

**Slides, videos, links and more:**

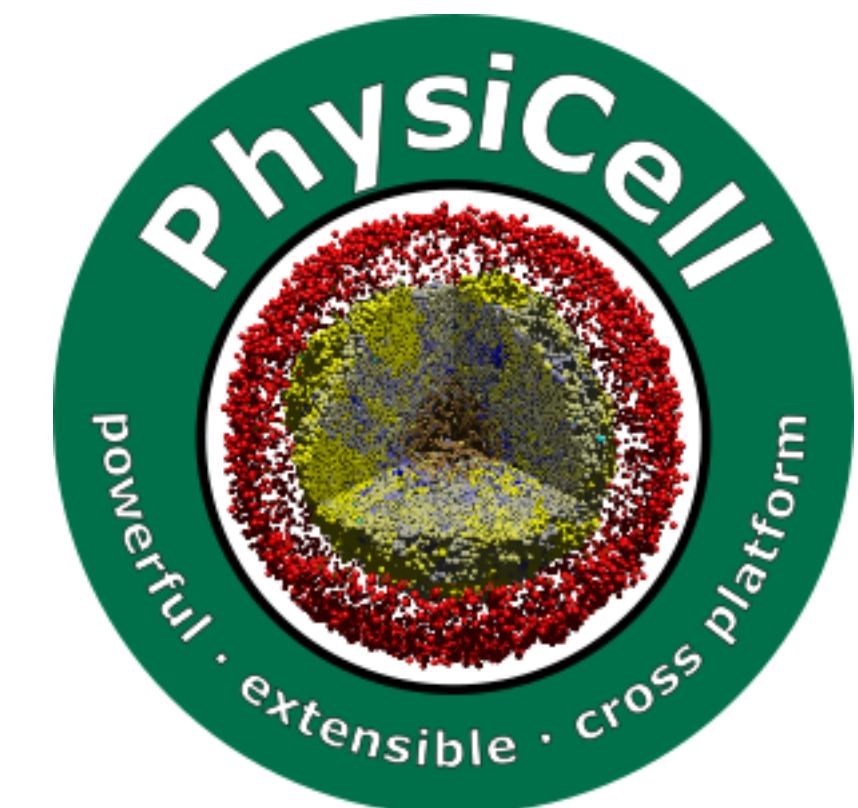
<https://github.com/physicell-training/cecam23>

# PhysiCell Tutorial: Modelling the ECM (1)



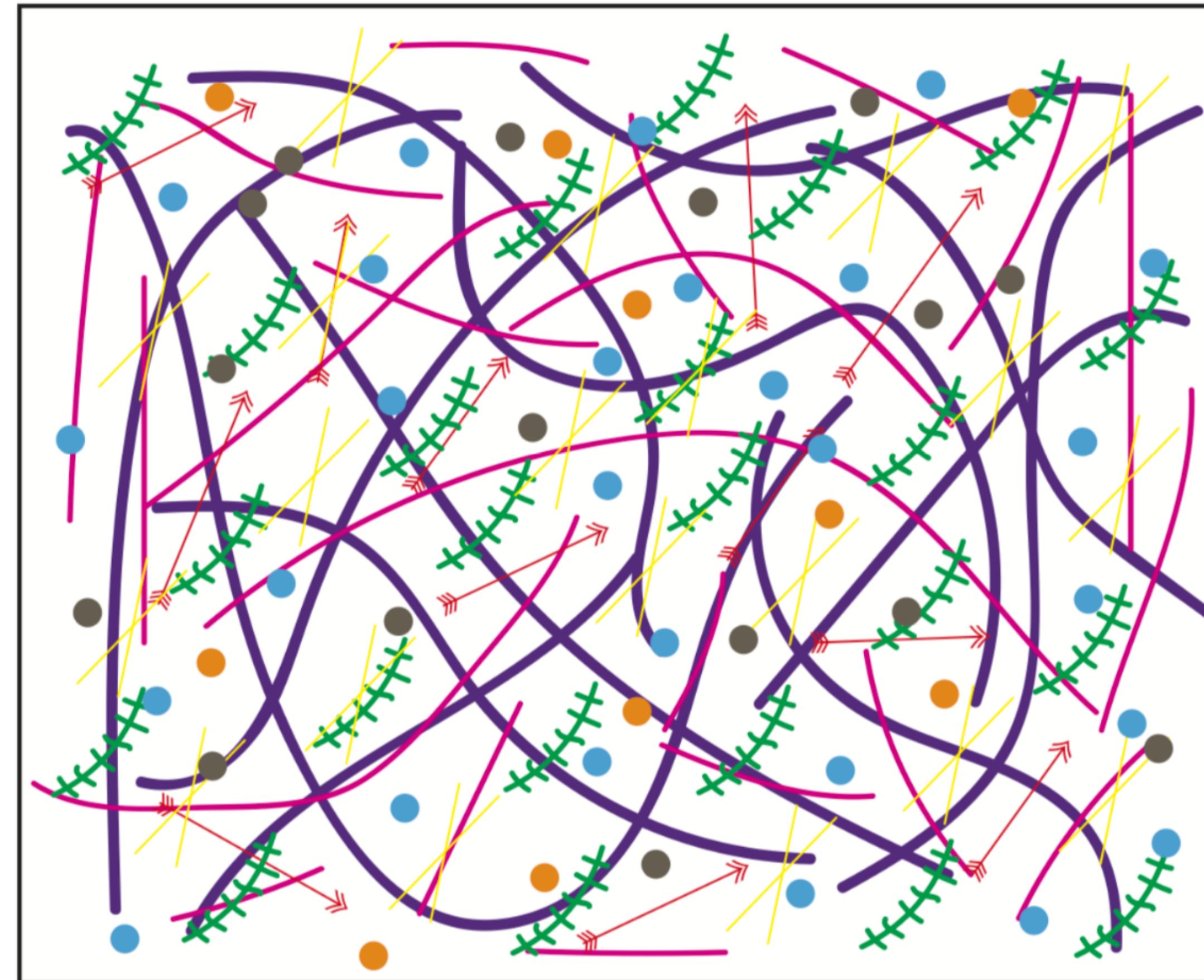
The Extracellular Matrix: How to model structure  
complexity

CECAM/Lorentz Workshop 2023



# Structure of the ECM

- Collagen Type I
- Collagen Type IV
- Fibronectin
- Elastin
- Laminin
- MMPs



# Structure of the ECM

- Collagen Type I

Function: Most abundant protein in the body ~70% of all proteins.  
Acts as structural support with binding partners for other  
ECM components.

Shape: Long, fibril shaped protein



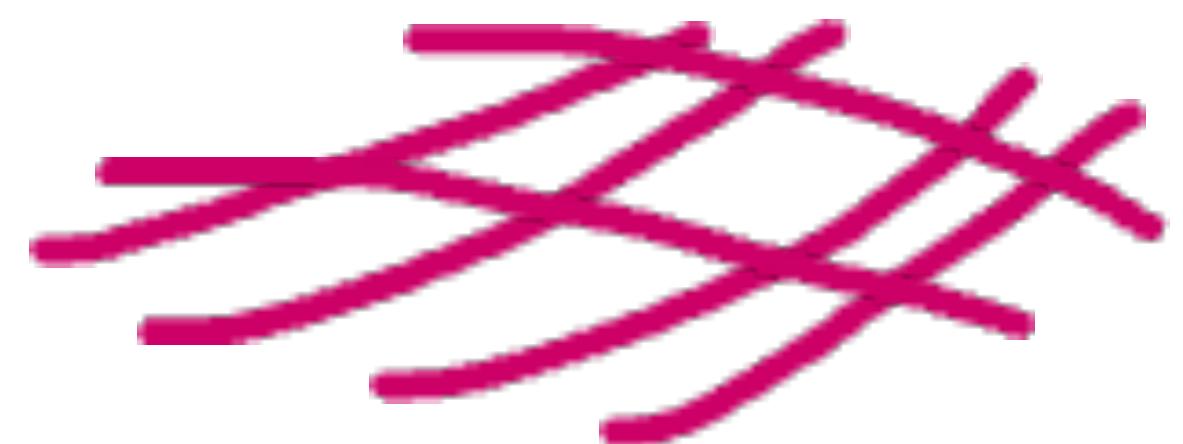
# Structure of the ECM

- Collagen Type IV

Function: A major structural component of the basal laminae (basement membrane).

Provides structure and support to basement membrane.

Shape: Interlinked fibril proteins, sheet-like formation



# Structure of the ECM

- Fibronectin

Function: Can bind to collagens and other proteoglycans.

Aids in the structural framework and contributes to cell-adhesion.

Shape: Smaller, thinner fibre (compared to collagen)



# Structure of the ECM

- Elastin

Function: Major structural protein.

Responsible for flexibility of a tissue.

