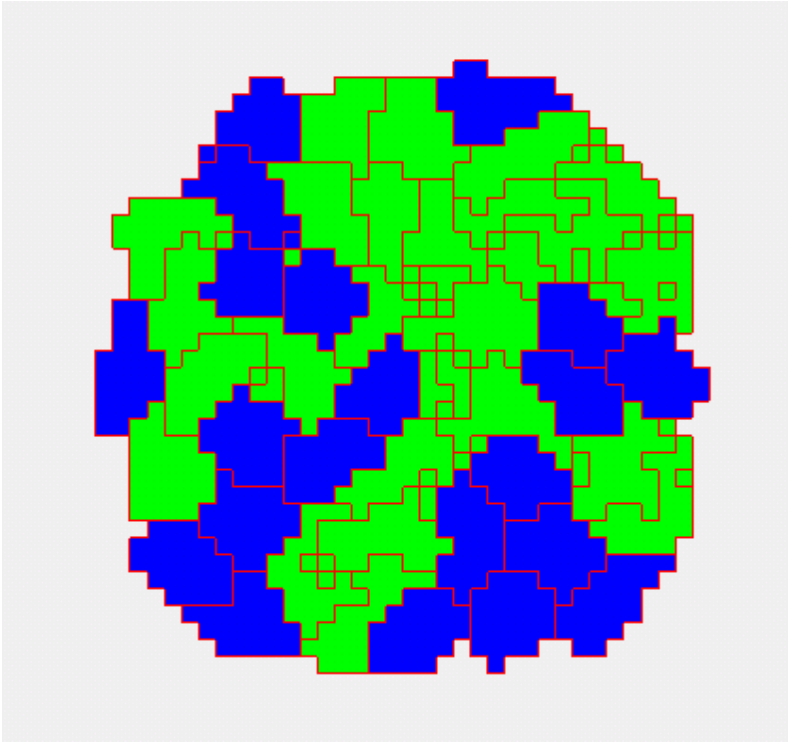
Enzyme Kinetics for Systems Biology

Herbert Sauro

www.sys-bio.org/sbwWiki/tutorials/bloomington2011

Cell-based modeling

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



Subcellular modelling

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

Subcellular modelling

- Biochemical Kinetics:
  - Cell-Cycle
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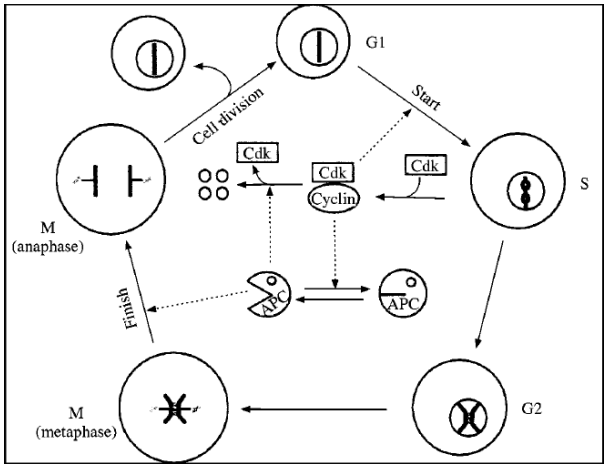

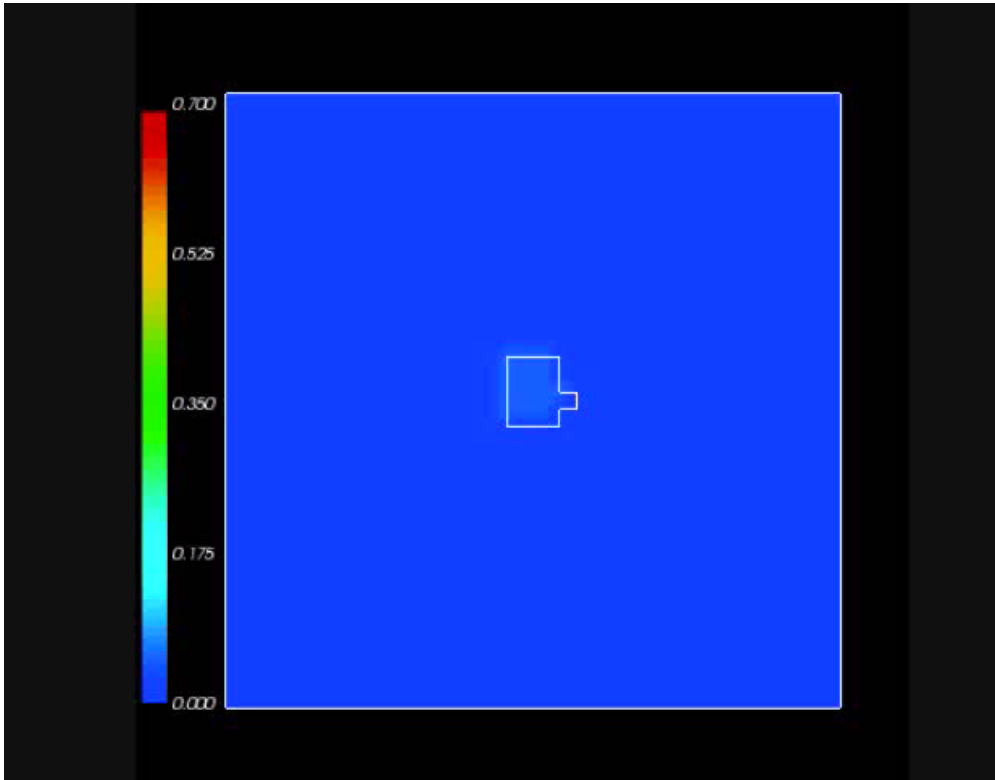

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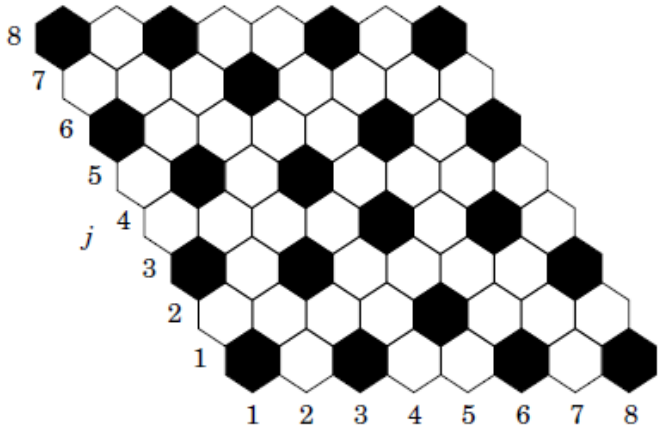

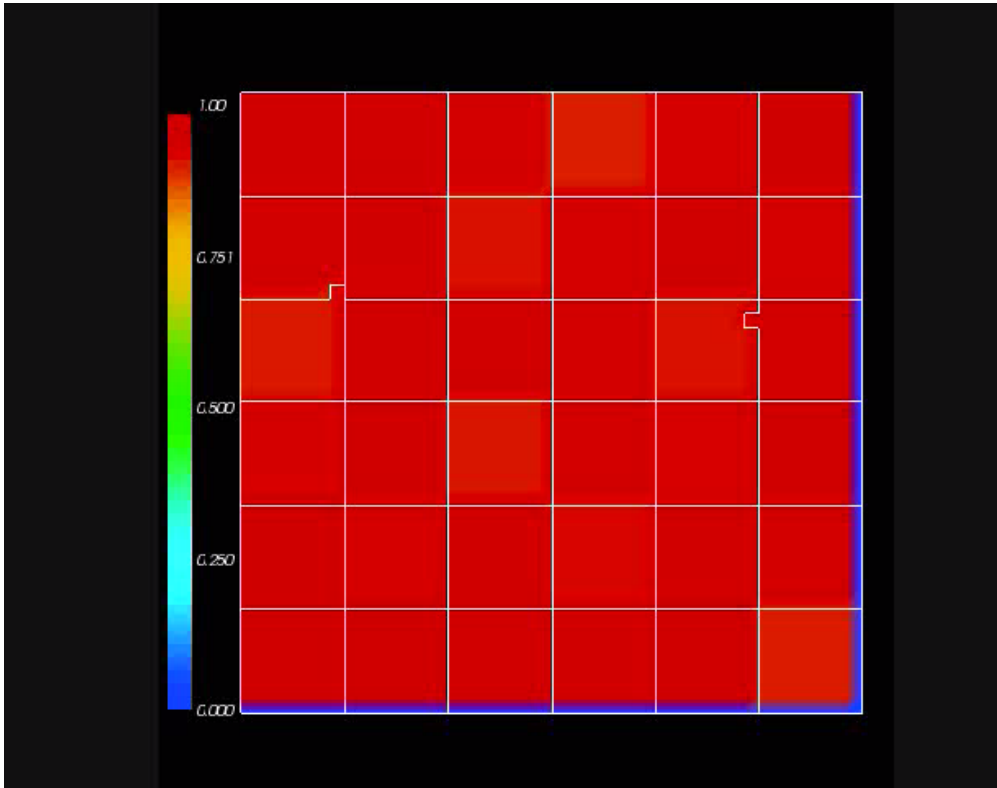

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   - Too slow

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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 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>
```

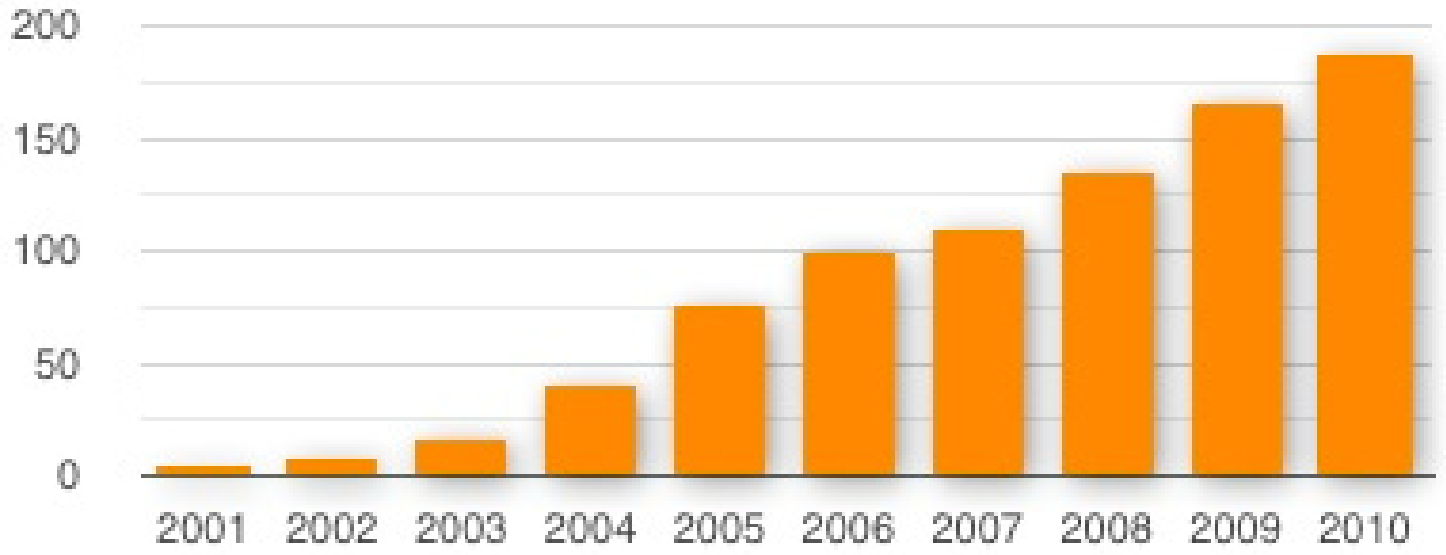
$$S_1 = 5 \ \text{nM}$$
$$S_2 = 0 \ \text{nM}$$

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

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

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

SBW/Jarnac

- SBW - Systems Biology Workbench:
  - Open-source software framework for systems biology
- Jarnac:
  - Software for writing and simulating reaction kinetics
  - Easy to use
  - Translate to SBML (C++, Matlab, Mathematica, etc..)
- Download at: http://www.sys-bio.org/

Integration with CC3D

- Reaction kinetic models can be easily added in CC3D when in SBML format.

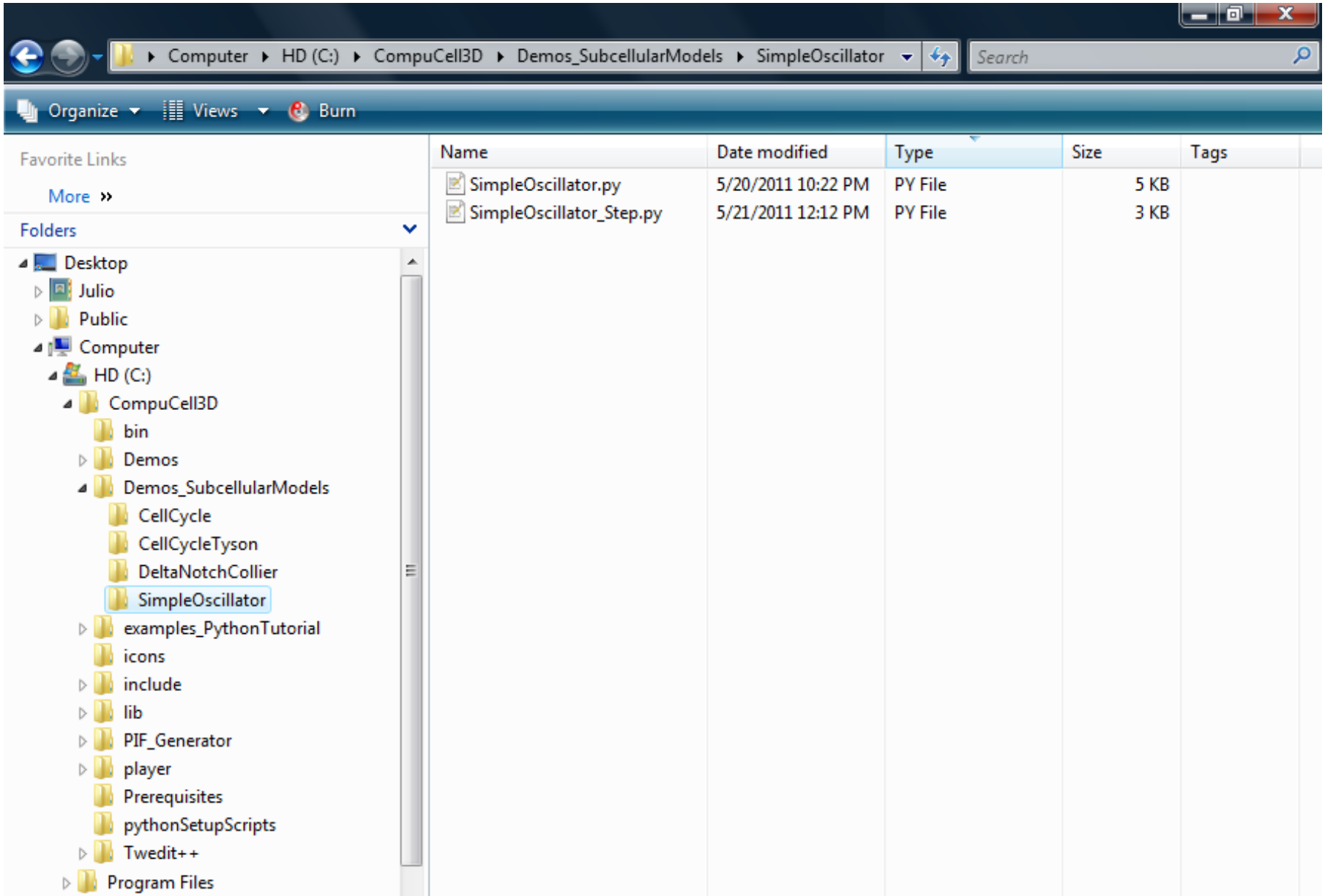
- Once loaded, the model is converted into a set of ODEs and is solved by the BionetSolver library inside CC3D.

- The commands used to load and manipulate the models inside CC4D are summarized on the “Quick Reference Guide” for Python in CC3D.

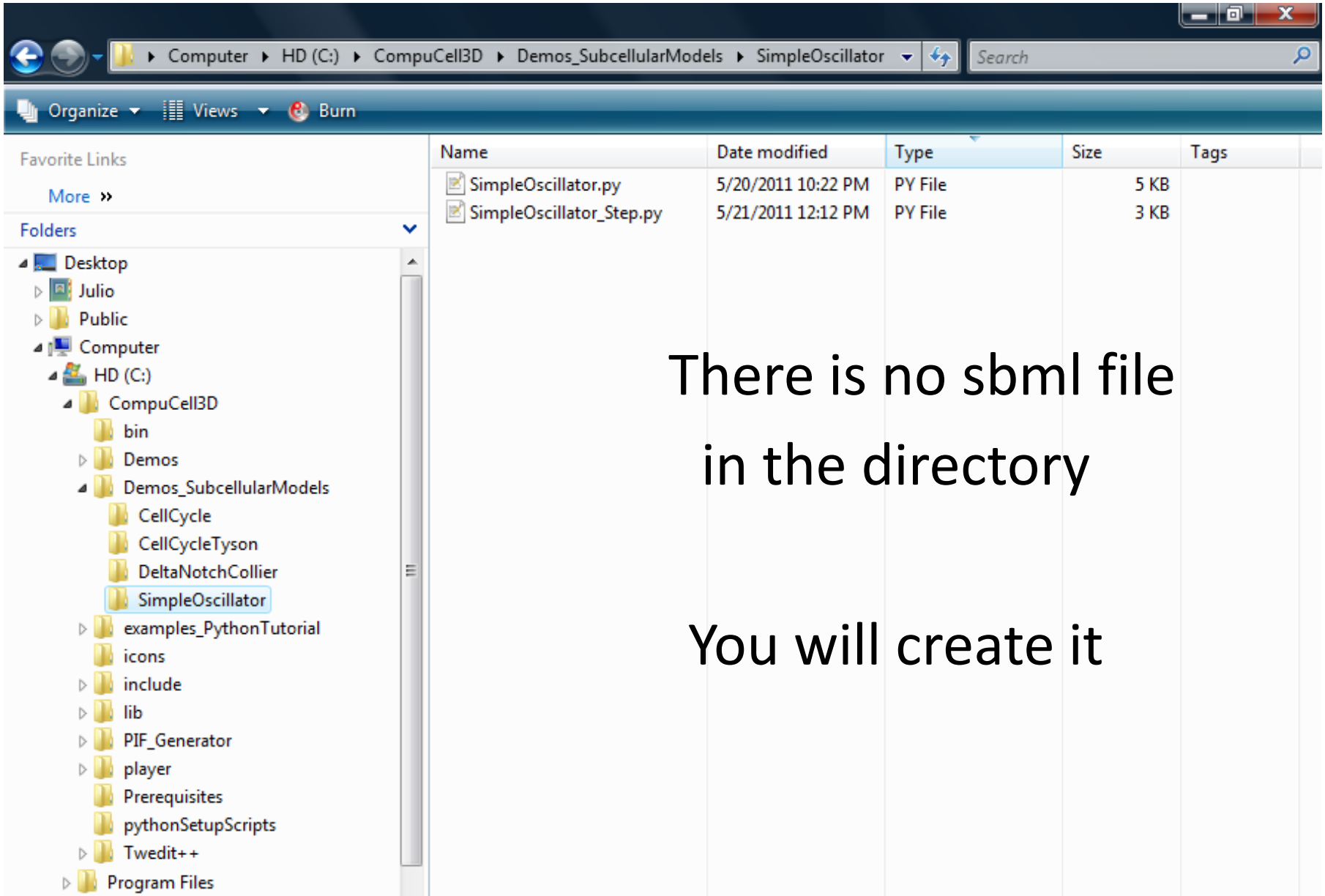
Integration with CC3D

