Cell colony predictor (using *Cell2DProl* toolkit)

Abstract

Notch signaling pathway is significant for tissue development and pattern formation. Those phenomena may not be observed on a signal cell, but signal cell also have the ability to generate macroscopic properties (e.g. spatial patterns, system dynamics, and network structure attributes). However, a proper model considering both spatial arrangement of cells and chemical reaction happening in and across cells haven't been reported yet. Here we introduce a framework to simulate cell colony based on signal cell properties, which makes it easy to transplant our ENABLE for macroscale systems [link here for software]. This part will illustrate how we use stochastic process and dynamic systems to predict cell-cell interaction from a community perspective. For more detail of our code implementation, please refer to our reusable toolkit War Predictor [link to our software].

Introduction

The cell is the element structural, functional, and biological unit of all known independent living organisms. A cell is the smallest unit of life. Cells are often called the "building blocks of life".

In our ENABLE project, we want to engineer single cells to transmembrane binary logic gates. The concept of logic gate which offers clues for further higher-layer system design [for more details, please refer to our project design page]. Some models are built for single cell property prediction.

However, many properties at a colony level, makes a difference. For example, if you want to engineer a CAR-T cell for therapeutics, we can not only pay attention to engineered cells, but also cancer cells and all kinds of normal cells in the body of a patient. Only so can we possibly develop targeted therapies without taking much side effect. What's more, when it comes to development and morphogenesis, adhesion and control among cells plays an important role in differentiation and pattern formation.

Here we introduce a model to describe multi-cell interactions and evolution with a population perspective. Using cellular automaton for cell cultures, ordinary differential equation for cellular chemical reactions, and Metropolis sampling for cell movement, our model is proper to simulate multiscale system for macroscopic properties (e.g. the distribution of protein expression in population). Our model links tiny cells to huge colonies, which offers clues for an ecological perspective.

Method

Cellular automaton for cell cultures

We abstract cell colonies into the grids of a cellular automaton, and a single cell can be

represented by a lattice in the grid. Each cell has some private attributions (like index, lifespan, kind and quantity of membrane proteins, age, and cellular chemicals) and some neighbors (each neighbor may be cell, barrier, or extracellular matrix).

However, for the sake of being consistent with biological reality, the rules introduced in our model are unlike usual rules of cellular automaton. Some of these rules are as follows.

1) Division.

Some parameters control this process.

Parameter	Explanation
Cycle	A threshold for cell to divide, refers to cell cycle.
Prol	A float number, records the aging of cells. When Prol > Cycle, the division may happen.
p_p	The growth rate of Prol in respect of time, which depends on observed cell only.
r_p	A float number, measures how much neighboring cell affects the growth rate of Prol in respect of time. It depends on neighboring cells.
r_r_p	A float number, measures how much cell react to neighbor cells' impact on proliferation rate. It depends on both observed cells and neighboring cells.
r_p	An integer, measures the migration ability of observed cells. r_p indicates that when Prol > Cycle, how can observed cells make space for division (if making space fails, the cell have to wait until accessible space appears.

2) Death.

Some parameters control this process.

Parameter	Explanation
Vitality	A float number, records the aging of cells. When Vitality < 0, the observed cell choose to go die.
p_d	The decrease rate of Vitality in respect of time, which depends on observed cell only.
r_d	A float number, measures how much neighboring cell affects the growth rate of Prol in respect of time. It depends on neighboring cells.
r_r_d	A float number, measures how much cell react to neighbor cells' impact on proliferation rate. It depends on both observed cells and neighboring cells.

Ordinary differential equation for cellular chemical reactions

Previous part seems to clarify the birth-death process of our cell colony. However, for a meaningful cell colony simulation, some of the parameters listed above may change during simulation with some chemical reactions happening. In our modeling, we use ODE (ordinary differential equation) to model chemical reactions in cells, which makes the simulation for cell colony more tunable.

For code implementation, Forward Euler method is used for numerical solutions.

Metropolis sampling for cell movement

How to simulate cell migration properly? We use Metropolis sampling to solve this problem. Assume that all the cells are smart creatures, so they may try to find an optimized position via migration. We define the general energy E as a function of cell site s

$$\mathrm{E} = \mathrm{f}(\mathrm{s}|\mathrm{self}, \mathrm{neighbors}, \mathrm{enviroment})$$

Here neighbors refer to the state of neighboring lattices, environment refers to some properties attributed by the environment (for example, nutrition gradient in a culture medium). A series of random walk route is generated by sampling, but whether such a route is executed is determined by

$$\mathrm{p}(\mathrm{executed}) = \begin{cases} 1, for\ \ \Delta E < 0 \\ e^{-\beta \Delta E}, for\ \ \Delta E > 0 \end{cases}$$

Here β is a constant related to general temperature, measuring the possibility for cell to walk randomly.

Results

Macroscopic properties can be tuned by atom-level parameters.