Shape: Thinner, run single file in formation



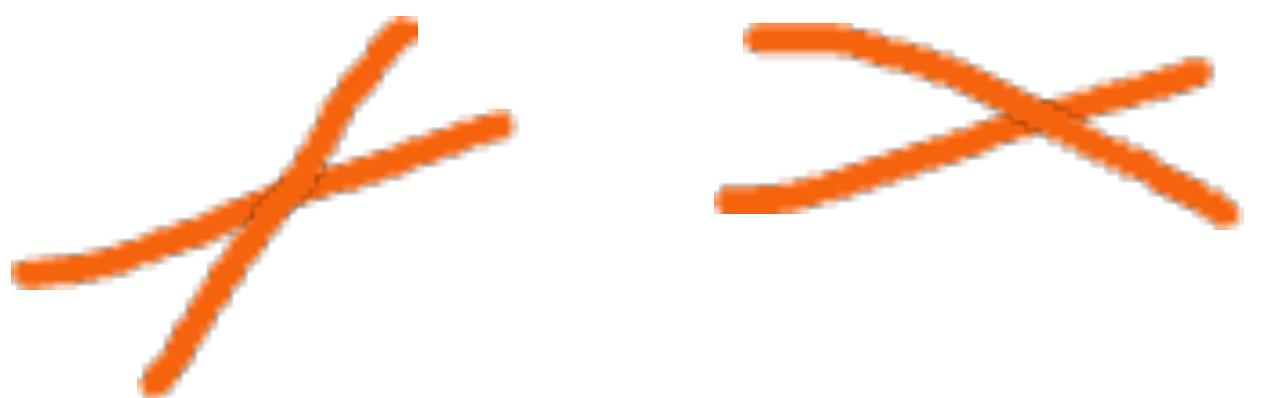
# Structure of the ECM

- Laminin

Function: Provides tensile strength of tissue.

Mainly present in basement membrane.

Shape: Cross shaped molecule

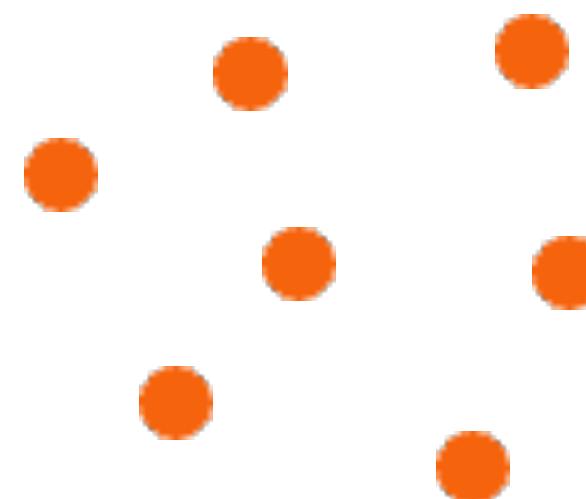


# Structure of the ECM

- MMPs (Matrix Metalloproteinases)

Function: Responsible for degrading the components of the extracellular matrix.

Shape: Small molecules



# Modelling the ECM

Modelling all components of the ECM would be incredibly difficult, especially if we try and mimic their true form.

Instead, we can consider the ECM to act as an underlying substrate.

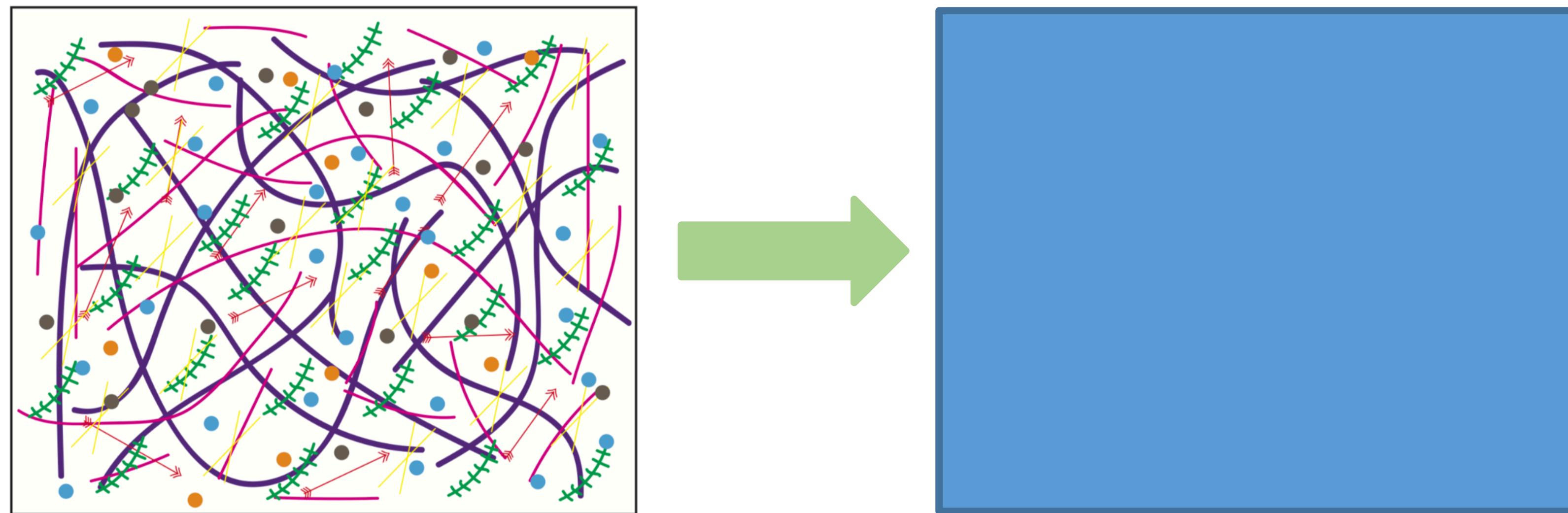
This allows us to think about the ECM as a density of some substrate, and related cell processes can be density dependent, according to the density of the underlying ECM.

# Modelling the ECM

Modelling all components of the ECM would be incredibly difficult, especially if we try and mimic their true form.

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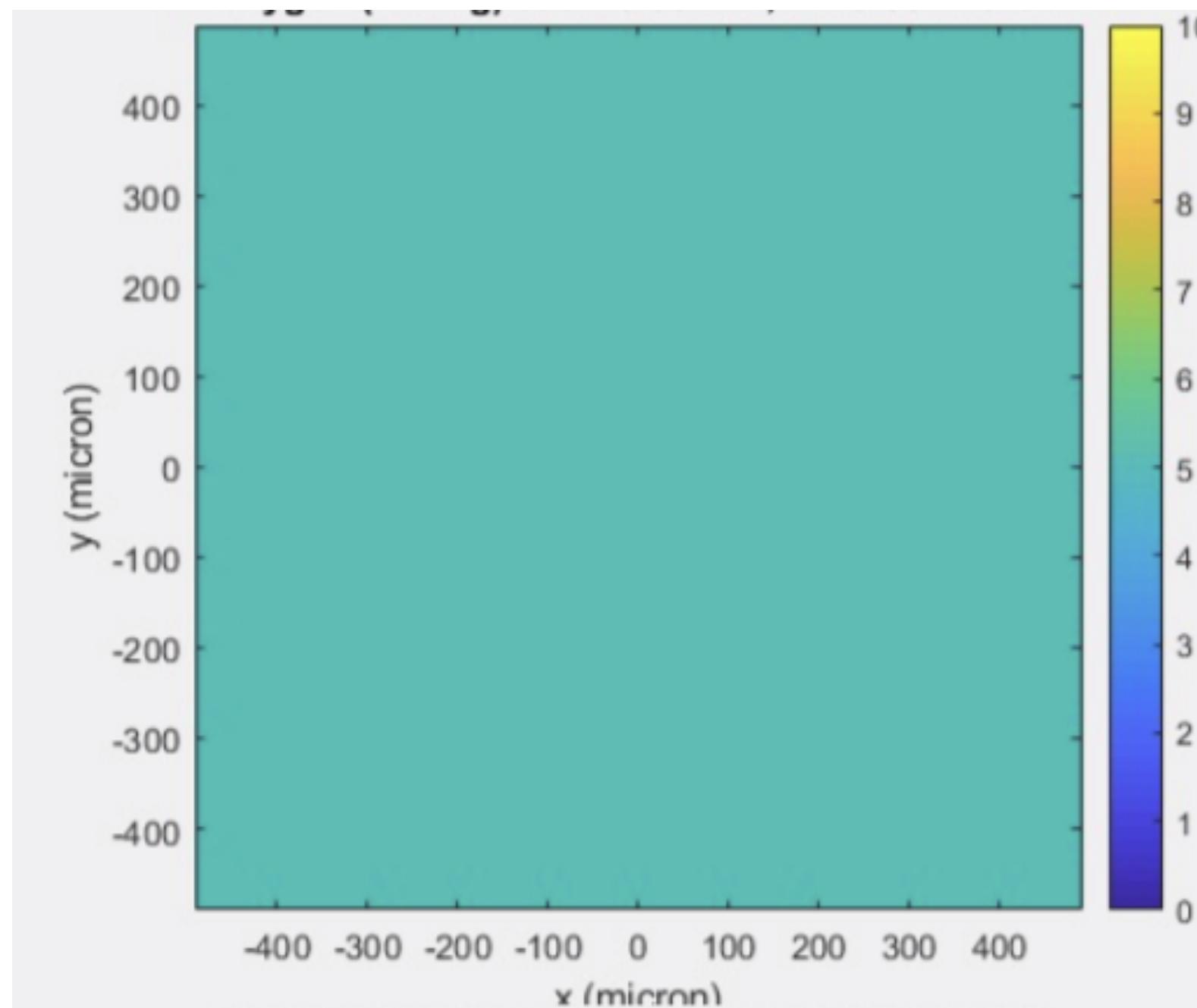
This allows us to think about the ECM as a density of some substrate, and related cell processes can be density dependent, according to the density of the underlying ECM.