```
import bionetAPI # Import bionetAPI functions
class <someClass>(SteppableBasePy):
  def __init__(self,_simulator,_frequency=1):
    SteppableBasePy.__init__(self,_simulator,_frequency)
    bionetAPI.initializeBionetworkManager(self.simulator) # Initialize bionet inside class

  def start(self):
    # Load a specific subcellular SBML submodel
    ModelName = <sbmlModelName>     # Name of the model
    ModelPath = <sbmlModelPath>     # Path where the model is stored
    ModelKey  = <modelKey>          # Nickname of the model
    IntegrationStep = <timeStep>    # Time step of integration
    bionetAPI.loadSBMLModel( ModelName, ModelPath, ModelKey, IntegrationStep )

    # Add SBML submodel to a group of cells or a single cell
    bionetAPI.addSBMLModelToTemplateLibrary(<sbmlModelName>, {<cellType> or <cellId>})
    …
    # Modify the parameter value or molecular concentration of a cell (or group of cells)
    bionetAPI.setBionetworkValue(<molecule/parameter>, <value>, {<cellType> or <cellId>})
    …
    # Initialize model
    bionetAPI.initializeBionetworks()

  def step(self,mcs):
    # Iterate the model (run it for the time step specified on the load command)
    bionetAPI.timestepBionetworks()
    …
    # Get the parameter value or molecular concentration from a cell (or group of cells)
    <var>=bionetAPI.getBionetworkValue({<parameter> or <molecule>},{<cellType> or <cellId>})
    …
    # Modify the parameter value or molecular concentration of a cell (or group of cells)
    bionetAPI.setBionetworkValue(<molecule/parameter>, <value>, {<cellType> or <cellId>})
```

First Example – Simple Oscillator



First Example – Simple Oscillator