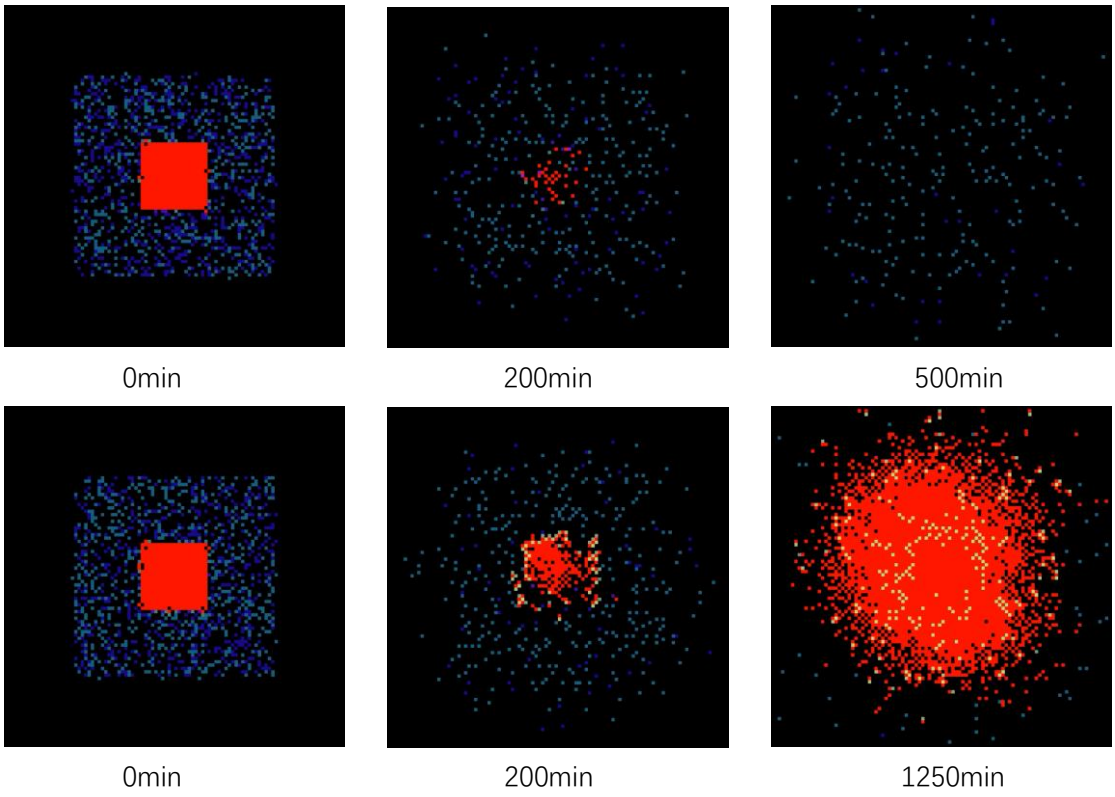

Fig. 1 | A therapeutic demo from the software. By tuning chemical reactions in engineered cells (blue and green lattices) to wipe out cancer cells (red lattices), bifurcation of system occurs. The label below each image refers to the simulation time.

Our model fits ecological model well.

For some certain parameters, cellular chemical reactions affect the whole cell colony in a

steady way, so the cell colony evolves in an ecological manner. For example, Fig. 2 shows how the system in Fig.1 evolved. The evolution of system fits an exponential law in steady state, satisfying ecological models well; while some other manners can be observed at unstable state, indicating the unsteady state this system in.

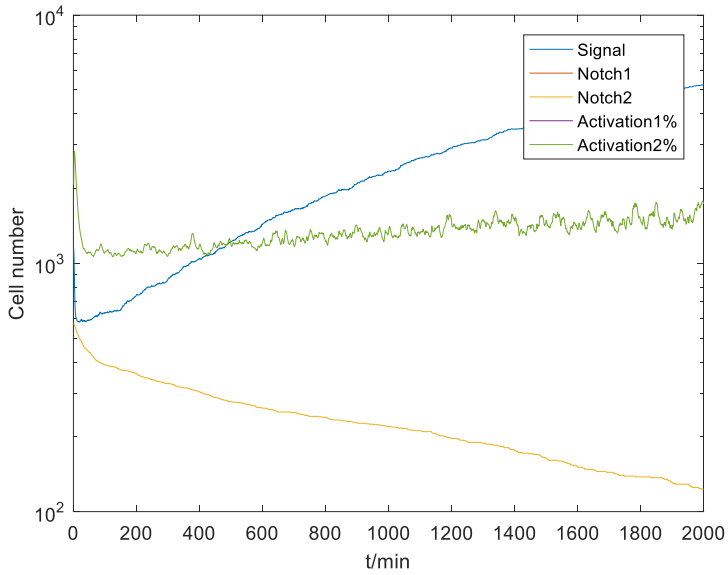

Fig. 2 | Cell census for system in Fig.1. Signal refers to the number of cancer cells, Notch1 refers to cells with Notch1 receptors, Notch2 refers to cells with Notch2 receptors, Activation1% and Activation 2% refers to activation percentage of those cells armed with correlated receptors (multiplied by 100).