# Modelling the ECM - Single Substrate

Let's consider a single, homogeneous substrate to act as proxy for the ECM.

Homogenous ECM



Let's add in a very simple cell dynamic, for example, ECM density dependent migration.

# Building the model

Initial configuration:

Config Basics Microenvironment | Cell Types | User Params | ICs | Run | Plot | Legend

Domain (micron)

Xmin -500 Xmax 500 dx 20  
Ymin -500 Ymax 500 dy 20  
Zmin -10 Zmax 10 dz 20  
 Virtual walls

Times

Max Time 7200 min  
Diffusion dt 0.01 min  
Mechanics dt 0.1 min  
Phenotype dt 6 min

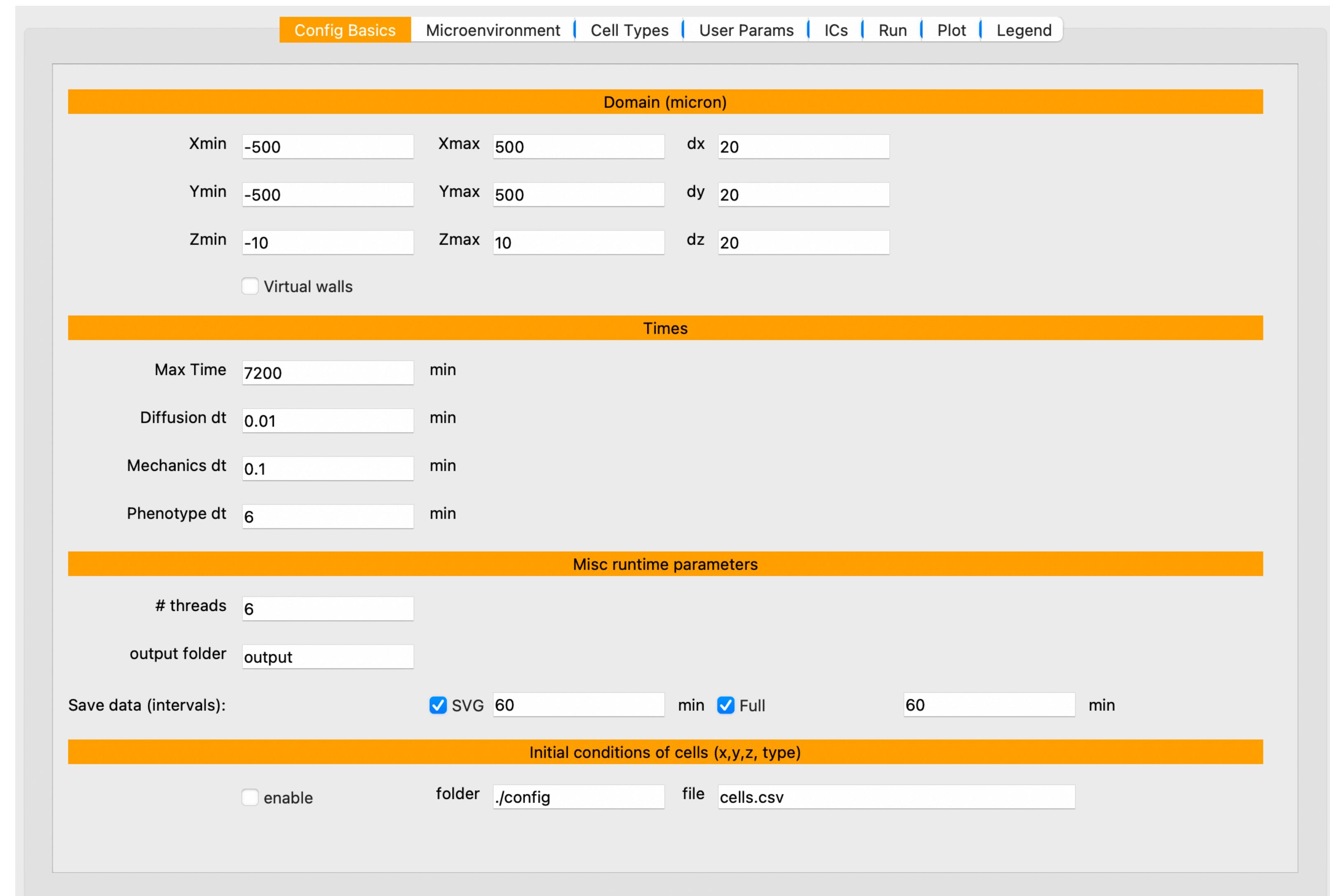
Misc runtime parameters

# threads 6  
output folder output

Save data (intervals):  SVG 60 min  Full 60 min

Initial conditions of cells (x,y,z, type)

enable folder ./config file cells.csv



# Building the model

## Microenvironment settings:

Set up a substrate to act as the underlying ECM

The screenshot shows the 'Microenvironment' tab selected in the top navigation bar. On the left, a sidebar lists substrates: '--- Substrate ---' and 'ECM'. Below the sidebar are buttons for 'New' (green), 'Copy' (green), and 'Delete' (yellow). The main panel contains the following configuration fields:

- diffusion coefficient: 10000.00 micron<sup>2</sup>/min
- decay rate: 0.01 1/min
- initial condition: 60 mmHg
- Dirichlet BC: 60 mmHg  on
- Dirichlet options per boundary:
  - xmin: 60  on
  - xmax: 60  on
  - ymin: 60  on
  - ymax: 60  on
  - zmin: 60  on
  - zmax: 60  on
- For all substrates:
  - calculate gradients
  - track in agents

# Building the model

## Cell behaviors:

We will assume the cells are migrating towards the ECM

The image displays two side-by-side screenshots of the PhysiCell software interface, specifically the 'Cell Types' tab.

**Top Screenshot (Cycle Tab):**

- Cell Type: **cell**
- Transition Type: **transition rate(s)** (selected)
- Phase: **live cells**
- Rate: **phase 0->0 transition rate** **0.00072** **1/min**

**Bottom Screenshot (Motility Tab):**

- Cell Type: **cell**
- Motility Settings:
  - speed**: 0.1 micron/min
  - persistence time**: 1 min
  - migration bias**: .5
  - enable motility**: checked
  - 2D**: checked
  - Chemotaxis**: selected (highlighted in orange)
  - enabled**: checked
  - ECM**: selected (highlighted in orange)
  - towards**: selected (radio button)
  - against**: unselected (radio button)

# Building the model

User parameters:

The screenshot shows the PhysiCell software interface with the "User Params" tab selected. The table displays the following parameters:

Name	Type	Value	Units
random_seed	int	0	dimensionless
number_of_cells	int	100	none

Buttons at the top include "Append 10 more rows" and "Clear selected rows".

# Plotting in Jupyter

We can plot the .xml output files using Jupyter Notebooks.