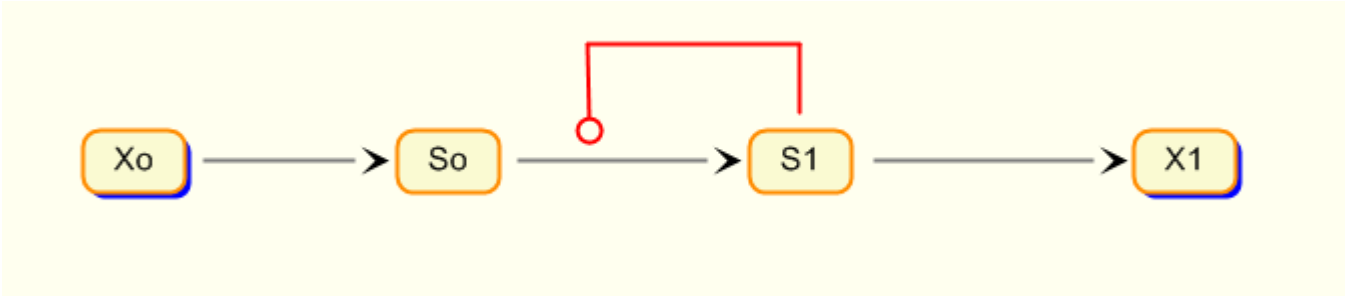


There is no sbml file in the directory

You will create it

First Example – Simple Oscillator

- Relaxation oscillator:

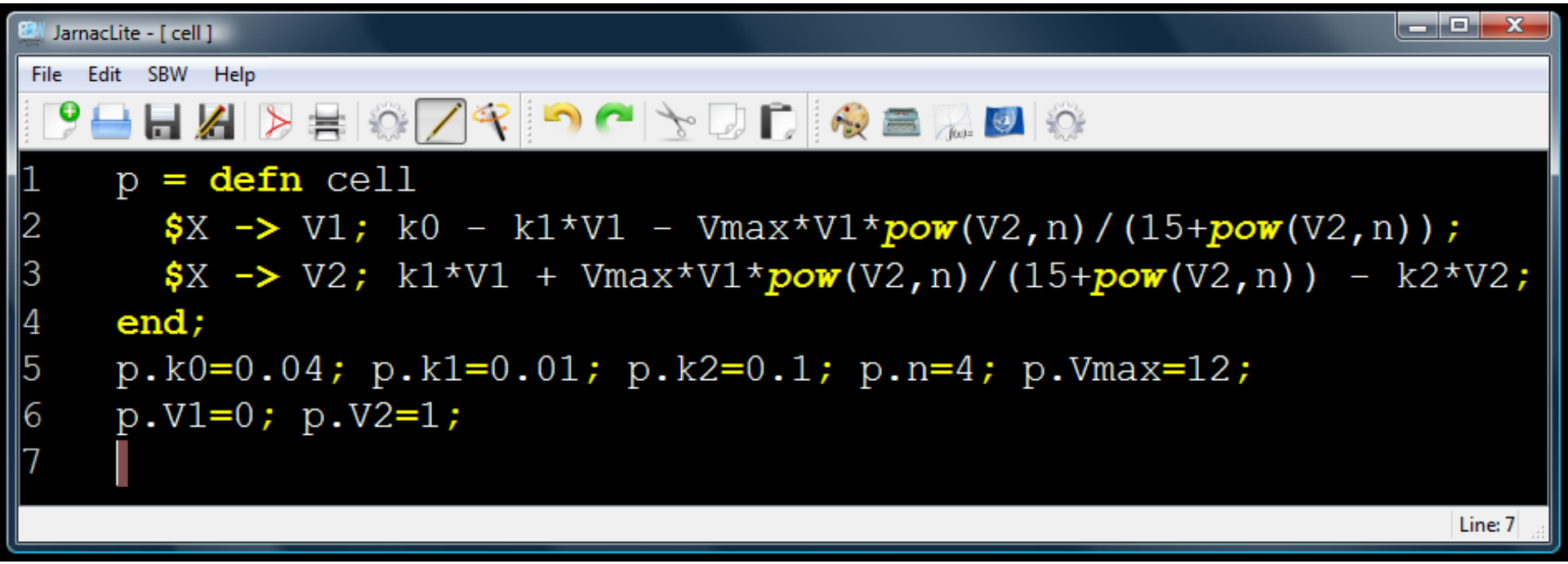


$$\frac{dV_1}{dt} = k_0 - k_1 \cdot V_1 - V_{\max} \cdot V_1 \frac{V_2^n}{15 + V_2^n}$$

$$\frac{dV_2}{dt} = k_1 \cdot V_1 + V_{\max} \cdot V_1 \frac{V_2^n}{15 + V_2^n} - k_2 \cdot V_2$$

First Example – Simple Oscillator

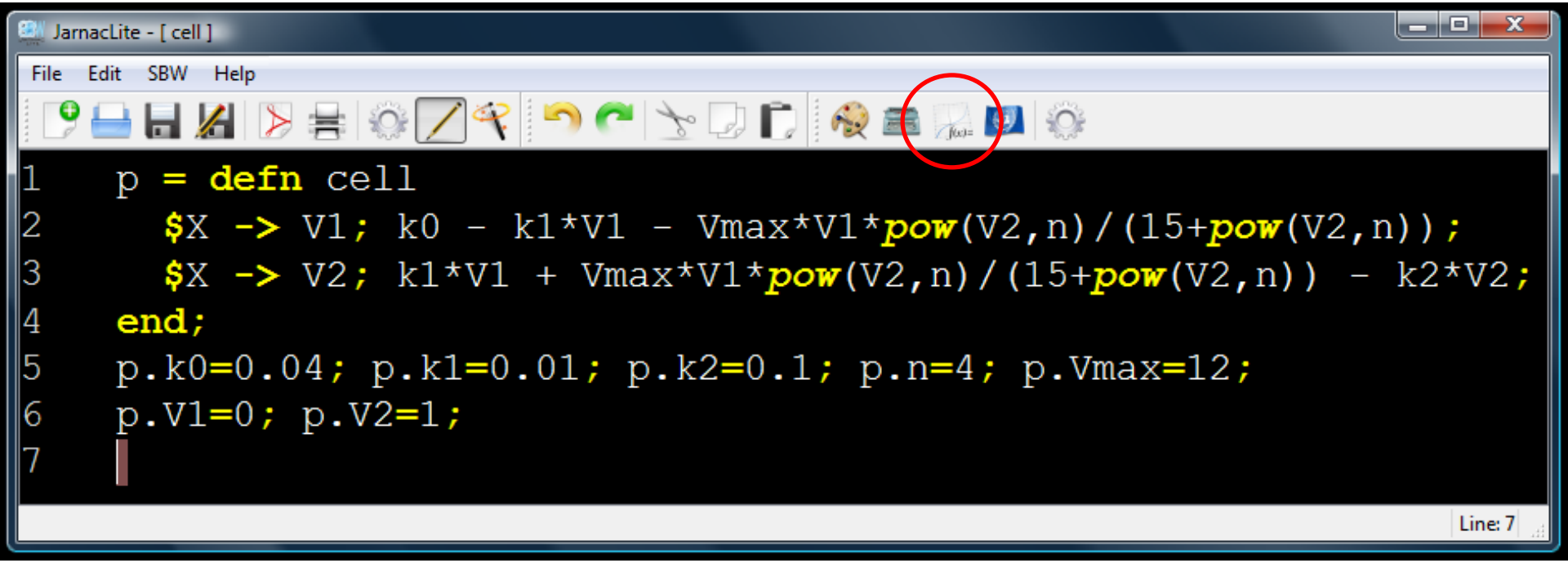
- Load your old exercise in Jarnac Lite.
- If you don't have it, it can be written as:



- Note that V_2^n should be written as pow(V2,n)

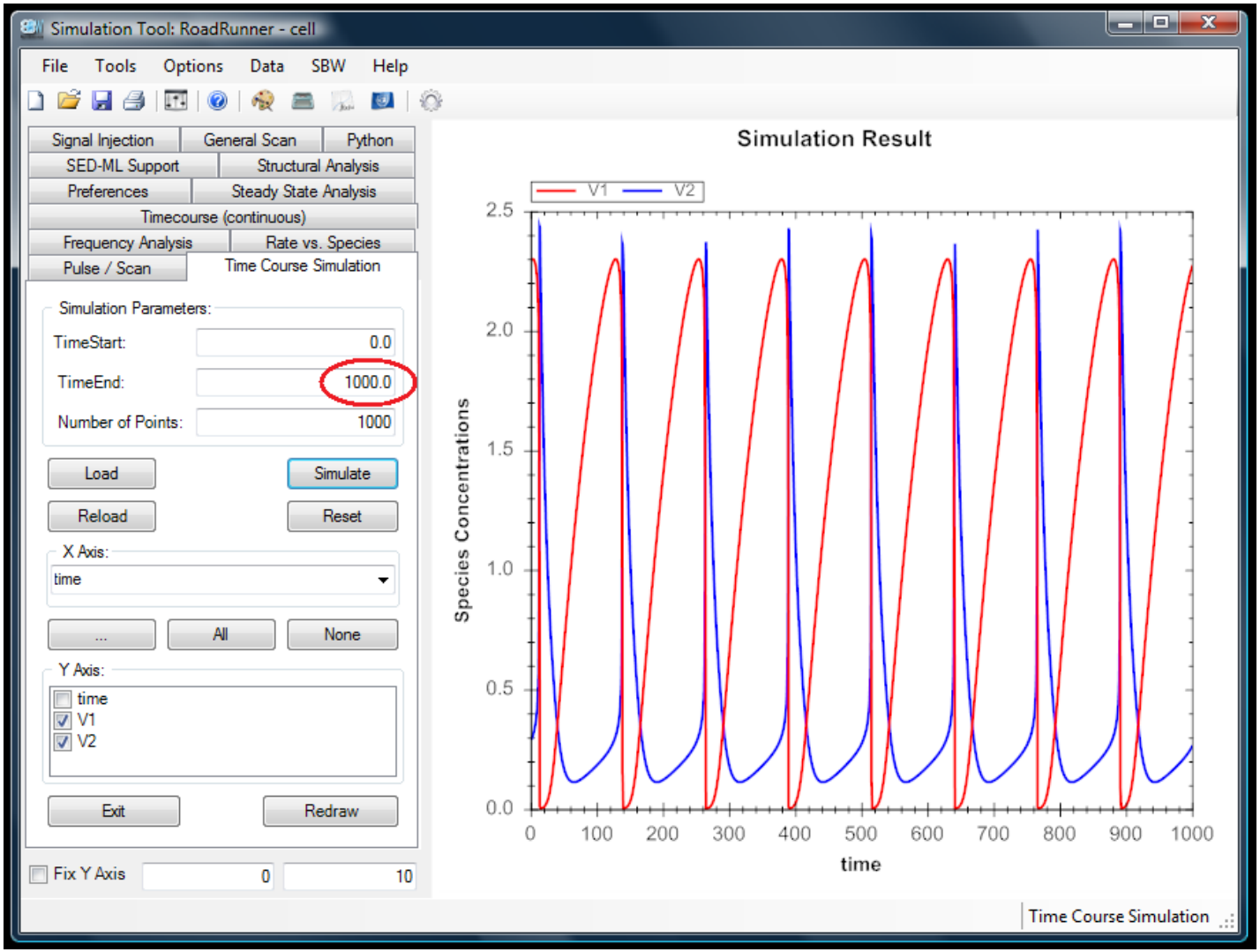
First Example – Simple Oscillator

- Click on the Simulation Tool icon:



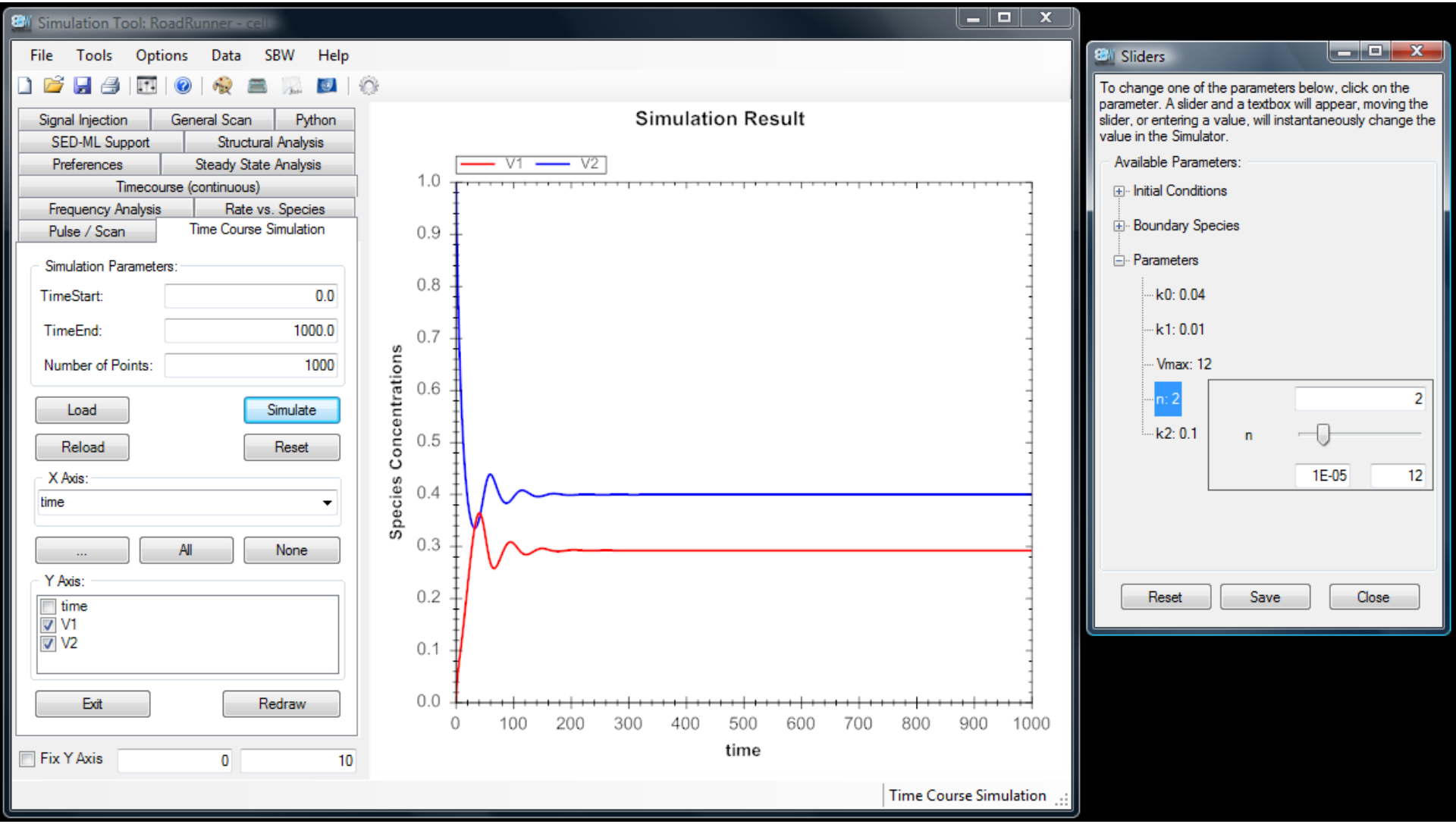
First Example – Simple Oscillator

- The parameter values give oscillations (set TimeEnd to 1000):



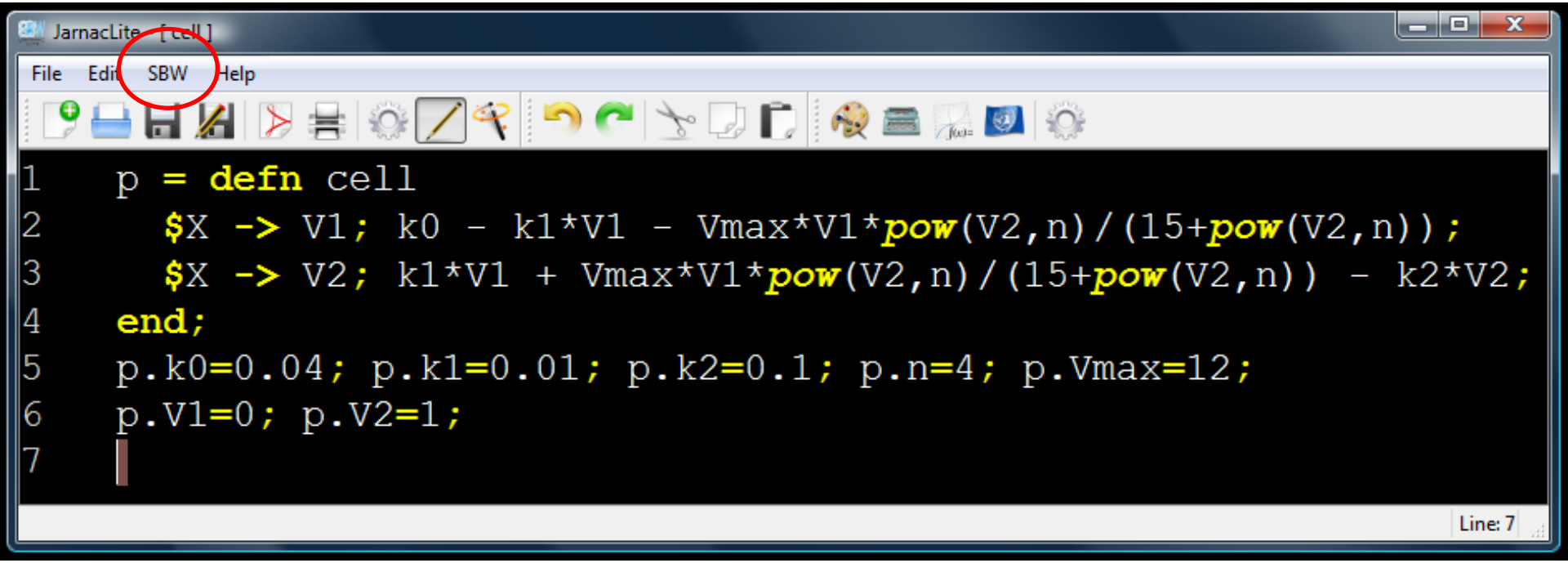
Simple Oscillator

- But the oscillations cease if *n* is changed to 2:



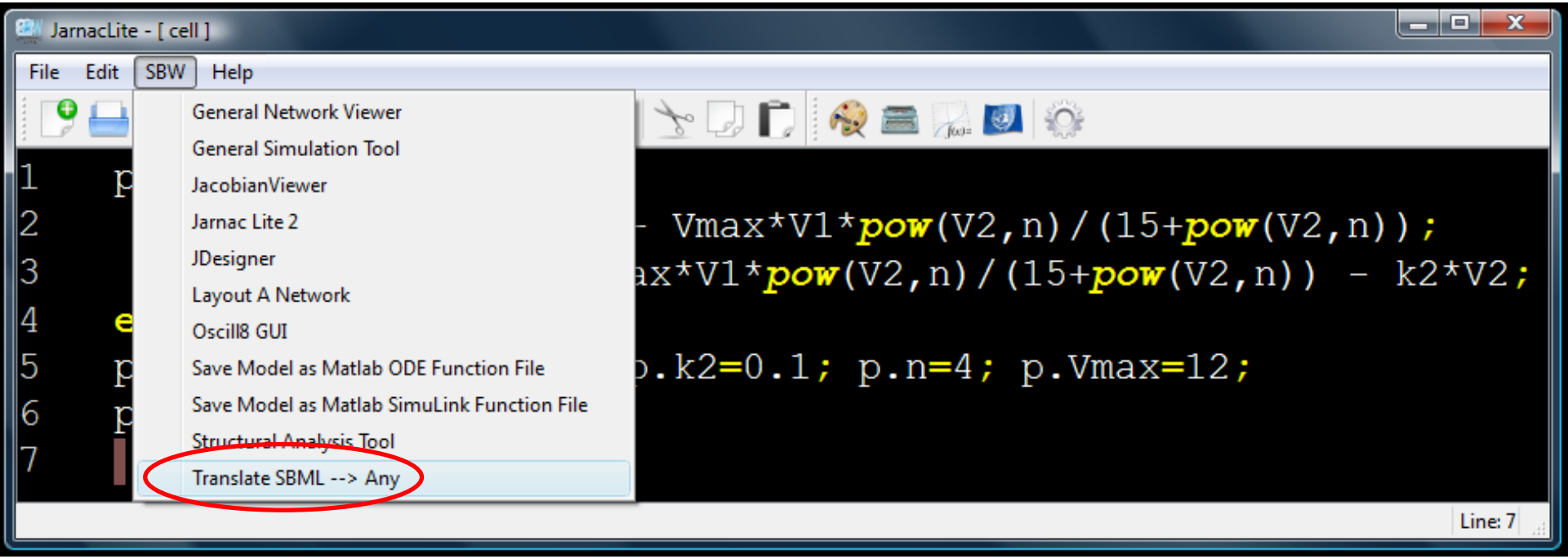
First Example – Simple Oscillator

- Go back to Jarnac Lite, click on SBW:

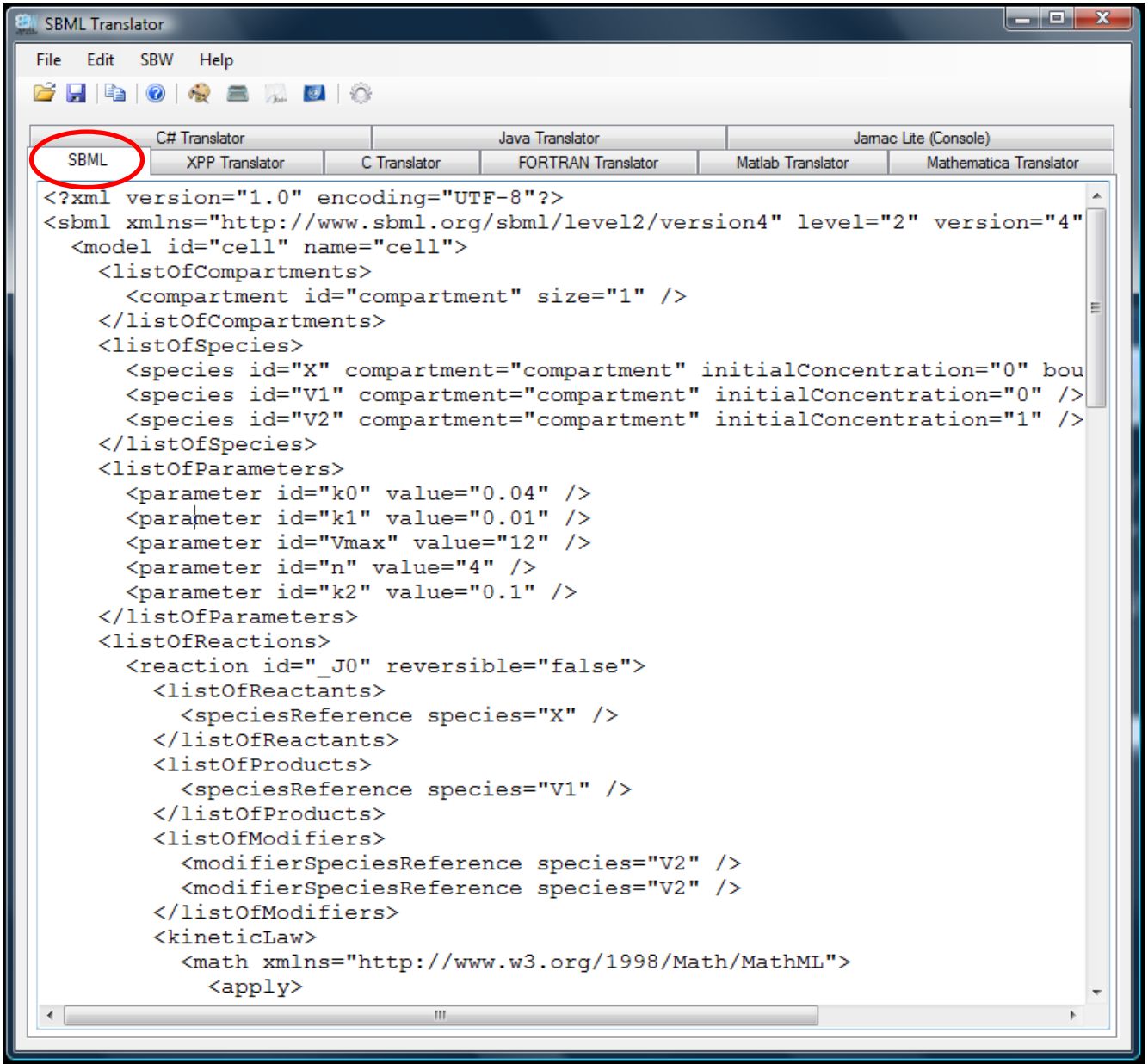


First Example – Simple Oscillator

- Then click on Translate SBML --> Any:

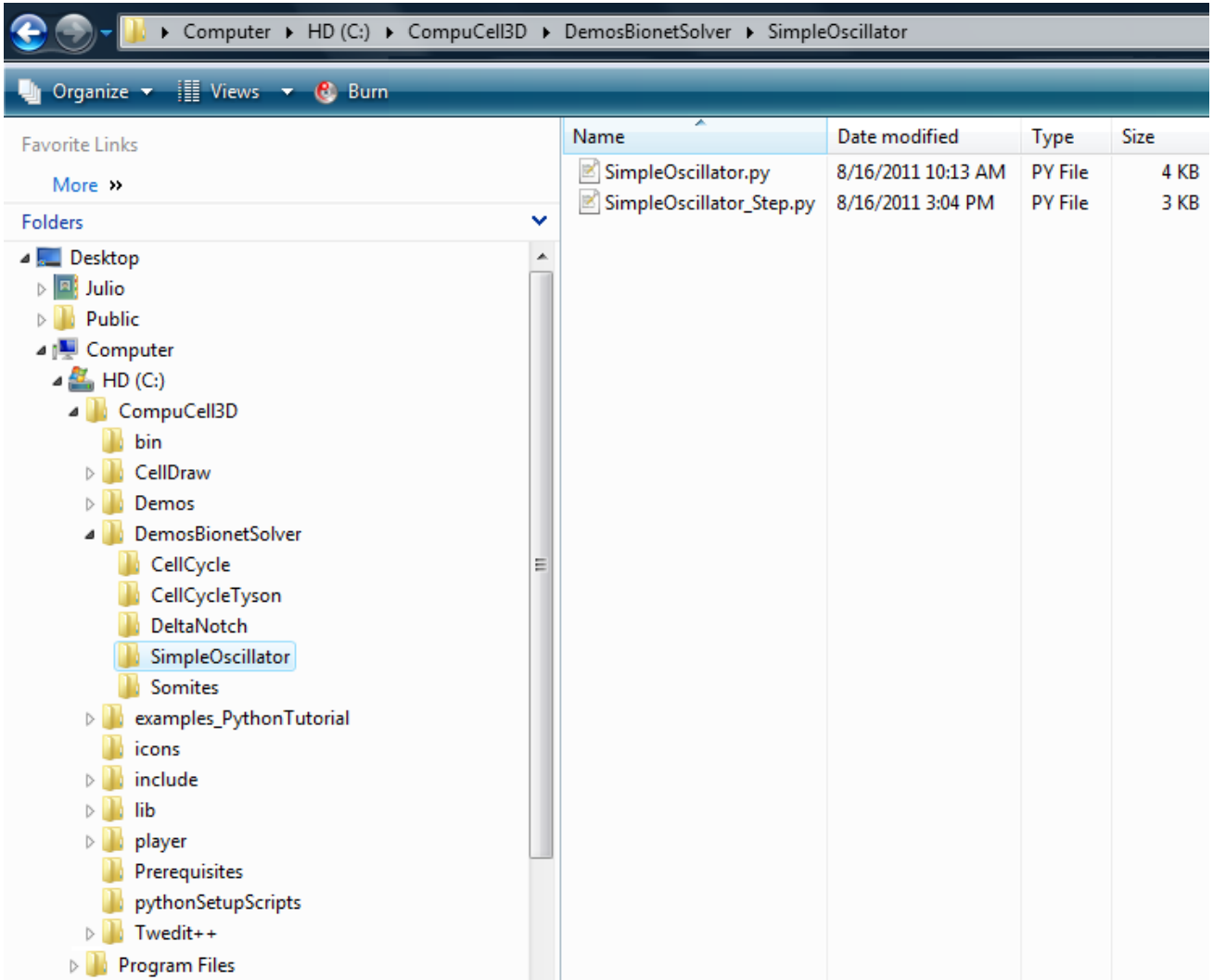


First Example – Simple Oscillator



First Example – Simple Oscillator

- Save it as "*SimpleOscillator.sbml*" inside:
  CompuCell3D\DemosBionetSolver\SimpleOscillator



First Example – Simple Oscillator

- The *SimpleOscillator.py* file contains the parameters of the cellular model.
- It is important to note that in this model there are 2 cell types: “TypeA” and “TypeB”