We'll grab the Python-loader and get the source code:

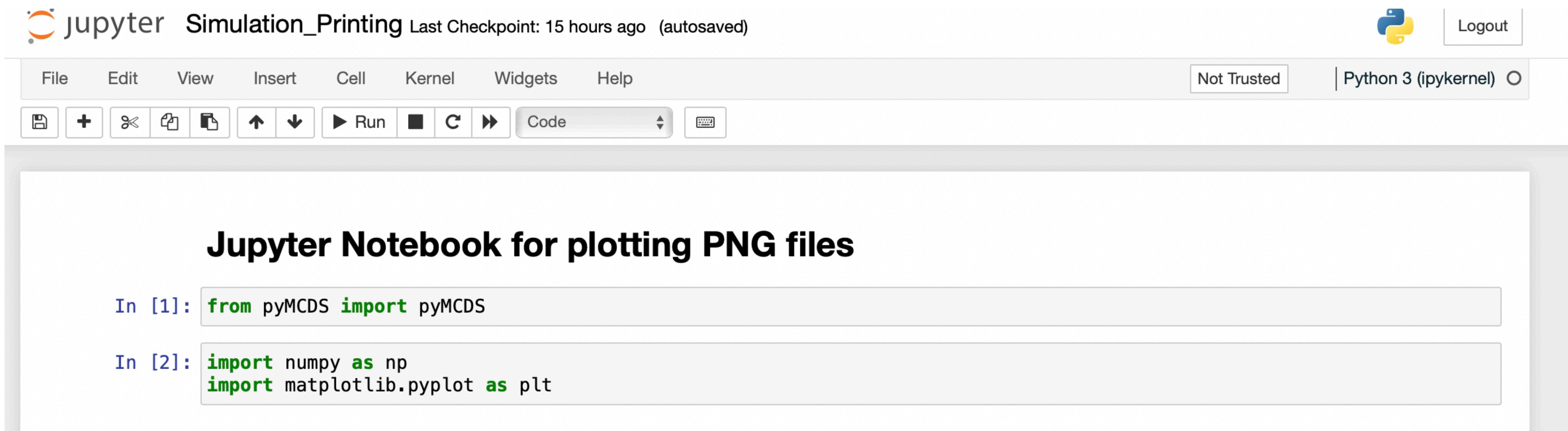
<https://github.com/PhysiCell-Tools/Python-loader>

Copy the following Python file (end in .py) to the root of PhysiCell:

- `pyMCDs`

# Plotting in Jupyter

We can plot the .xml output files using Jupyter Notebooks.

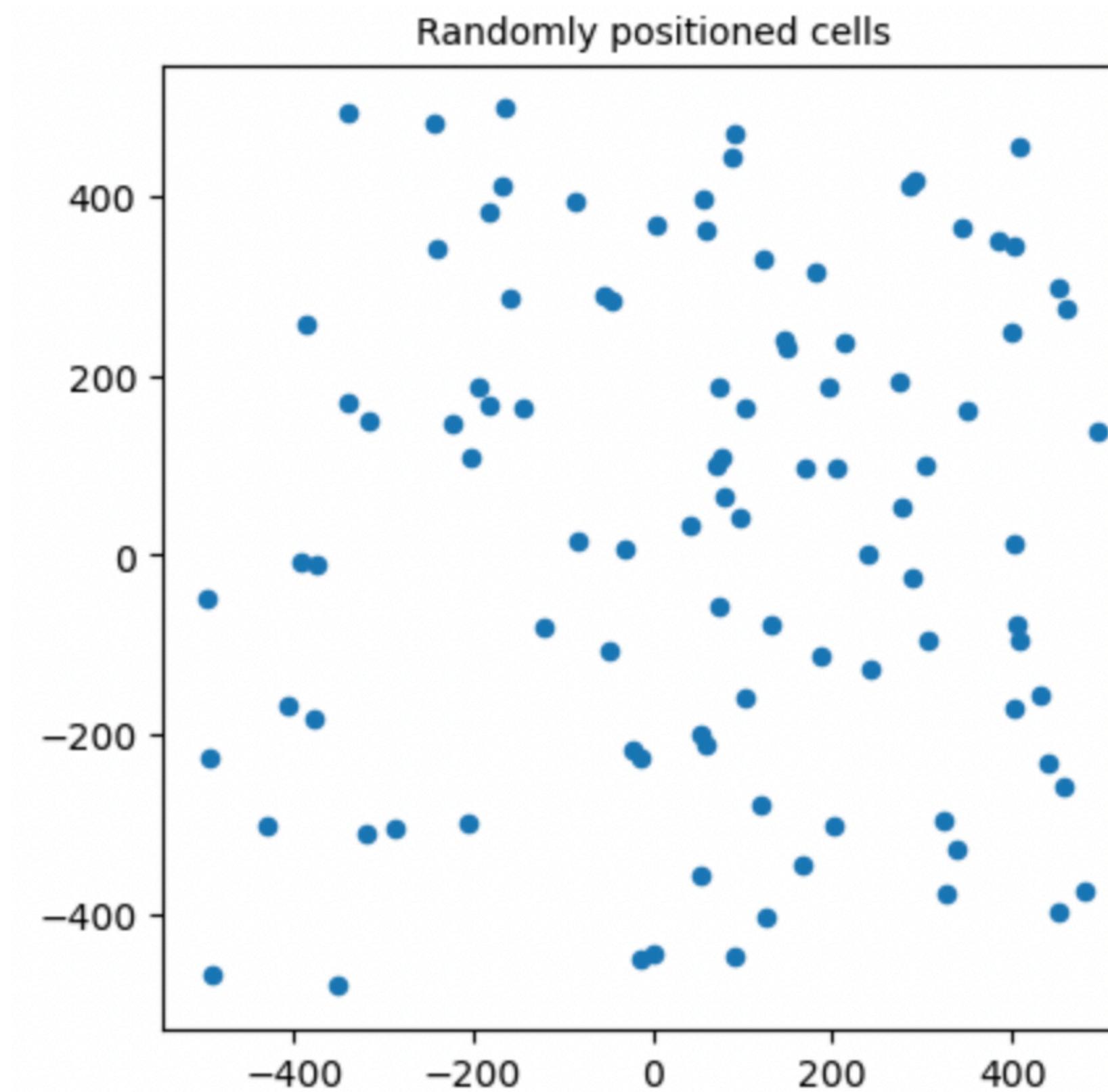
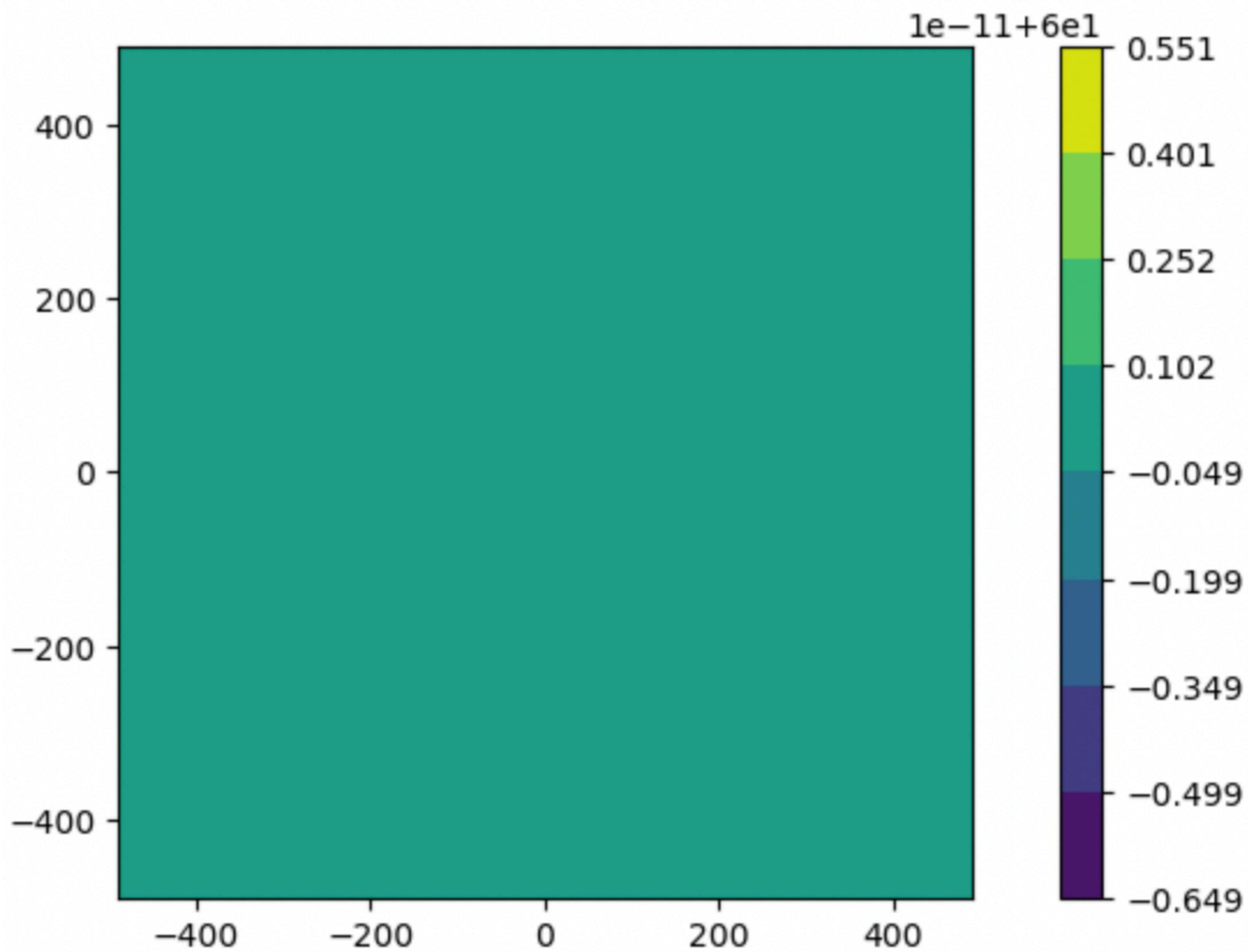


The screenshot shows a Jupyter Notebook interface with the following details:

- Title Bar:** jupyter Simulation\_Printing Last Checkpoint: 15 hours ago (autosaved)
- Toolbar:** File, Edit, View, Insert, Cell, Kernel, Widgets, Help, Not Trusted, Python 3 (ipykernel)
- Buttons:** Save, New, Cell Type, Run, Cell Kernel, Cell Mode, Code, Keyboard Shortcuts
- Section Header:** Jupyter Notebook for plotting PNG files
- In [1]:** `from pyMCDS import pyMCDS`
- In [2]:** `import numpy as np  
import matplotlib.pyplot as plt`

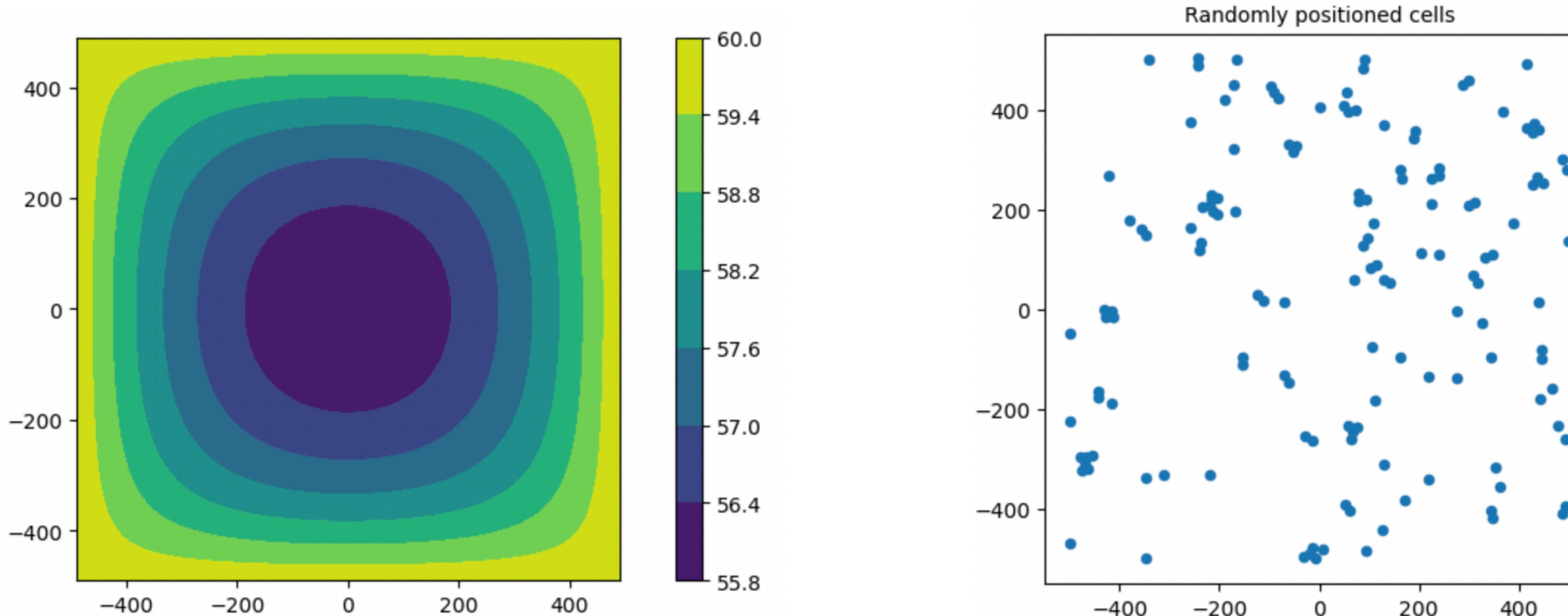
# Single Substrate - Homogeneous

Let's consider a single, homogeneous substrate to act as proxy for the ECM.



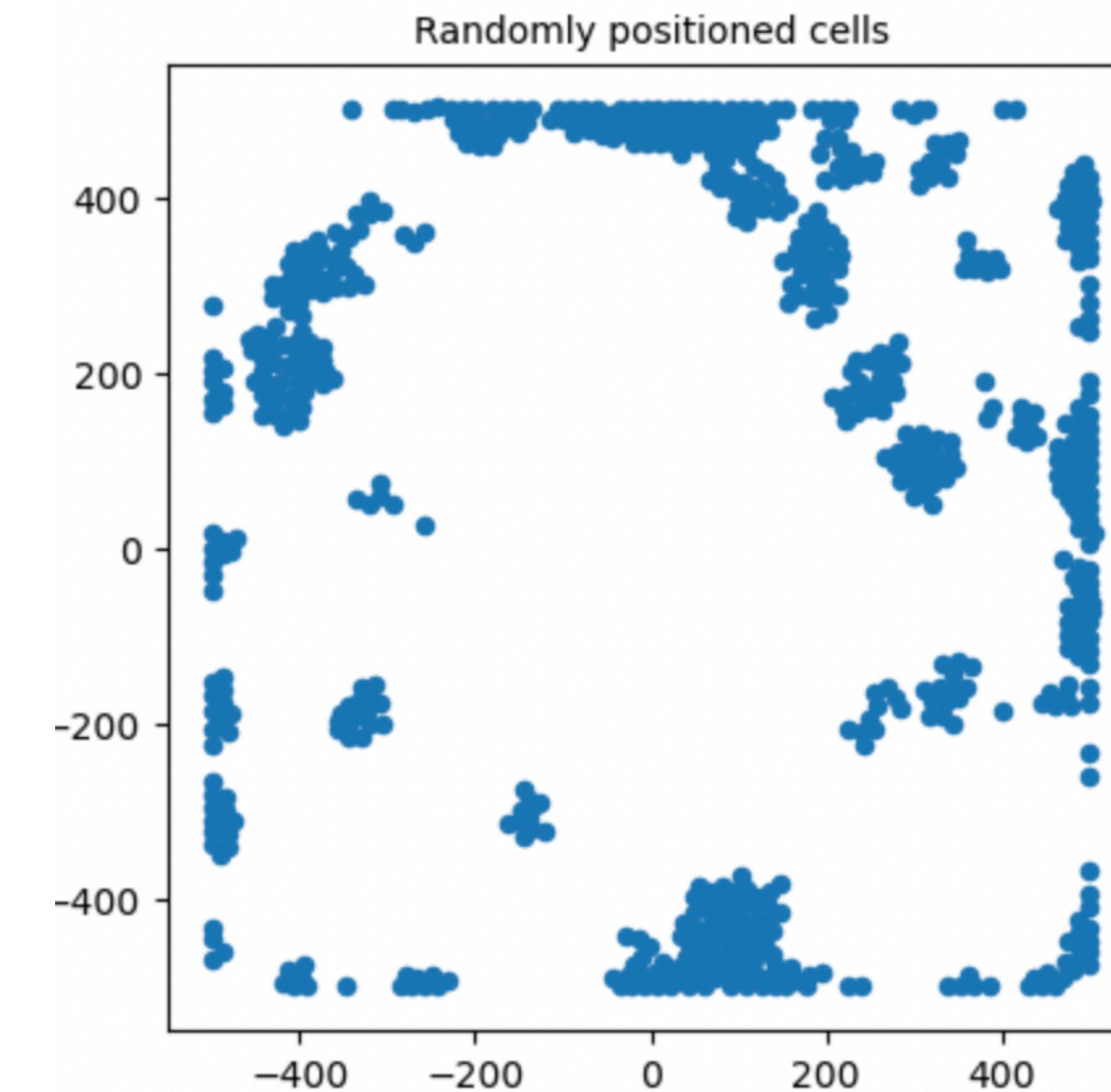
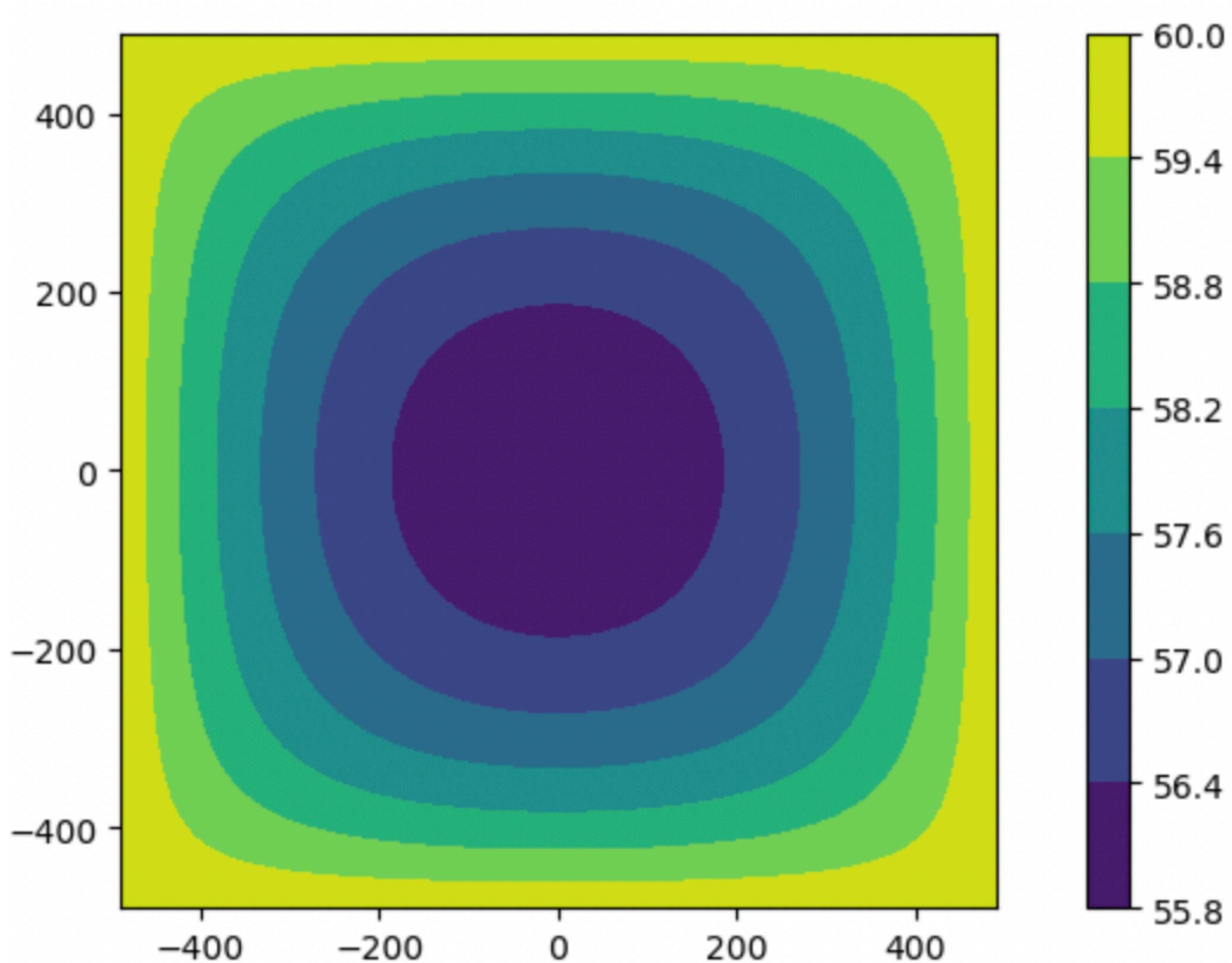
# Single Substrate - Homogeneous