```
34
35      cellType=cc3d.ElementCC3D("Plugin",{"Name":"CellType"})
36      cellType.ElementCC3D("CellType", {"TypeName":"Medium","TypeId":"0"})
37      cellType.ElementCC3D("CellType", {"TypeName":"TypeA", "TypeId":"1"})
38      cellType.ElementCC3D("CellType", {"TypeName":"TypeB", "TypeId":"2"})
39
40      #CONTACT
41      contact=cc3d.ElementCC3D("Plugin",{"Name":"Contact"})
42      contact.ElementCC3D("Energy", {"Type1":"Medium", "Type2": "Medium"},0)
43      contact.ElementCC3D("Energy", {"Type1":"Medium", "Type2": "TypeA"},10)
44      contact.ElementCC3D("Energy", {"Type1":"Medium", "Type2": "TypeB"},10)
45      contact.ElementCC3D("Energy", {"Type1":"TypeA", "Type2": "TypeA"},10)
46      contact.ElementCC3D("Energy", {"Type1":"TypeA", "Type2": "TypeB"},10)
47      contact.ElementCC3D("Energy", {"Type1":"TypeB", "Type2": "TypeB"},10)
48      #-neighbor order
49      contact.ElementCC3D("NeighborOrder",{},nOrder)
50
```

First Example – Simple Oscillator

- The *SimpleOscillator.py* file calls 3 steppables:
  - InitCond: where the initial conditions are set
  - Oscillator: where the SBML model will be loaded
  - ExtraFields: used to visualize one of the model's variable

```
81  from SimpleOscillator_Step import InitCond
82  initCond=InitCond(_simulator=sim,_frequency=1,_LamV=LamV,_tV=tV)
83  steppableRegistry.registerSteppable(initCond)
84
85  from SimpleOscillator_Step import Oscillator
86  oscillator=Oscillator(_simulator=sim,_frequency=1)
87  steppableRegistry.registerSteppable(oscillator)
88
89  #Create extra player fields here or add attributes
90  dim=sim.getPotts().getCellFieldG().getDim()
91  Field=simthread.createScalarFieldCellLevelPy("Osc")
92
93  from SimpleOscillator_Step import ExtraFields
94  extraFields=ExtraFields(_simulator=sim,_frequency=5)
95  extraFields.setScalarFields(Field)
96  steppableRegistry.registerSteppable(extraFields)
97
98  CompuCellSetup.mainLoop(sim,simthread,steppableRegistry)
99  ##sys.exit()
```

First Example – Simple Oscillator

- Let's open the *SimpleOscillator_Step.py* file and look at the beginning of the Oscillator steppable:

```
21  import bionetAPI
22  class Oscillator(SteppableBasePy):
23      def __init__(self,_simulator,_frequency):
24          SteppableBasePy.__init__(self,_simulator,_frequency)
25          bionetAPI.initializeBionetworkManager(self.simulator)
26
27      def start(self):
28          #Loading model
29          ModelName = "SimpleOscillator"
30          ModelKey  = "SO"
31          ModelPath = os.getcwd() + "/DemosBionetSolver/SimpleOscillator/SimpleOscillator.sbml"
32          IntegrationStep = 1.0
33          bionetAPI.loadSBMLModel(ModelName, ModelPath, ModelKey, IntegrationStep)
34
35          bionetAPI.addSBMLModelToTemplateLibrary(ModelName,"TypeA")
36          bionetAPI.addSBMLModelToTemplateLibrary(ModelName,"TypeB")
37
38          #Initial conditions
39          bionetAPI.initializeBionetworks()
40          # bionetAPI.setBionetworkValue("SO_n",2,"TypeB")
```

First Example – Simple Oscillator

- The first thing to be done is to import the BionetSolver library by this command:

```
21  import bionetAPI
22  class Oscillator(SteppableBasePy):
23      def __init__(self,_simulator,_frequency):
24          SteppableBasePy.__init__(self,_simulator,_frequency)
25          bionetAPI.initializeBionetworkManager(self.simulator)
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27      def start(self):
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```

First Example – Simple Oscillator

- Next, inside the steppable, we initialize the solver by using this command:

```
21  import bionetAPI
22  class Oscillator(SteppableBasePy):
23      def __init__(self,_simulator,_frequency):
24          SteppableBasePy.__init__(self,_simulator,_frequency)
25          bionetAPI.initializeBionetworkManager(self.simulator)
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40          # bionetAPI.setBionetworkValue("SO_n",2,"TypeB")
```

First Example – Simple Oscillator

- Once the BionetSolver is loaded and initialized, it is time to load the model:

```
21  import bionetAPI
22  class Oscillator(SteppableBasePy):
23      def __init__(self,_simulator,_frequency):
24          SteppableBasePy.__init__(self,_simulator,_frequency)
25          bionetAPI.initializeBionetworkManager(self.simulator)
26
27      def start(self):
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29          ModelName = "SimpleOscillator"
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```

First Example – Simple Oscillator

- This takes 4 parameters:
  - First is the model name:

```
21  import bionetAPI
22  class Oscillator(SteppableBasePy):
23      def __init__(self,_simulator,_frequency):
24          SteppableBasePy.__init__(self,_simulator,_frequency)
25          bionetAPI.initializeBionetworkManager(self.simulator)
26
27      def start(self):
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```

  - For convenience the name will be SimpleOscillator, but it can be anything.

First Example – Simple Oscillator

- This takes 4 parameters:
  - Second is the model pathway:

```
21  import bionetAPI
22  class Oscillator(SteppableBasePy):
23      def __init__(self,_simulator,_frequency):
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37
38          #Initial conditions
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40          # bionetAPI.setBionetworkValue("SO_n",2,"TypeB")
```

  - os.getcwd() gives the CompuCell3D root directory.
  - Here it is crucial that the correct path and model name are given.

First Example – Simple Oscillator

- This takes 4 parameters:
  - Third is the model nickname:

```
21  import bionetAPI
22  class Oscillator(SteppableBasePy):
23      def __init__(self,_simulator,_frequency):
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35          bionetAPI.addSBMLModelToTemplateLibrary(ModelName,"TypeA")
36          bionetAPI.addSBMLModelToTemplateLibrary(ModelName,"TypeB")
37
38          #Initial conditions
39          bionetAPI.initializeBionetworks()
40          # bionetAPI.setBionetworkValue("SO_n",2,"TypeB")
```

  - This is used as an abbreviation of the model name when referring to parameters of this model.

First Example – Simple Oscillator

- This takes 4 parameters:
  - And the last one is the size of the integration step:

```
21  import bionetAPI
22  class Oscillator(SteppableBasePy):
23      def __init__(self,_simulator,_frequency):
24          SteppableBasePy.__init__(self,_simulator,_frequency)
25          bionetAPI.initializeBionetworkManager(self.simulator)
26
27      def start(self):
28          #Loading model
29          ModelName = "SimpleOscillator"
30          ModelKey  = "SO"
31          ModelPath = os.getcwd() + "/DemosBionetSolver/SimpleOscillator/SimpleOscillator.sbml"
32          IntegrationStep = 1.0
33          bionetAPI.loadSBMLModel(ModelName, ModelPath, ModelKey, IntegrationStep)
34
35          bionetAPI.addSBMLModelToTemplateLibrary(ModelName,"TypeA")
36          bionetAPI.addSBMLModelToTemplateLibrary(ModelName,"TypeB")
37
38          #Initial conditions
39          bionetAPI.initializeBionetworks()
40          # bionetAPI.setBionetworkValue("SO_n",2,"TypeB")
```

  - This specifies the correspondence between MCS and the unit of time of the model.

First Example – Simple Oscillator

- Now we have to add this model to the cells in our simulation:

```
21  import bionetAPI
22  class Oscillator(SteppableBasePy):
23      def __init__(self,_simulator,_frequency):
24          SteppableBasePy.__init__(self,_simulator,_frequency)
25          bionetAPI.initializeBionetworkManager(self.simulator)
26
27      def start(self):
28          #Loading model
29          ModelName = "SimpleOscillator"
30          ModelKey  = "SO"
31          ModelPath = os.getcwd() + "/DemosBionetSolver/SimpleOscillator/SimpleOscillator.sbml"
32          IntegrationStep = 1.0
33          bionetAPI.loadSBMLModel(ModelName, ModelPath, ModelKey, IntegrationStep)
34
35          bionetAPI.addSBMLModelToTemplateLibrary(ModelName,"TypeA")
36          bionetAPI.addSBMLModelToTemplateLibrary(ModelName,"TypeB")
37
38          #Initial conditions
39          bionetAPI.initializeBionetworks()
40          # bionetAPI.setBionetworkValue("SO_n",2,"TypeB")
```

  - The first line add the SimpleOscillator model to all cells of type “TypeA”, and the second to all cells of type “TypeB”.

First Example – Simple Oscillator

- Finally, we initialize the SBML model in each cell by using the following command:

```
21  import bionetAPI
22  class Oscillator(SteppableBasePy):
23      def __init__(self,_simulator,_frequency):
24          SteppableBasePy.__init__(self,_simulator,_frequency)
25          bionetAPI.initializeBionetworkManager(self.simulator)
26
27      def start(self):
28          #Loading model
29          ModelName = "SimpleOscillator"
30          ModelKey  = "SO"
31          ModelPath = os.getcwd() + "/DemosBionetSolver/SimpleOscillator/SimpleOscillator.sbml"
32          IntegrationStep = 1.0
33          bionetAPI.loadSBMLModel(ModelName, ModelPath, ModelKey, IntegrationStep)
34
35          bionetAPI.addSBMLModelToTemplateLibrary(ModelName,"TypeA")
36          bionetAPI.addSBMLModelToTemplateLibrary(ModelName,"TypeB")
37
38          #Initial conditions
39          bionetAPI.initializeBionetworks()
40          # bionetAPI.setBionetworkValue("SO_n",2,"TypeB")
```

First Example – Simple Oscillator

- On the step function we create a dictionary where the two variables of the SimpleOscillator will be stored:

```
41
42  def step(self,mcs):
43      for cell in self.cellList:
44          if (cell):
45              #Storing V1 and V2 levels of each cell
46              cellDict=CompuCell.getPyAttrib(cell)
47              cellDict["V1"]=bionetAPI.getBionetworkValue("SO_V1",cell.id)
48              cellDict["V2"]=bionetAPI.getBionetworkValue("SO_V2",cell.id)
49      #Iterating the ODEs
50      bionetAPI.timestepBionetworks()
51
```

First Example – Simple Oscillator

- To extract the current value of a variable or parameter from the SBML model inside the cell, we use the command:

```
41
42  def step(self,mcs):
43    for cell in self.cellList:
44      if (cell):
45        #Storing V1 and V2 levels of each cell
46        cellDict=CompuCell.getPyAttrib(cell)
47        cellDict["V1"]=bionetAPI.getBionetworkValue("SO_V1",cell.id)
48        cellDict["V2"]=bionetAPI.getBionetworkValue("SO_V2",cell.id)
49    #Iterating the ODEs
50    bionetAPI.timestepBionetworks()
51
```

  - Where the first parameter indicate the model (by its nickname) followed by a underscore "_" and the name of the variable.
  - The second parameter indicate the cell from which this information will be extracted.

First Example – Simple Oscillator

- The last command runs the SBML model inside each cell for one time step of integration:

```
41
42  def step(self,mcs):
43    for cell in self.cellList:
44      if (cell):
45        #Storing V1 and V2 levels of each cell
46        cellDict=CompuCell.getPyAttrib(cell)
47        cellDict["V1"]=bionetAPI.getBionetworkValue("SO_V1",cell.id)
48        cellDict["V2"]=bionetAPI.getBionetworkValue("SO_V2",cell.id)
49    #Iterating the ODEs
50    bionetAPI.timestepBionetworks()
51
```

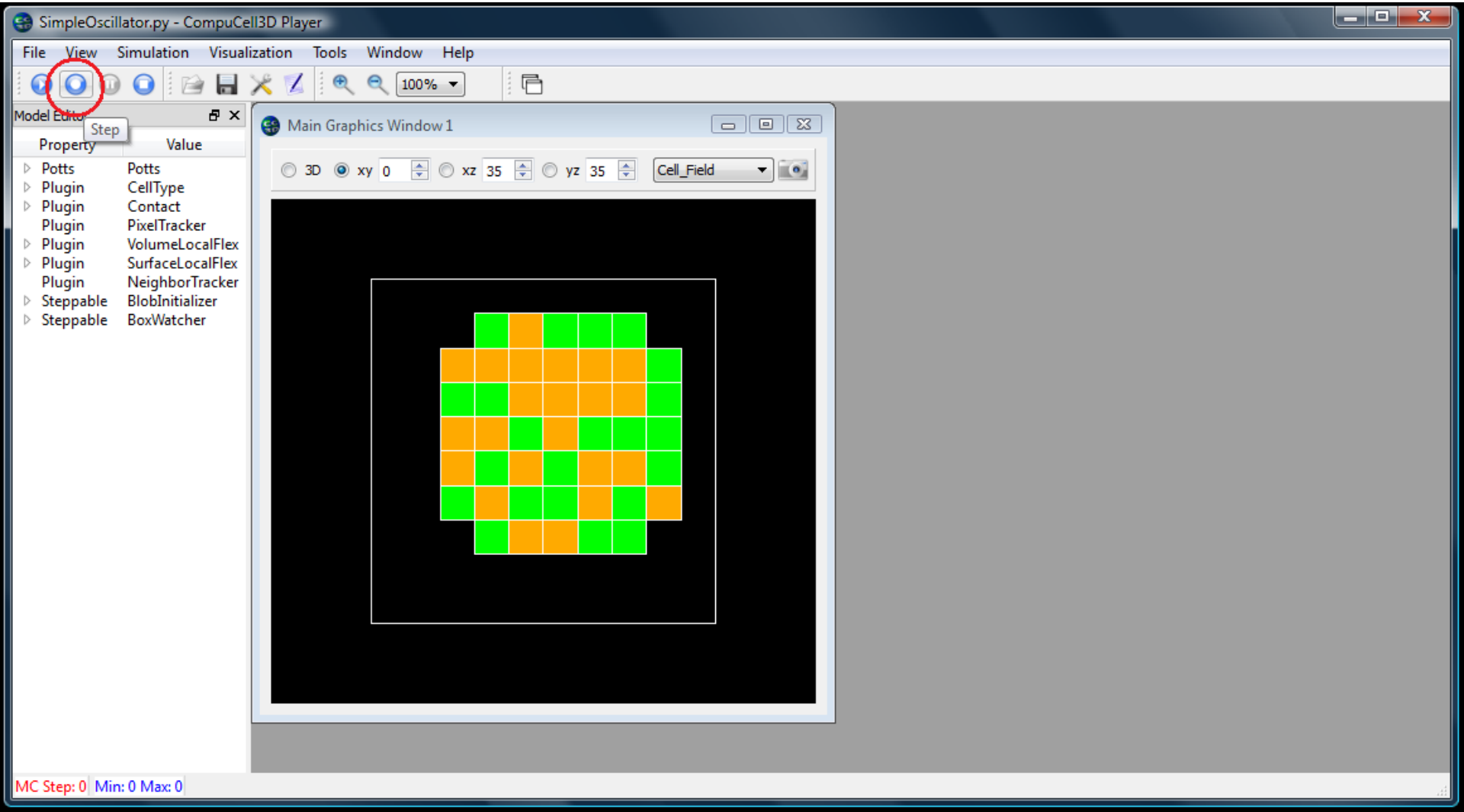
  - If this command is not called, the ODE model will not run and all variables will stay at their initial values.