- After 10 time steps



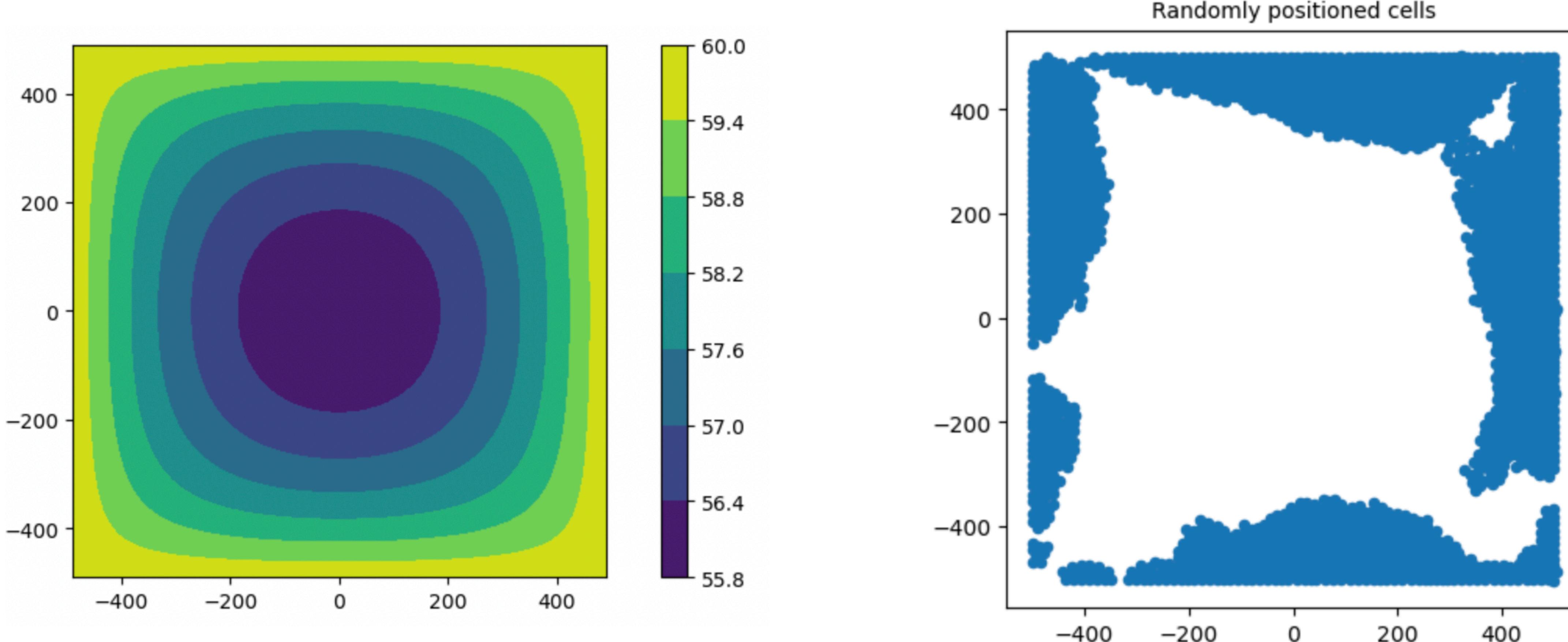
# Single Substrate - Homogeneous

- After 60 time steps



# Single Substrate - Homogeneous

- After 100 time steps



# Single Substrate - Degradation

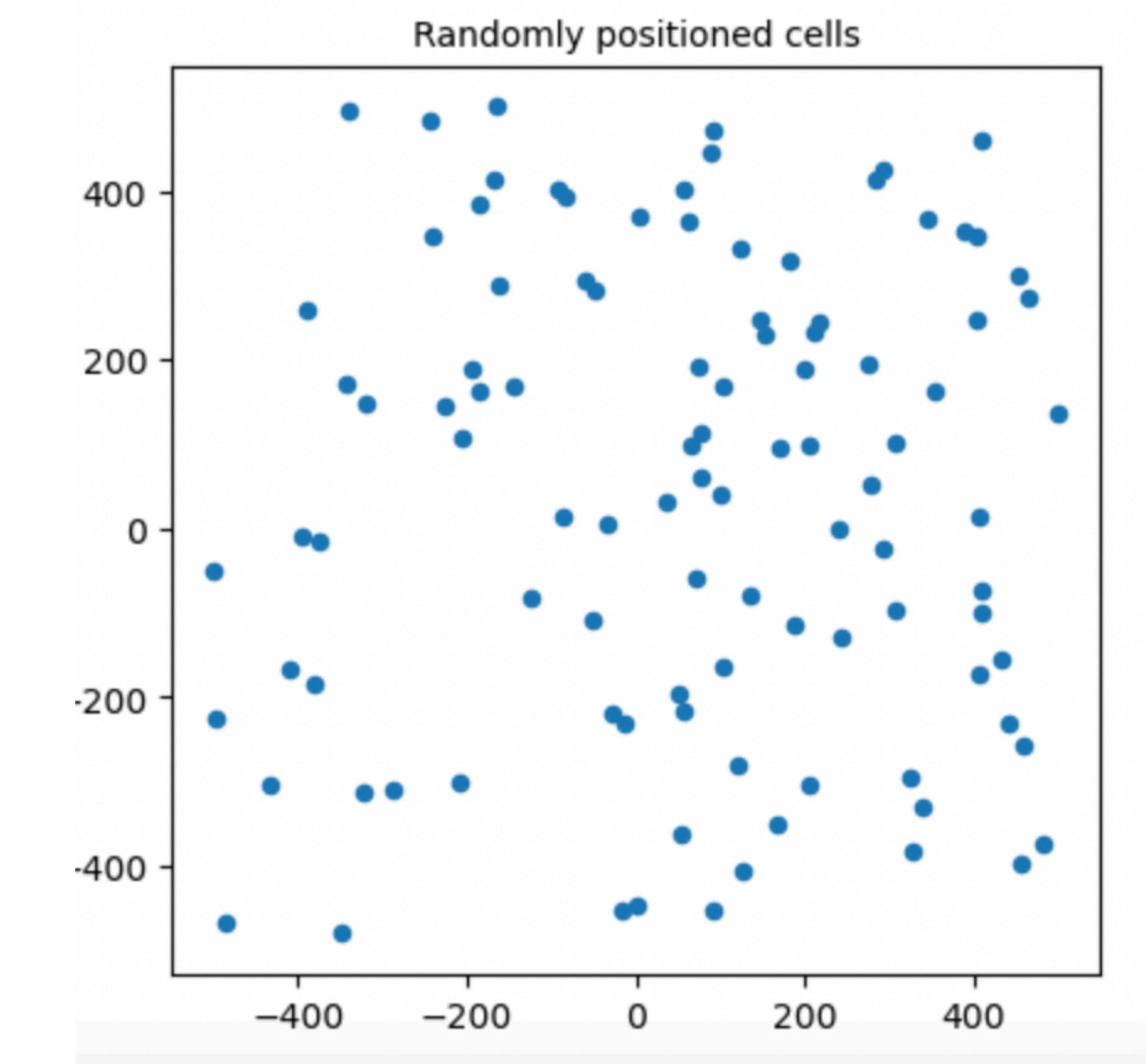
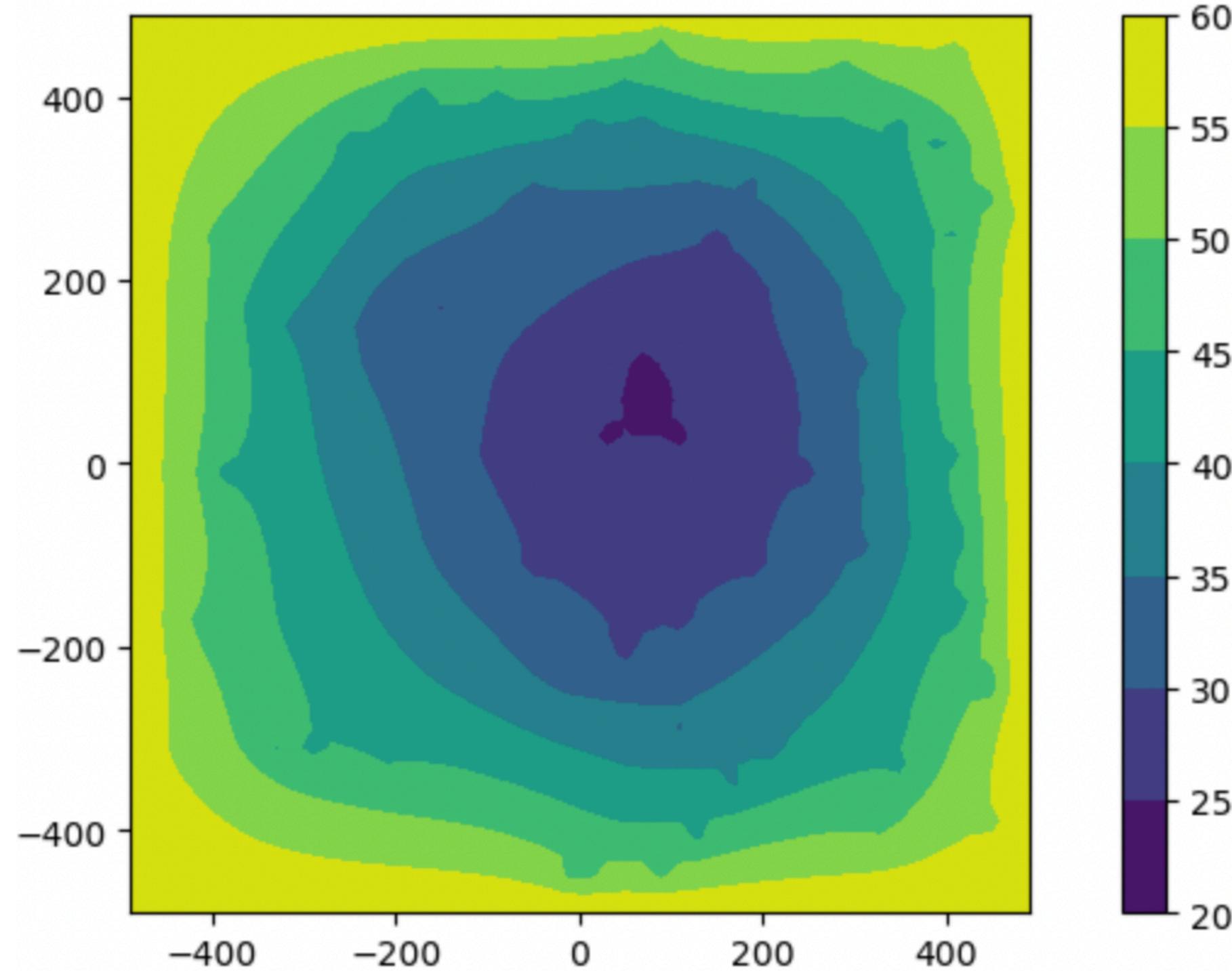
Let's now include ECM degradation term (use uptake as a proxy).

The screenshot shows the PhysiCell software interface. At the top, there is a navigation bar with tabs: Config Basics, Microenvironment, Cell Types, User Params, ICs, Run, Plot, and Legend. The 'Cell Types' tab is active, highlighted in orange. Below the navigation bar, there is another set of tabs for a specific cell type: Cycle, Death, Volume, Mechanics, Motility, Secretion, Interactions, Intracellular, and