First Example – Simple Oscillator

- Next, open the file *SimpleOscillator.py* on the CC3D player.

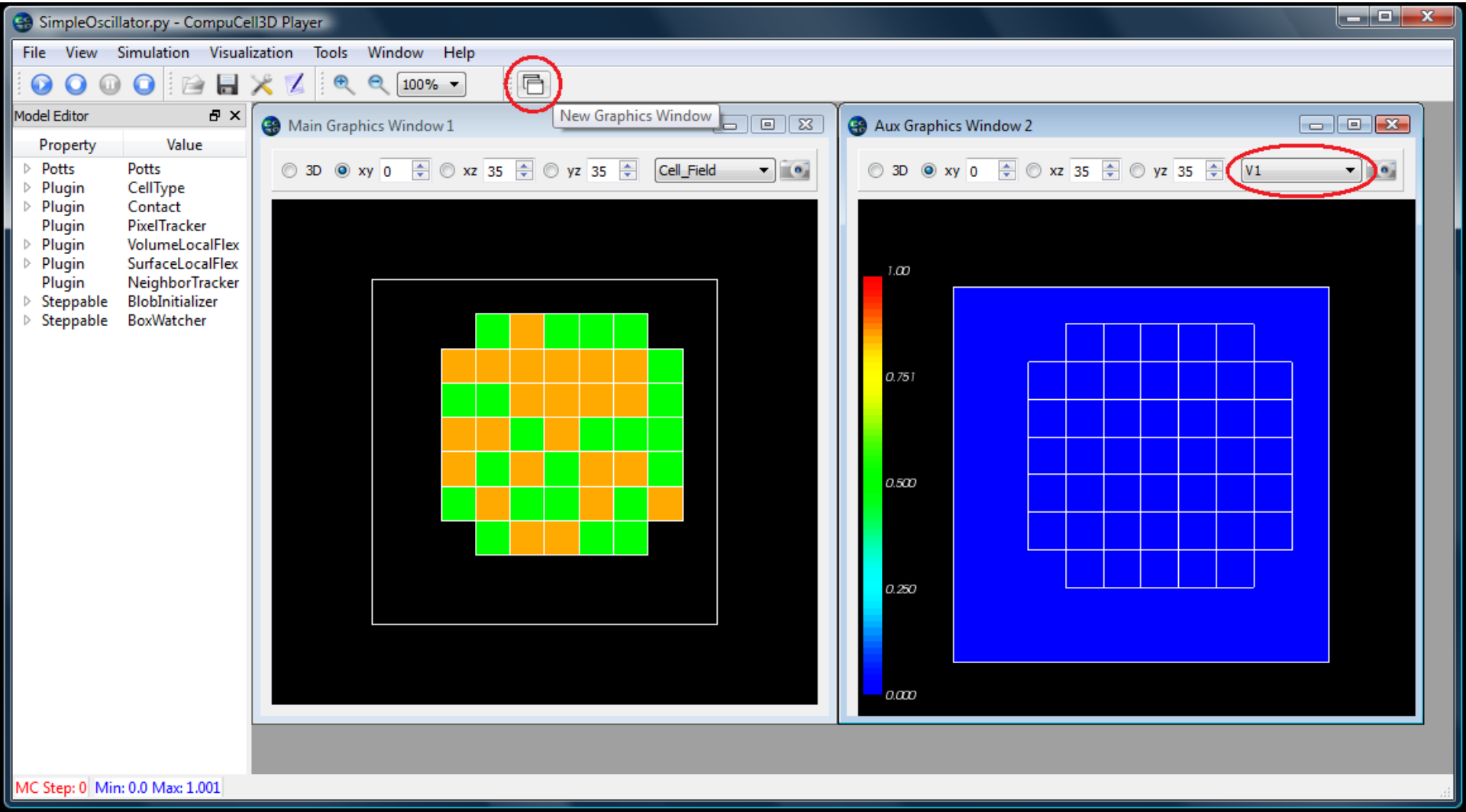
First Example – Simple Oscillator

- Hit the “step” button, as indicated below, to run the simulation just one MCS.



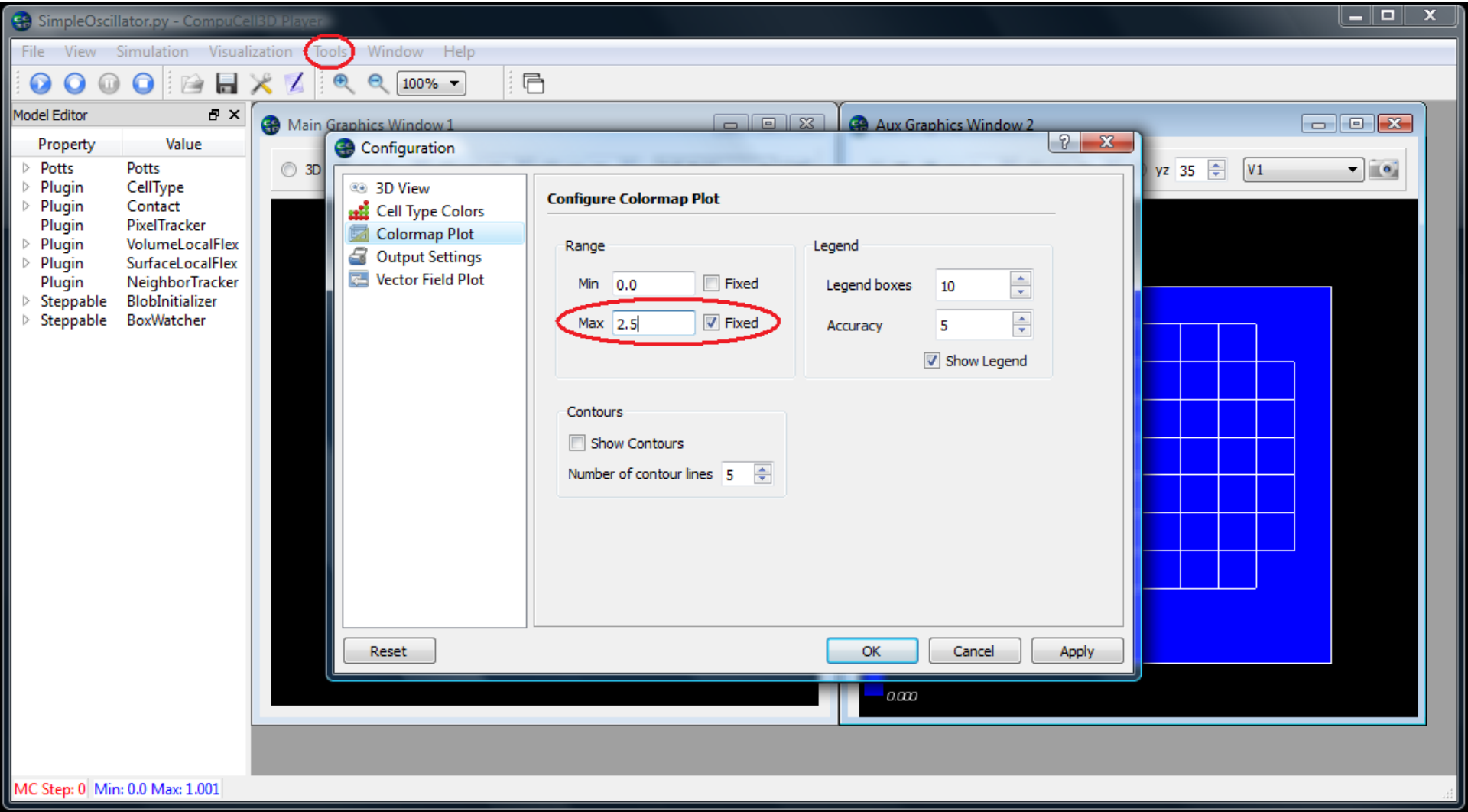
First Example – Simple Oscillator

- Click the indicated button to open a new graphics window and select *V1* in place of *Cell_field* in it:



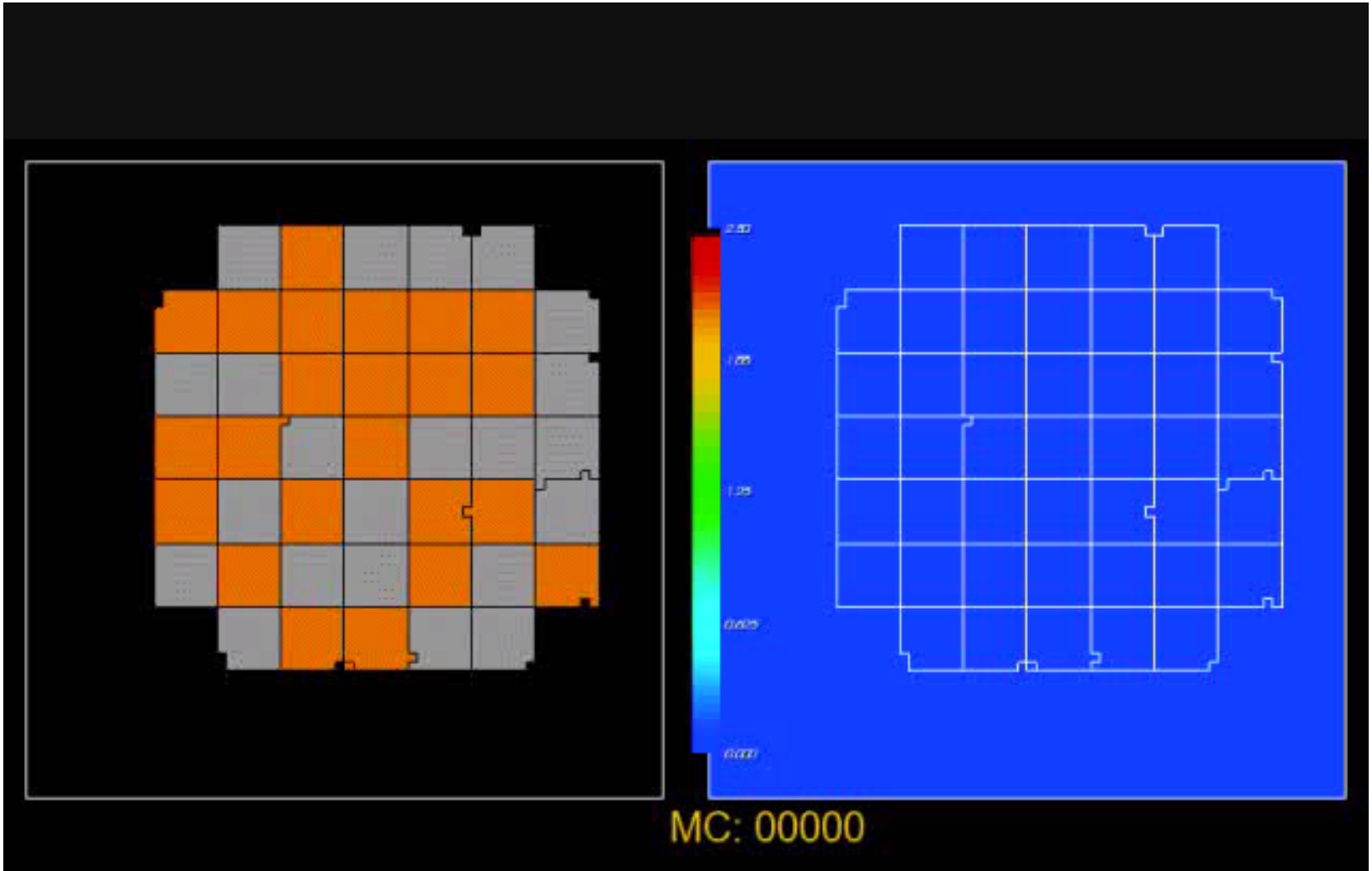
First Example – Simple Oscillator

- Next go to Tools -> Configuration, and under “Colormap Plot”, fix the maximum range at 2.5:



First Example – Simple Oscillator

- When you run the simulation, the second graphics window should display an oscillating V1 concentration similar to this:



Second Example – Simple Oscillator 2

- In the last example both cell types, “TypeA” and “TypeB”, had exactly the same oscillator with the same parameters and initial conditions.

- In this second example we are going to assign the same SBML model to both cell types, but change the parameter “n” for one of them.

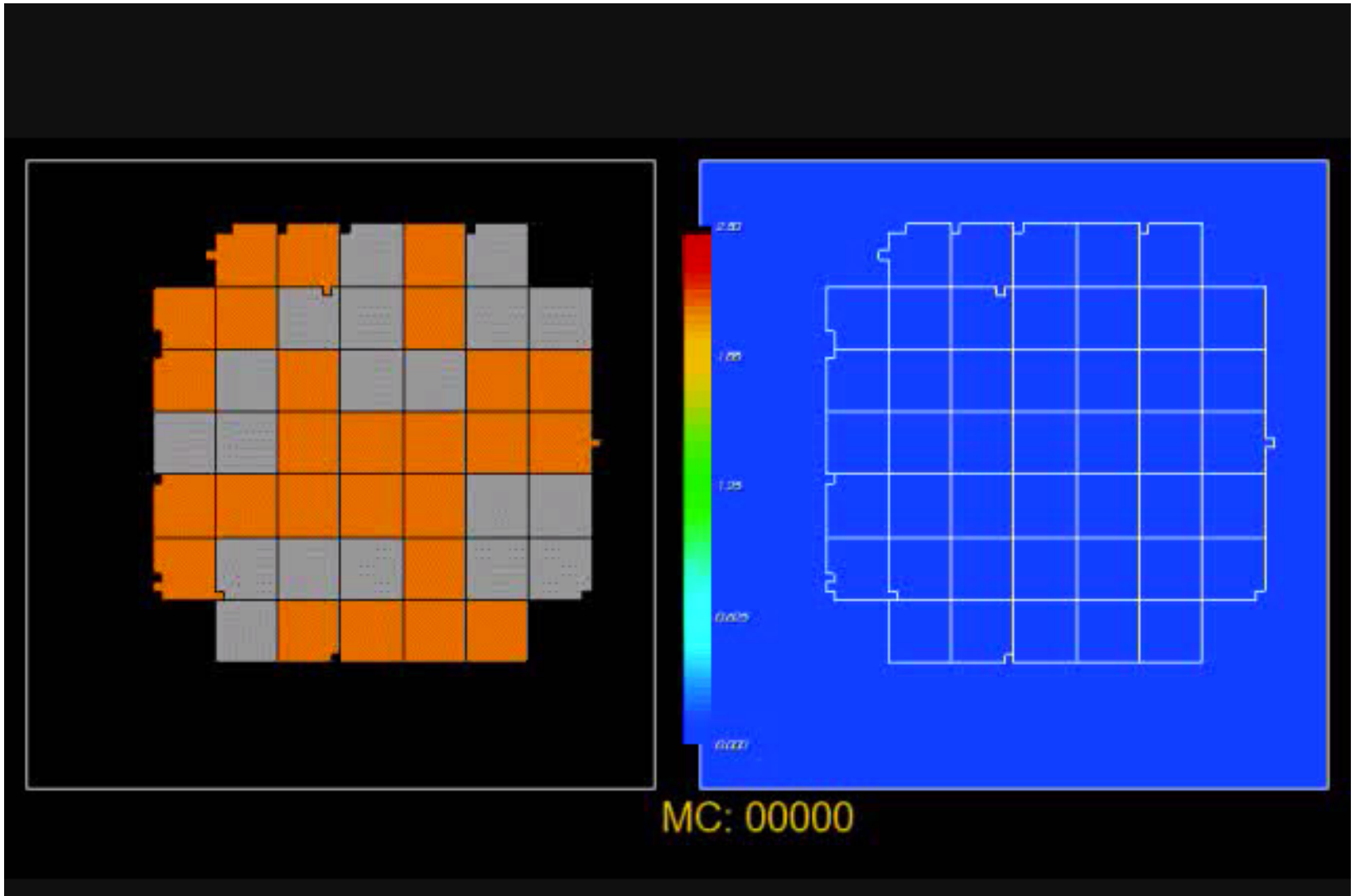
Second Example – Simple Oscillator 2

- To do this, uncomment the following line from the steppable file *SimpleOscillator_Step.py*:

```
21  import bionetAPI
22  class Oscillator(SteppableBasePy):
23      def __init__(self,_simulator,_frequency):
24          SteppableBasePy.__init__(self,_simulator,_frequency)
25          bionetAPI.initializeBionetworkManager(self.simulator)
26
27      def start(self):
28          #Loading model
29          ModelName = "SimpleOscillator"
30          ModelKey  = "SO"
31          ModelPath = os.getcwd() + "/DemosBionetSolver/SimpleOscillator/SimpleOscillator.sbml"
32          IntegrationStep = 1.0
33          bionetAPI.loadSBMLModel(ModelName, ModelPath, ModelKey, IntegrationStep)
34
35          bionetAPI.addSBMLModelToTemplateLibrary(ModelName,"TypeA")
36          bionetAPI.addSBMLModelToTemplateLibrary(ModelName,"TypeB")
37
38          #Initial conditions
39          #bionetAPI.initializeBionetworks()
40          bionetAPI.setBionetworkValue("SO_n",2,"TypeB")
41
```

Second Example – Simple Oscillator 2

- As a result, cells of type “TypeB” will cease to oscillate:



Third Example – Cell Cycle from web

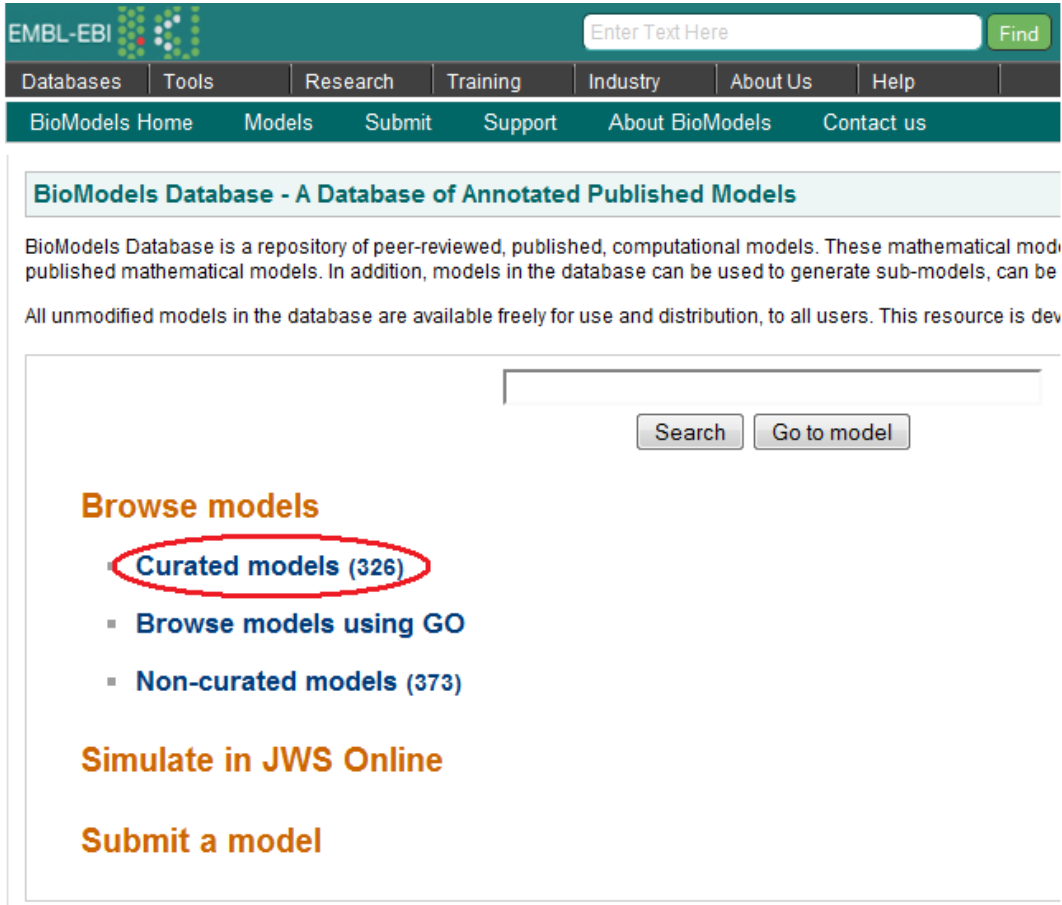
- In our third example, instead of building our own SBML model, we are going to use an existing one.

- 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

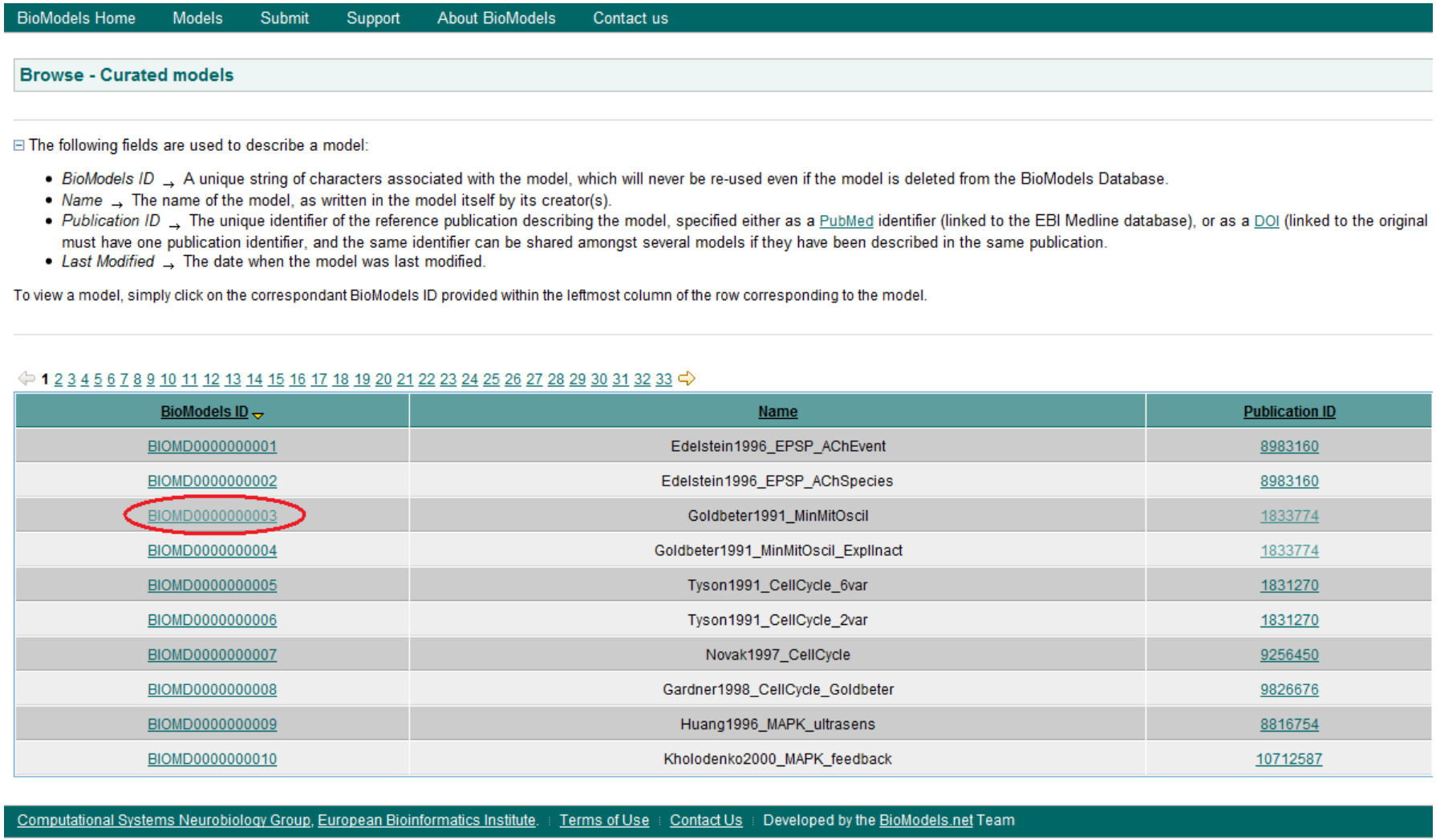
Third Example – Cell Cycle from web

- To access the SBML model repository click on the link "BioModels Database" and then on "Curated models":



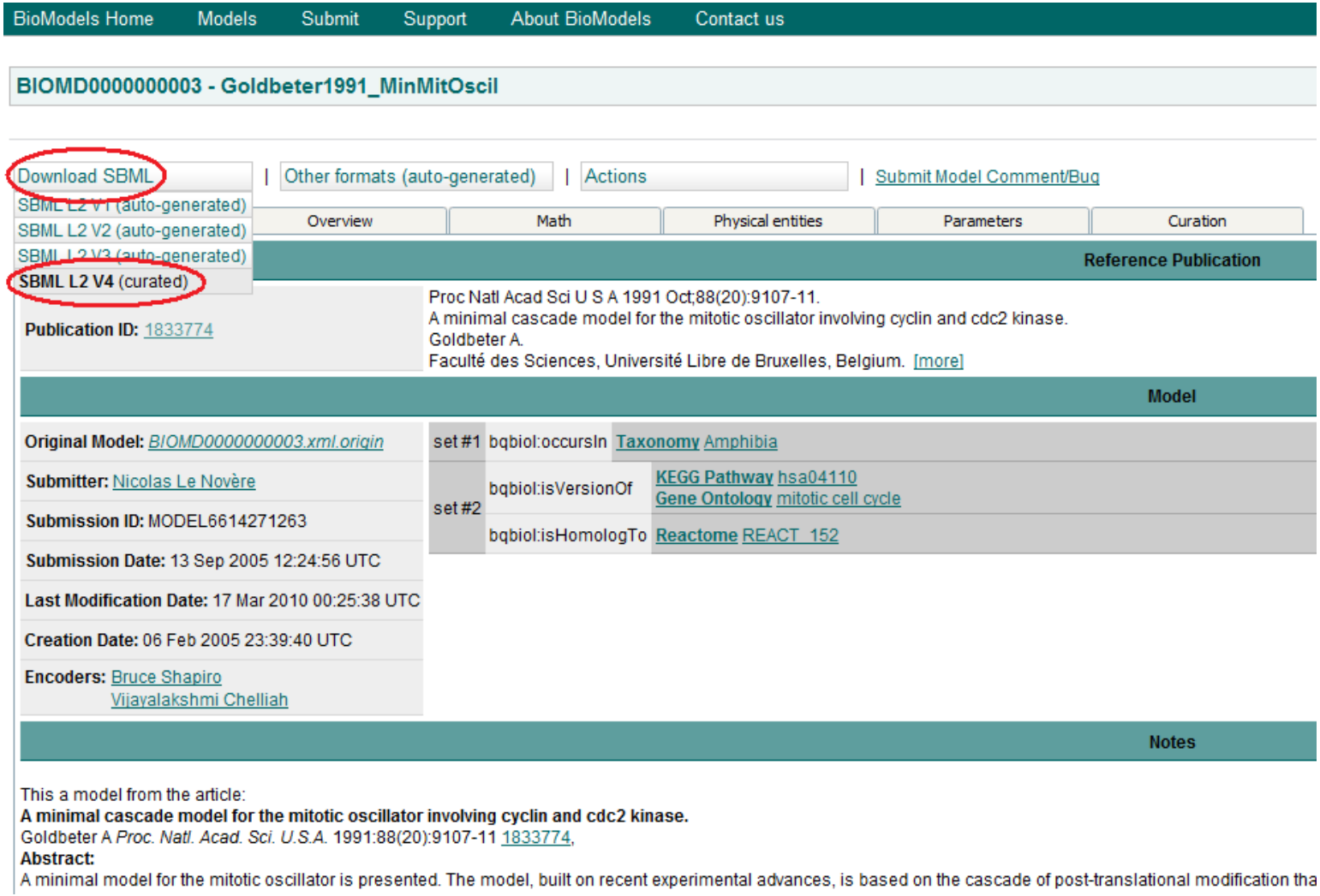
Third Example – Cell Cycle from web

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



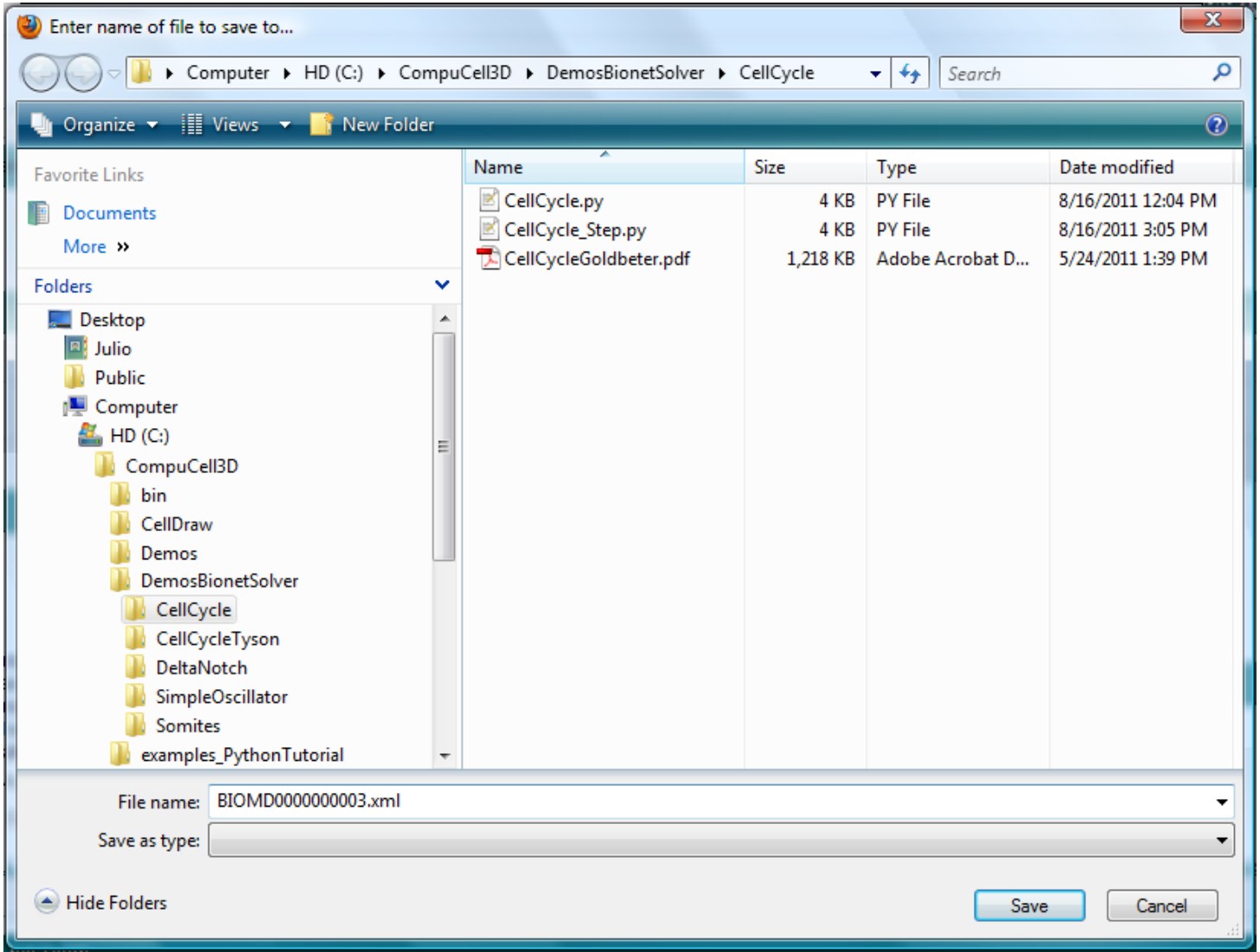
Third Example – Cell Cycle from web

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



Third Example – Cell Cycle from web

- Save the file *BIOMD0000000003.xml* inside the directory *CompuCell3D\DemosBionetSolver\CellCycle*