Custom Data. The 'Secretion' tab is also active here. On the left, there is a sidebar labeled '--- Cell Type ---' which contains a dropdown menu with the option 'cell' selected. The main panel displays parameters for the 'ECM' category under the 'Secretion' tab. These parameters are: secretion rate (0 1/min), target (1 sub. density), uptake rate (0.5 1/min), and net export rate (0 total/min). The entire interface has a light gray background with white and orange highlights for the active tabs.

# Single Substrate - Degradation

Let's now include ECM degradation term (use uptake as a proxy).

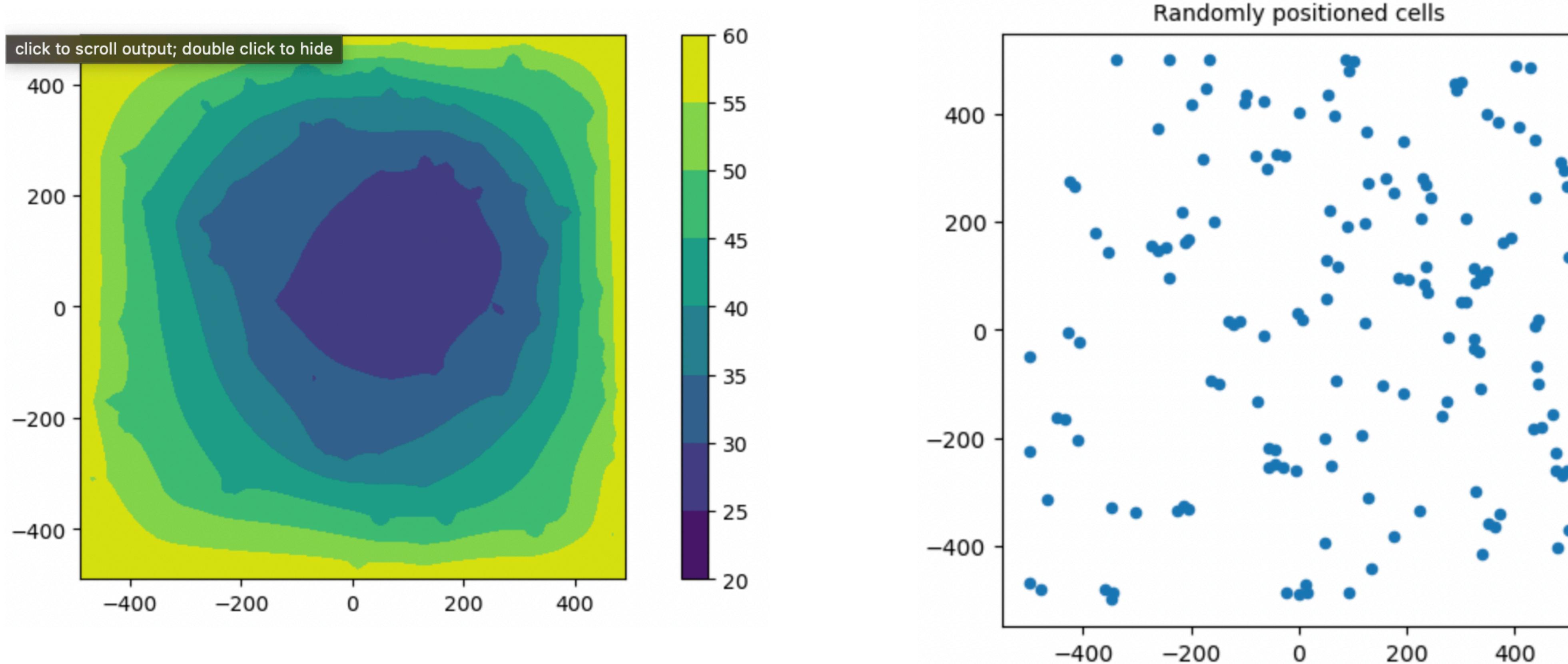
- After 1 time step



# Single Substrate - Degradation

Let's now include ECM degradation term (use uptake as a proxy).