Third Example – Cell Cycle from web

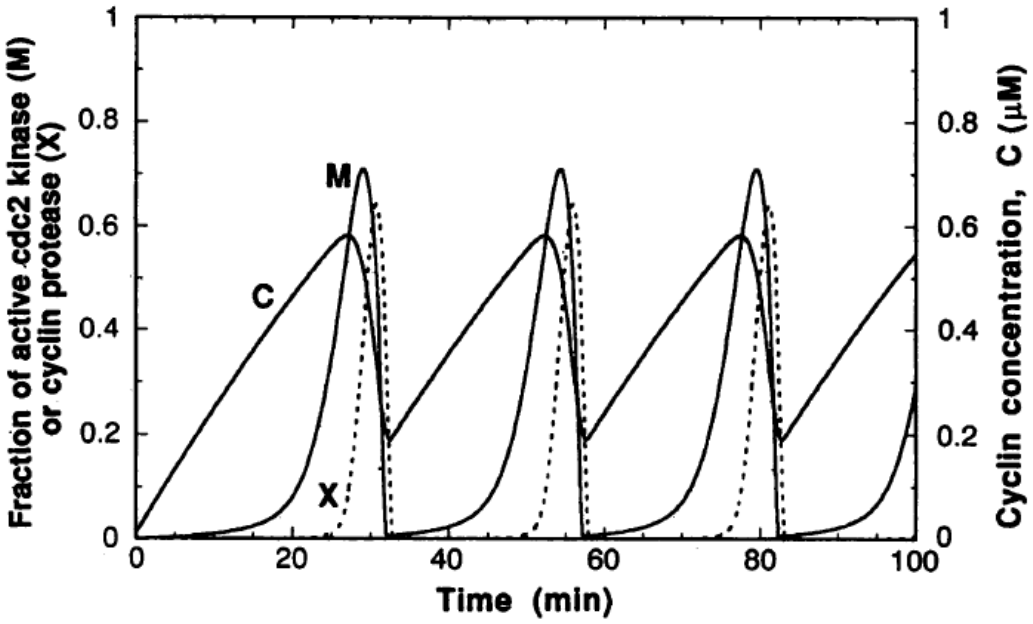
- This model is composed of 3 ODEs that forms an oscillating system:

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

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

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

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



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

Third Example – Cell Cycle from web

- The model is implemented into CC3D in the same ways as in the first example, but this time we just have 1 cell type:

```
30  import bionetAPI
31  class Cycle(SteppableBasePy):
32    def __init__(self,_simulator,_frequency,_tV):
33      SteppableBasePy.__init__(self,_simulator,_frequency)
34      bionetAPI.initializeBionetworkManager(self.simulator)
35      self.tV=_tV
36
37    def start(self):
38      #Loading model
39      ModelName = "CellCycle"
40      ModelKey  = "CC"
41      ModelPath = os.getcwd() + "/DemosBionetSolver/CellCycle/BIOMD0000000003.xml"
42      IntegrationStep = 0.05
43      bionetAPI.loadSBMLModel(ModelName, ModelPath, ModelKey, IntegrationStep)
44
45      #Initial conditions
46      bionetAPI.addSBMLModelToTemplateLibrary(ModelName,"TypeA")
47      bionetAPI.initializeBionetworks()
48      for cell in self.cellList:
49        cellDict=CompuCell.getPyAttrib(cell)
50        cellDict["M"]=bionetAPI.getBionetworkValue("CC_M",cell.id)
51        cellDict["C"]=bionetAPI.getBionetworkValue("CC_C",cell.id)
```

Third Example – Cell Cycle from web

- According to the original paper, mitosis happens after the fraction of active cdc2 kinase (M) reaches its maximum at around 0.7.

- To implement this we store the value of M at each MCS and the previous MCS:

```
52
53  def step(self,mcs):
54    for cell in self.cellList:
55      #Storing CycB and Cdh1 levels of each cell
56      cellDict=CompuCell.getPyAttrib(cell)
57      cellDict["M0"]=cellDict["M"]
58      cellDict["M"]=bionetAPI.getBionetworkValue("CC_M",cell.id)
59      cellDict["C"]=bionetAPI.getBionetworkValue("CC_C",cell.id)
60    #Iterating the ODEs
61    bionetAPI.timestepBionetworks()
```

Third Example – Cell Cycle from web

- Then, inside the Mitosis steppable, we check if the cell's internal fraction of M crosses the 0.7 threshold:

```
64  class MitosisSteppable(MitosisSteppableBase):
65      def __init__(self,_simulator,_frequency,_tV):
66          MitosisSteppableBase.__init__(self,_simulator,_frequency)
67          self.tV=_tV;
68
69      def step(self,mcs):
70          cells2divide=[]
71          for cell in self.cellList:
72              cellDict=CompuCell.getPyAttrib(cell)
73              if (cellDict["M"]>=0.7 and cellDict["M0"]<0.7):
74                  cells2divide.append(cell)
75          for cell in cells2divide:
76              self.divideCellRandomOrientation(cell)
```

Third Example – Cell Cycle from web

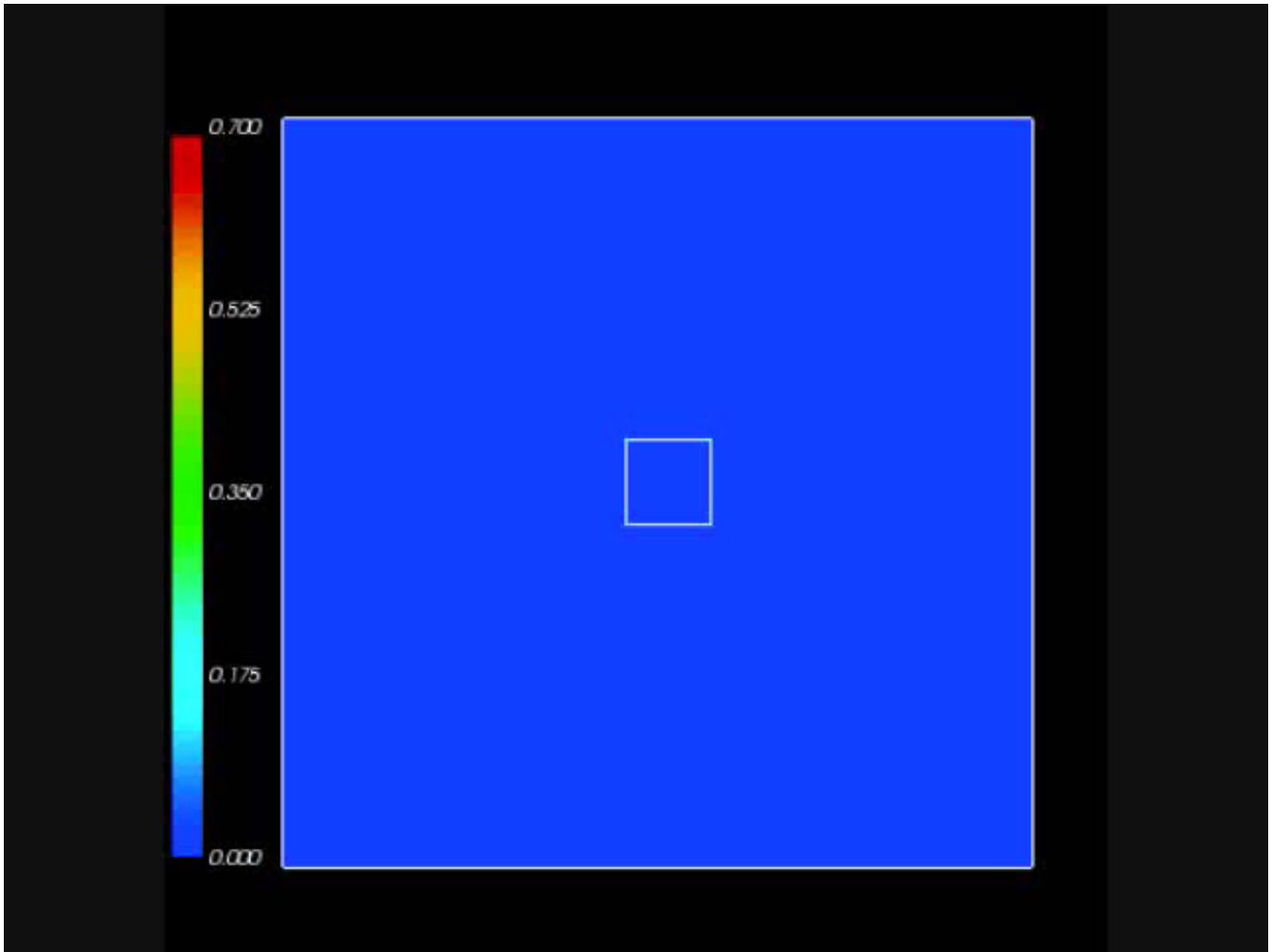
- Inside the updateAtrributes function, we must copy the SBML model network from the parent to the child:

```
78      def updateAttributes(self):
79          parentCell=self.mitosisSteppable.parentCell
80          childCell=self.mitosisSteppable.childCell
81
82          #transfering attributes
83          childCell.type=parentCell.type
84          bionetAPI.copyBionetworkFromParent(parentCell,childCell)
```

- But before doing this, we must assign a cell type to the child cell:

Third Example – Cell Cycle from web

- Next, open the model in CC3D, set the maximum concentration of the “Colormap Plot” to 0.75, and run the simulation:



Fourth Example – Tyson's Cell Cycle

- In the last example all cells divided in synchrony.
- The reason for this is the absence of any flow of information from the cell level to the subcellular level that would alter the state of the cell cycle oscillations.
- A more realistic model, where the cells do not maintain their cell cycle's phase, is the one proposed by Tyson and Novak.

Fourth Example – Tyson's Cell Cycle

- This model has 5 variables, from which only the first 2 forms the core of the cell cycle oscillations:

$$\frac{d[\mathrm{CycB}]}{dt} = k_1 - (k_2' + k_2''\,[\mathrm{Cdh1}])\,[\mathrm{CycB}],$$

$$\frac{d[\mathrm{Cdh1}]}{dt} = \frac{(k_3' + k_3'' A)(1 - [\mathrm{Cdh1}])}{J_3 + 1 - [\mathrm{Cdh1}]} - \frac{k_4 m[\mathrm{CycB}]\,[\mathrm{Cdh1}]}{J_4 + [\mathrm{Cdh1}]},$$

$$\frac{d[\mathrm{Cdc20}_T]}{dt} = k_5' + k_5'' \frac{([\mathrm{CycB}]\,m/J_5)^n}{1 + ([\mathrm{CycB}]\,m/J_5)^n} - k_6\,[\mathrm{Cdc20}_T],$$

$$\frac{d[\mathrm{Cdc20}_A]}{dt} = \frac{k_7\,[\mathrm{IEP}]([\mathrm{Cdc20}_T] - [\mathrm{Cdc20}_A])}{J_7 + [\mathrm{Cdc20}_T] - [\mathrm{Cdc20}_A]} - \frac{k_8[\mathrm{Mad}]\cdot[\mathrm{Cdc20}_A]}{J_8 + [\mathrm{Cdc20}_A]} - k_6[\mathrm{Cdc20}_A],$$

$$\frac{d[\mathrm{IEP}]}{dt} = k_9 m[\mathrm{CycB}](1 - [\mathrm{IEP}]) - k_{10}[\mathrm{IEP}].$$

Fourth Example – Tyson's Cell Cycle

- The crucial difference from the previous model lies in the presence of the parameter "m", which is the normalized total mass of the cell:

$$\frac{\mathrm{d}[\mathrm{CycB}]}{\mathrm{d}t} = k_1 - (k_2' + k_2''\,[\mathrm{Cdh1}])\,[\mathrm{CycB}],$$

$$\frac{\mathrm{d}[\mathrm{Cdh1}]}{\mathrm{d}t} = \frac{(k_3' + k_3'' A)(1 - [\mathrm{Cdh1}])}{J_3 + 1 - [\mathrm{Cdh1}]} - \frac{k_4 m [\mathrm{CycB}]\,[\mathrm{Cdh1}]}{J_4 + [\mathrm{Cdh1}]},$$

- This parameter varies between ~0.5 (right after mitosis) and ~1 (at normal size) and corresponds in CC3D to the ratio of volume to target volume:

$$V_\sigma / V_{\text{target}}$$

Fourth Example – Tyson's Cell Cycle

- In the steppable file, *CellCycle_Tyson_Step.py*, this is implemented as:

```
55
56  def step(self,mcs):
57      for cell in self.cellList:
58          if (cell):
59              #Setting volume parameter for each cell
60              bionetAPI.setBionetworkValue("CC_m",cell.volume/self.tV,cell.id)
61              #Storing CycB and Cdh1 levels of each cell
62              cellDict=CompuCell.getPyAttrib(cell)
63              cellDict["CycB0"]=cellDict["CycB"]
64              cellDict["CycB"]=bionetAPI.getBionetworkValue("CC_CycB",cell.id)
65              cellDict["Cdh1"]=bionetAPI.getBionetworkValue("CC_Cdh1",cell.id)
66      #Iterating the ODEs
67      bionetAPI.timestepBionetworks()
```

- Where "self.tV" is a variable which contains the original target volume of the cells and is passed into the steppable class from the main Python file.

Fourth Example – Tyson's Cell Cycle

- This passage of variables is done in the following way:
  - At the beginning of the *CellCycle_Tyson.py* file I declare and define global variables, from which tV – target volume – is one:

```
7
8   global Lx; global Ly; global cd; global T; global nOrder
9   global LamV; global tV
10
11  #PARAMETERS:
12  cd=7                #typical cell diameter
13  Lx=5*cd             #Lattice size - x
14  Ly=5*cd             #Lattice size - y
15  T=10                #Temperature
16  nOrder=4            #Distance of interaction
17  #
18  #VOLUME/SURFACE PARAMETERS:
19  LamV=10           #Lambda Volume
20  tV=cd*cd          #Target Volume
21
22
23  def configureSimulation(sim):
24      import CompuCellSetup
25      from XMLUtils import ElementCC3D
26      cc3d=ElementCC3D("CompuCell3D")
27      potts=cc3d.ElementCC3D("Potts")
```

Fourth Example – Tyson's Cell Cycle

- This passage of variables is done in the following way:
  - Later, when the steppable is called, the variable is passed as an argument:

```
82
83  from CellCycle_Tyson_Step import Cycle
84  cycle=Cycle(_simulator=sim,_frequency=1,_tV=tV)
85  steppableRegistry.registerSteppable(cycle)
86
```

  - And in the *CellCycle_Tyson_Step.py* file, the argument is stored in the following way:

```
30  import bionetAPI
31  class Cycle(SteppableBasePy):
32      def __init__(self,_simulator,_frequency,_tV):
33          SteppableBasePy.__init__(self,_simulator,_frequency)
34          bionetAPI.initializeBionetworkManager(self.simulator)
35          self.tV=_tV
36
```

  - The storage of the parameter as self.tV is necessary for it to be accessible to all functions inside the class.

Fourth Example – Tyson's Cell Cycle

- We went through all this trouble because the right way to implement cell growth in CC3D is by gradual increases in its target volume after mitosis:

```
23  def step(self,mcs):
24    for cell in self.cellList:
25      if (cell):
26        if (cell.volume<self.tV):
27          cell.targetVolume+=0.1
```

- If we keep the target volume (Vt) constant after mitosis, instead of resetting it to the actual cell volume (V), the difference between V and Vt would be too great, leading to unrealistic cell dynamics.

```
85  def updateAttributes(self):
86    parentCell=self.mitosisSteppable.parentCell
87    childCell=self.mitosisSteppable.childCell
88
89    #transfering attributes
90    childCell.type=parentCell.type
91    bionetAPI.copyBionetworkFromParent(parentCell,childCell)
92    #volume
93    parentCell.targetVolume=parentCell.volume
94    childCell.targetVolume=childCell.volume
95    childCell.lambdaVolume=parentCell.lambdaVolume
```

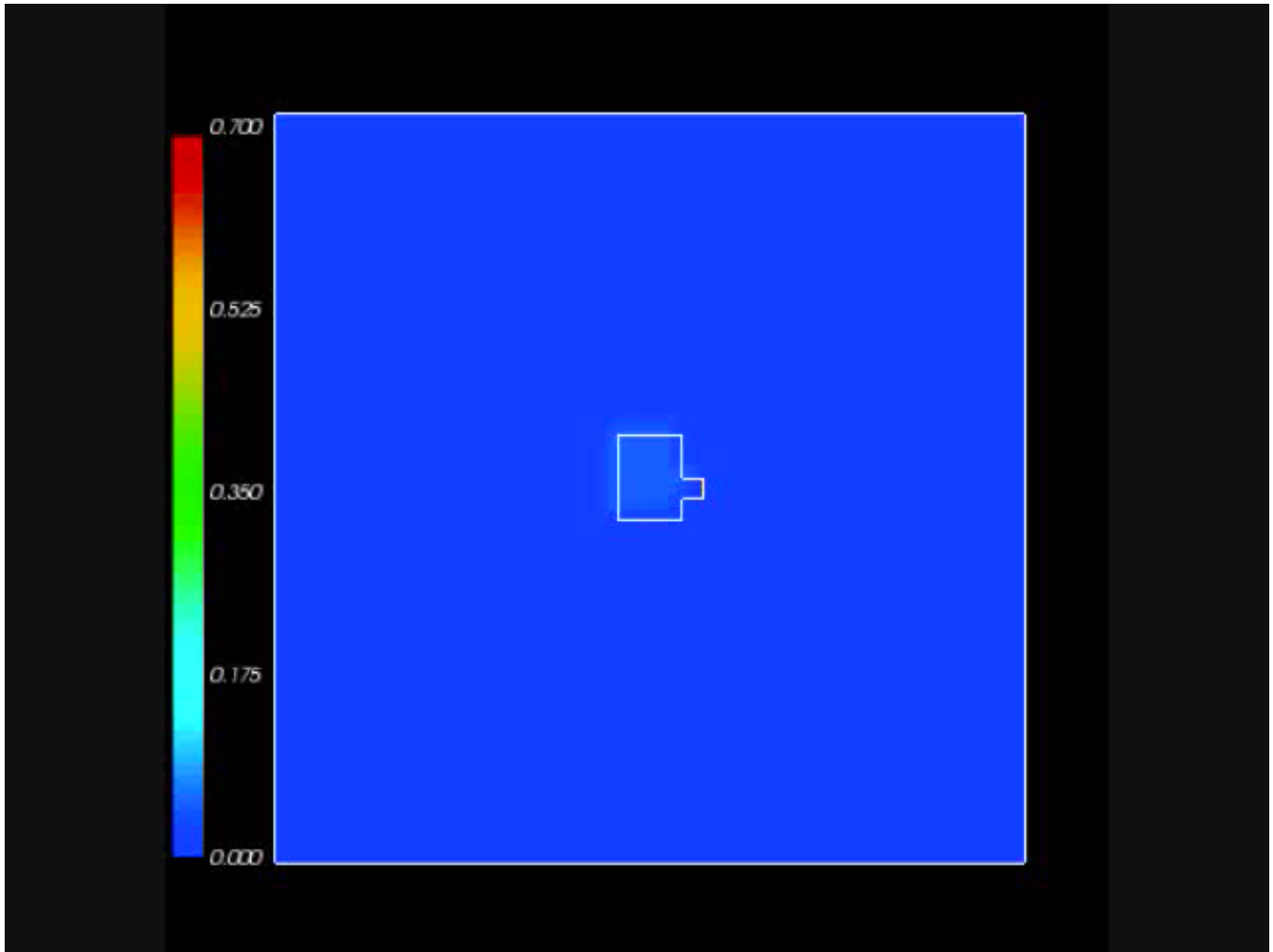
Fourth Example – Tyson's Cell Cycle

- Back to Tyson's cell cycle model.
- Here, the criteria for cell division is a low level of cycling B variable.
  - Once cycling B drops below a concentration of 0.1 grams of protein per gram of total cell mass, the cell undergoes mitosis

```
75  def step(self,mcs):
76      cells2divide=[]
77      for cell in self.cellList:
78          if cell:
79              cellDict=CompuCell.getPyAttrib(cell)
80              if (cellDict["CycB"]<=0.1 and cellDict["CycB0"]>0.1):
81                  cells2divide.append(cell)
82      for cell in cells2divide:
83          self.divideCellRandomOrientation(cell)
84
```

Fourth Example – Tyson's Cell Cycle

- When we run this model we can see that due to the fluctuations in cell volume, the divisions get out of sync:



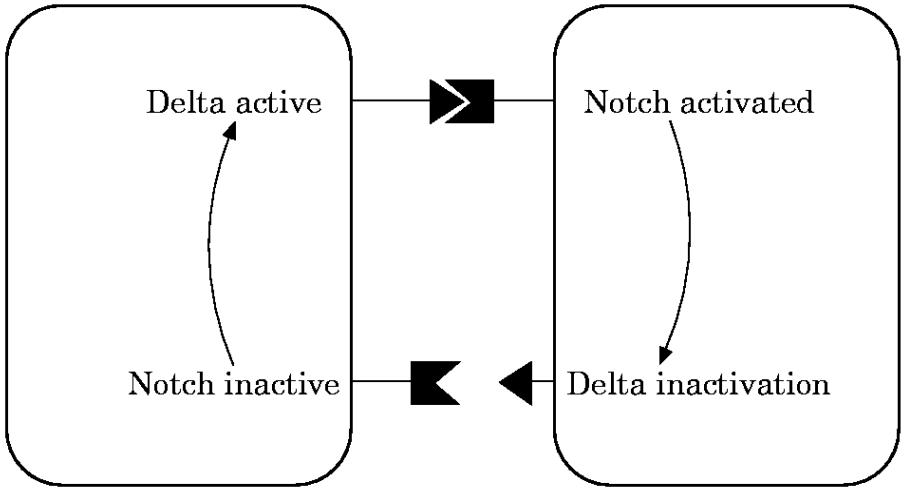
Fifth Example – Delta-Notch Patterning

- The fourth example (Tyson's cell cycle model) illustrated how changes at the single cell level can affect the subcellular level (and in turn affect the cell behavior by initiating mitosis).

- This last example will show how conditions external to the cell (the neighboring cells' Delta) can affect the cell internal state (its Notch levels).

Fifth Example – Delta-Notch Patterning

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



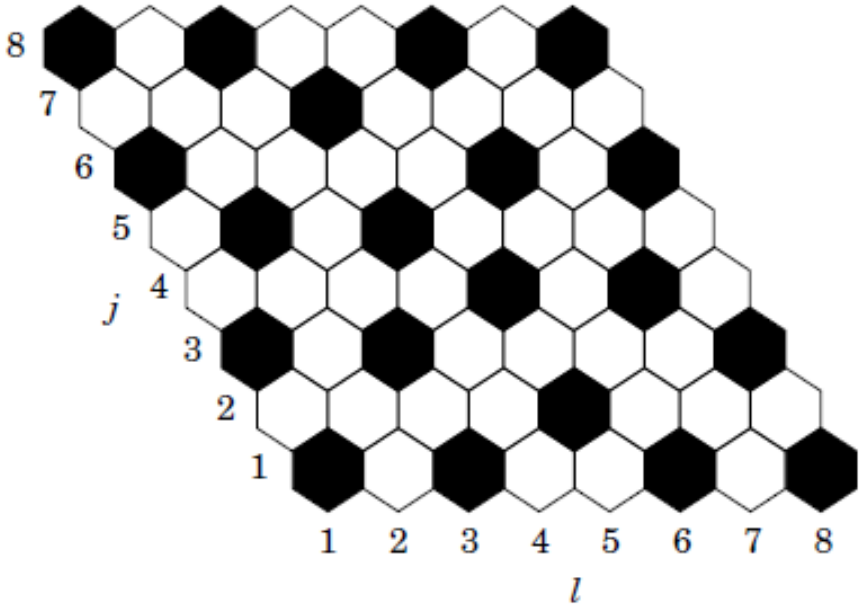
$$\frac{dD}{dt} = \nu \cdot \left(\frac{1}{1 + b \cdot N^{h}} - N \right)$$

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

  - N : Notch
  - D : Delta
  - $\overline{D}$: average Delta from neighbors

Fifth 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:



Fifth Example – Delta-Notch Patterning

- In CC3D we first loop over all cells' neighbors and store their Delta:

```
37  def step(self,mcs):
38    for cell in self.cellList:
39      if (cell):
40        D=0.0; nn=0
41        cellNeighborList=self.getCellNeighbors(cell)
42        for neighbor in cellNeighborList:
43          if (neighbor.neighborAddress):
44            nn+=1
45            D+=bionetAPI.getBionetworkValue("DN_D",neighbor.neighborAddress.id)
46        if (nn>0):
47          D=D/nn
48        bionetAPI.setBionetworkValue("DN_Davg",D,cell.id)
49        cellDict=CompuCell.getPyAttrib(cell)
50        cellDict["D"]=D
51        cellDict["N"]=bionetAPI.getBionetworkValue("DN_N",cell.id)
52    bionetAPI.timestepBionetworks()
```

- Then we average it and use it as the new $\overline{D}$ parameter of that cell:

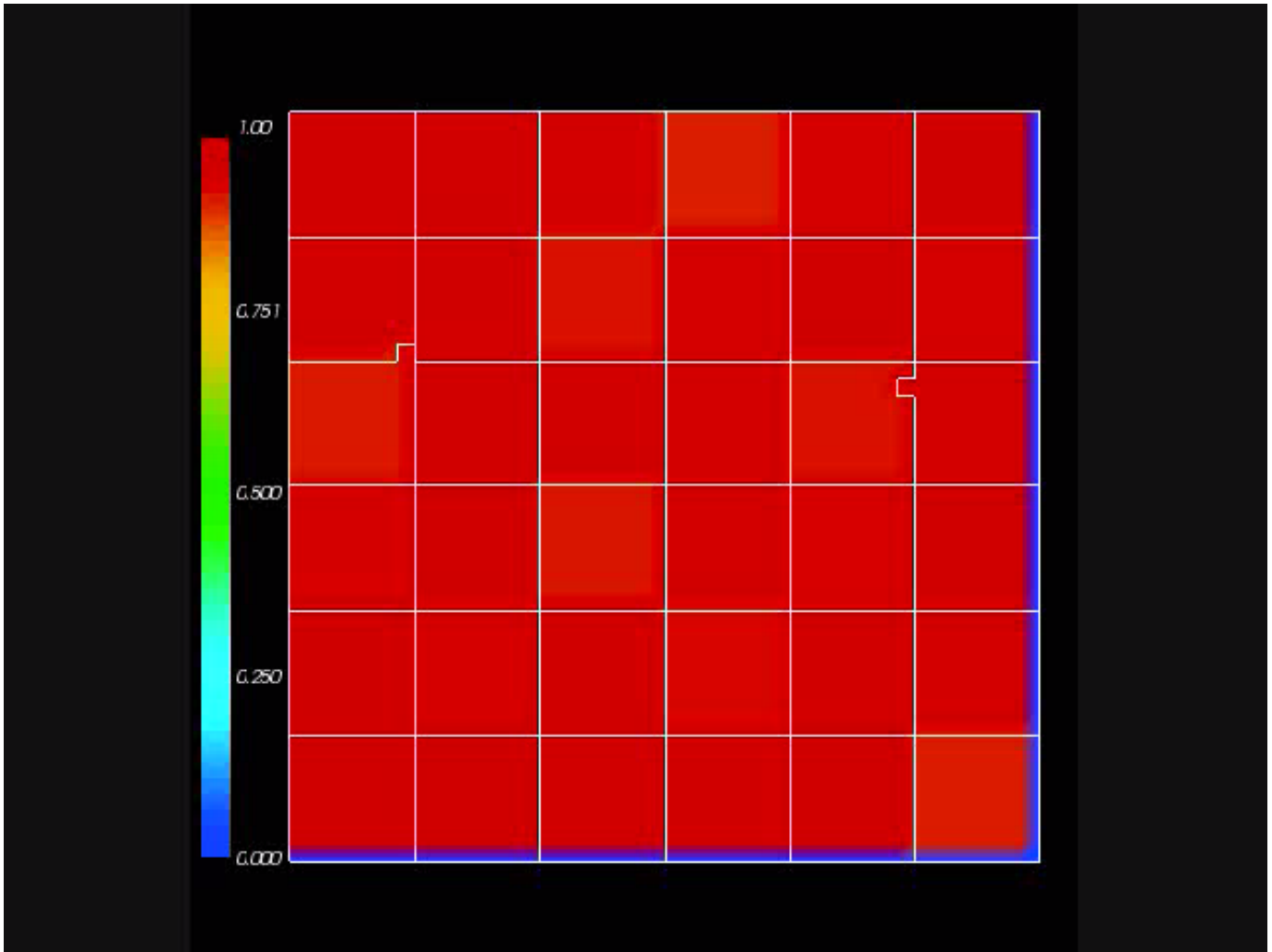
Fifth Example – Delta-Notch Patterning

- As an initial condition all cells start with random values of Delta and Notch around 0.9.
- To implement this we use the Python random function as shown below:

```
25      #Initial conditions
26      import random
27      for cell in self.cellList:
28        if (cell):
29          D = random.uniform(0.9,1.0)
30          N = random.uniform(0.9,1.0)
31          bionetAPI.setBionetworkValue("DN_D",D,cell.id)
32          bionetAPI.setBionetworkValue("DN_N",N,cell.id)
33          cellDict=CompuCell.getPyAttrib(cell)
34          cellDict["D"]=D
35          cellDict["N"]=N
```

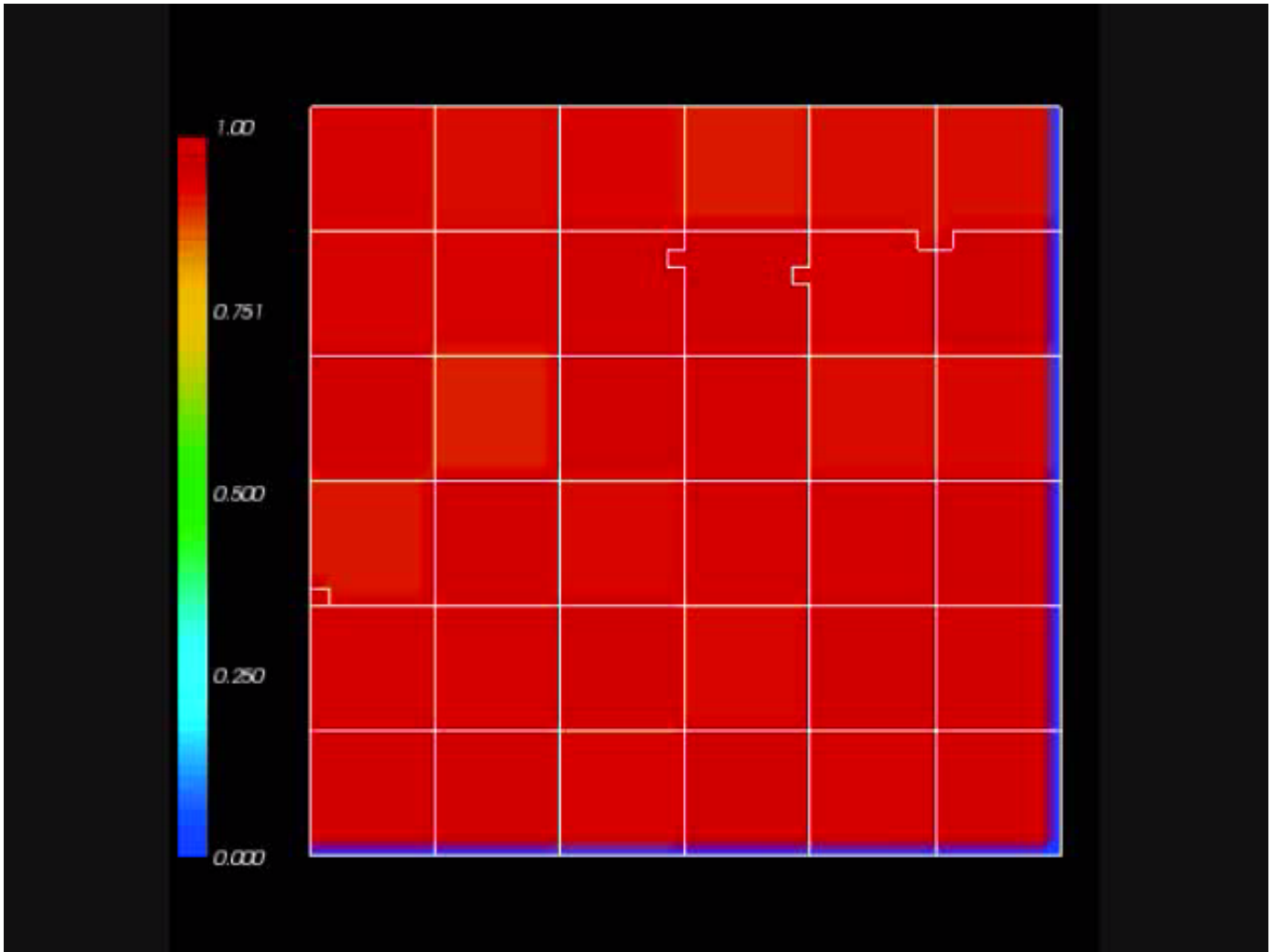
Fifth Example – Delta-Notch Patterning

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



Fifth Example – Delta-Notch Patterning

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



Sixth Example – 2 ODE models

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