- After 10 time steps



# Single Substrate - Remodelling

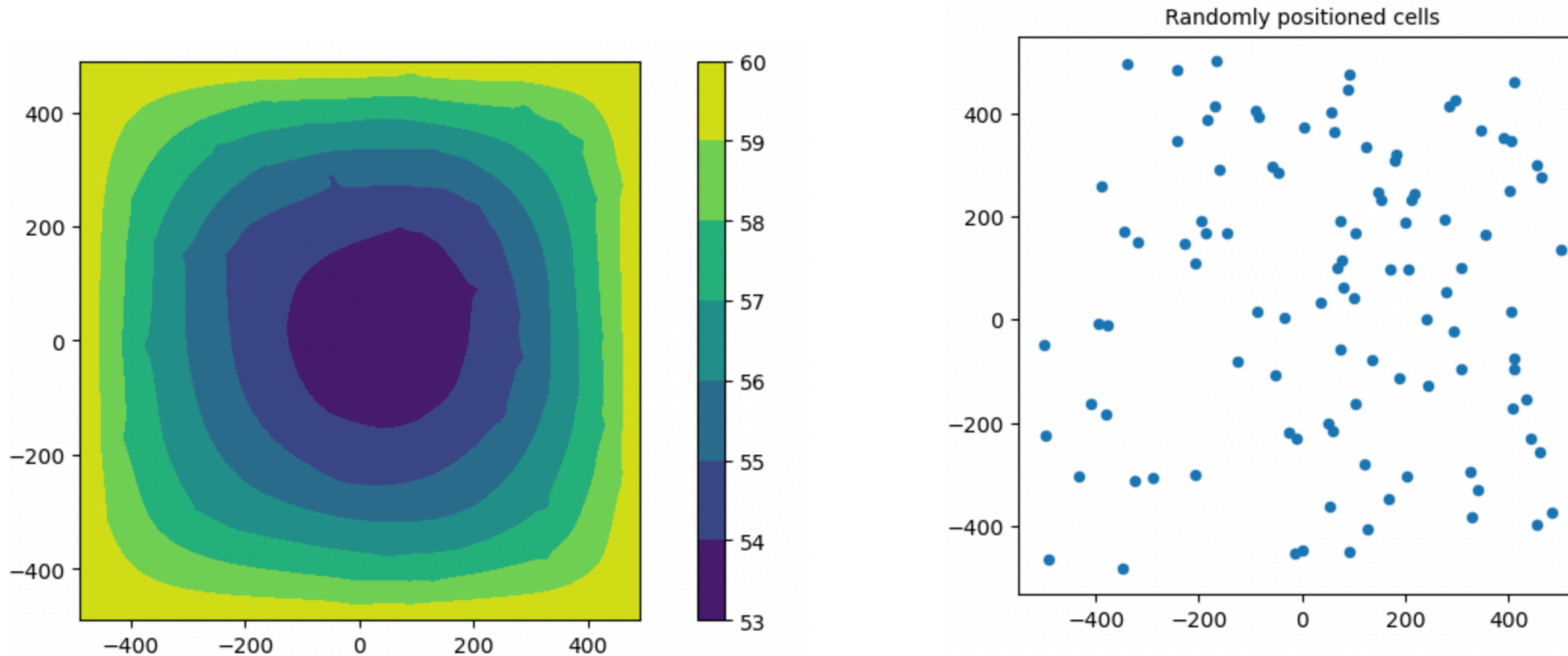
Let's now include ECM degradation term (use secretion as a proxy)

The screenshot shows the PhysiCell software interface. At the top, there are two tabs: 'Config Basics' and 'Microenvironment'. Below them is a main navigation bar with several tabs: 'Cell Types' (highlighted in orange), 'User Params', 'ICs', 'Run', 'Plot', and 'Legend'. Under 'Cell Types', there is a dropdown menu titled '--- Cell Type ---' with 'cell' selected. To the right of this, there is another navigation bar with tabs: 'Cycle', 'Death', 'Volume', 'Mechanics', 'Motility', 'Secretion' (highlighted in orange), 'Interactions', 'Intracellular', and 'Custom Data'. The 'Secretion' tab is currently active. Below these tabs, there is a dropdown menu set to 'ECM'. Underneath the dropdown, there are four parameter inputs: 'secretion rate' with value '0.5' (unit: 1/min), 'target' with value '1' (unit: sub. density), 'uptake rate' with value '0' (unit: 1/min), and 'net export rate' with value '0' (unit: total/min).

# Single Substrate - Remodelling

Let's now include ECM degradation term (use secretion as a proxy).

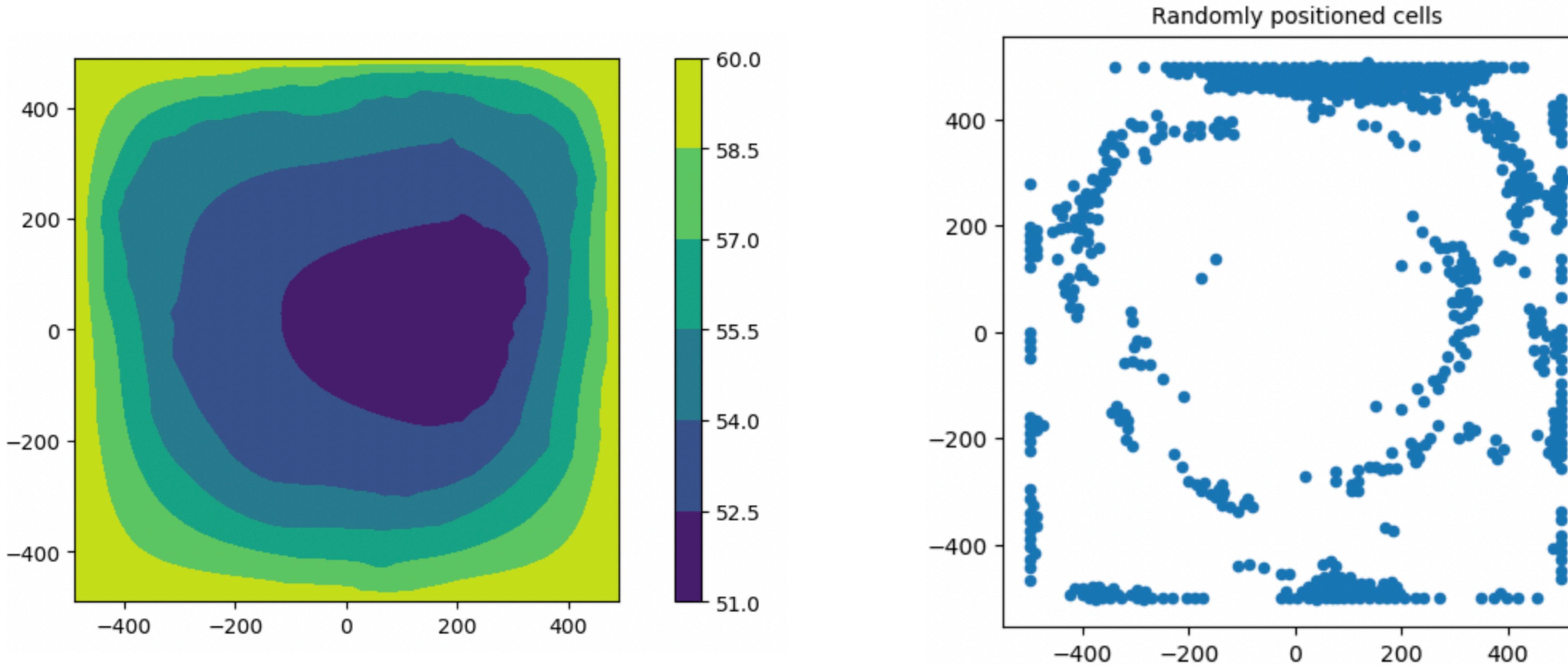
- After 1 time step



# Single Substrate - Remodelling

Let's now include ECM degradation term (use secretion as a proxy).

- After 60 time steps



# Advancing models of the ECM

Let's consider a different ECM structure, namely, a heterogeneous environment.

A heterogeneous environment is one in which the substrate density is nonuniform.

This can take two forms:

- Considers several ECM components.
- Considers regions of different density.

This can act as a proxy for describing a stiff (high density) or loose (low density) extracellular matrix.