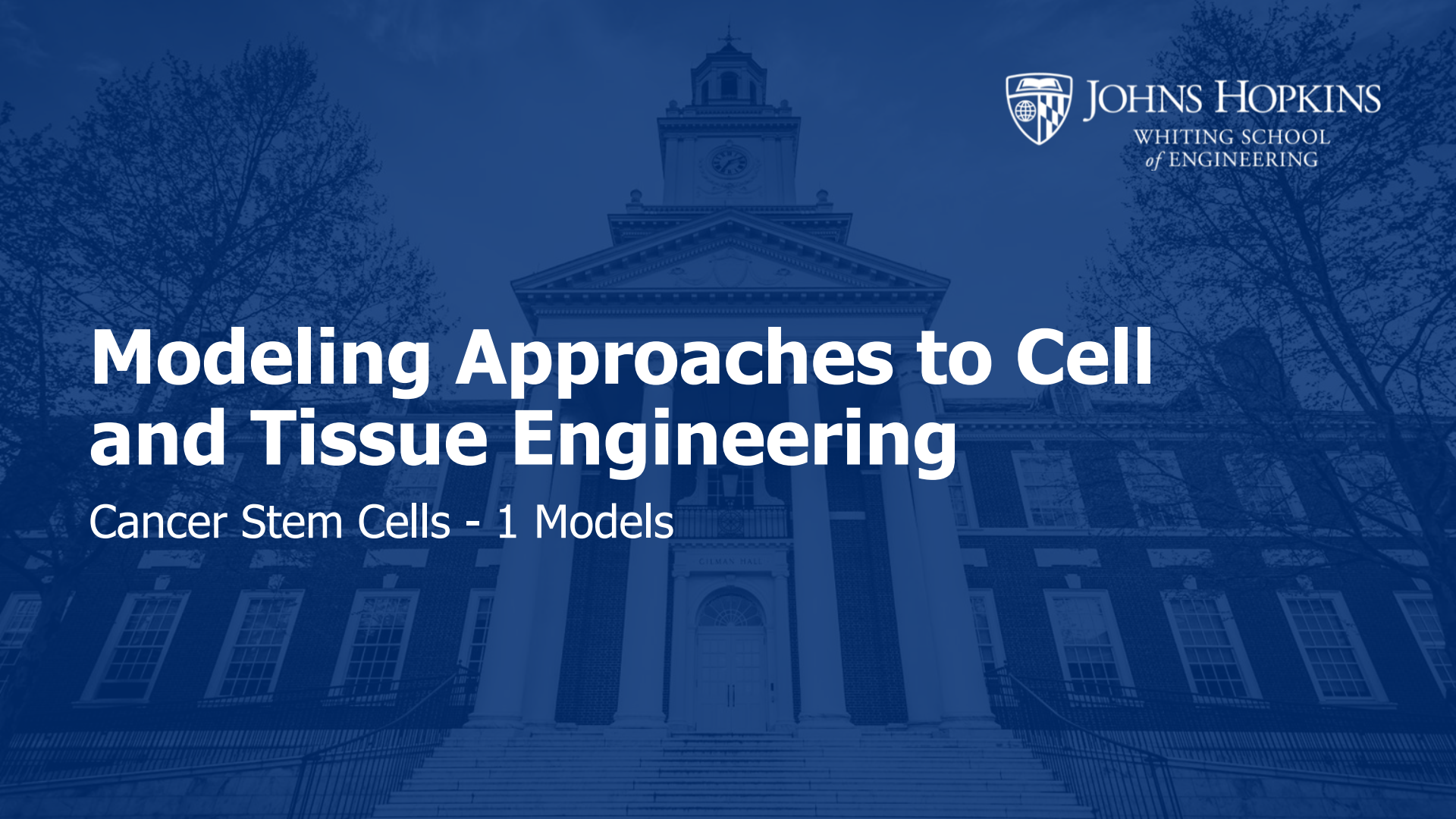

Modeling Approaches to Cell and Tissue Engineering

Cancer Stem Cells - 1 Models

Cancer Stem Cells - 1 Models

Alexander A. Spector (From Vainstein et al., 2012)

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CA Structure

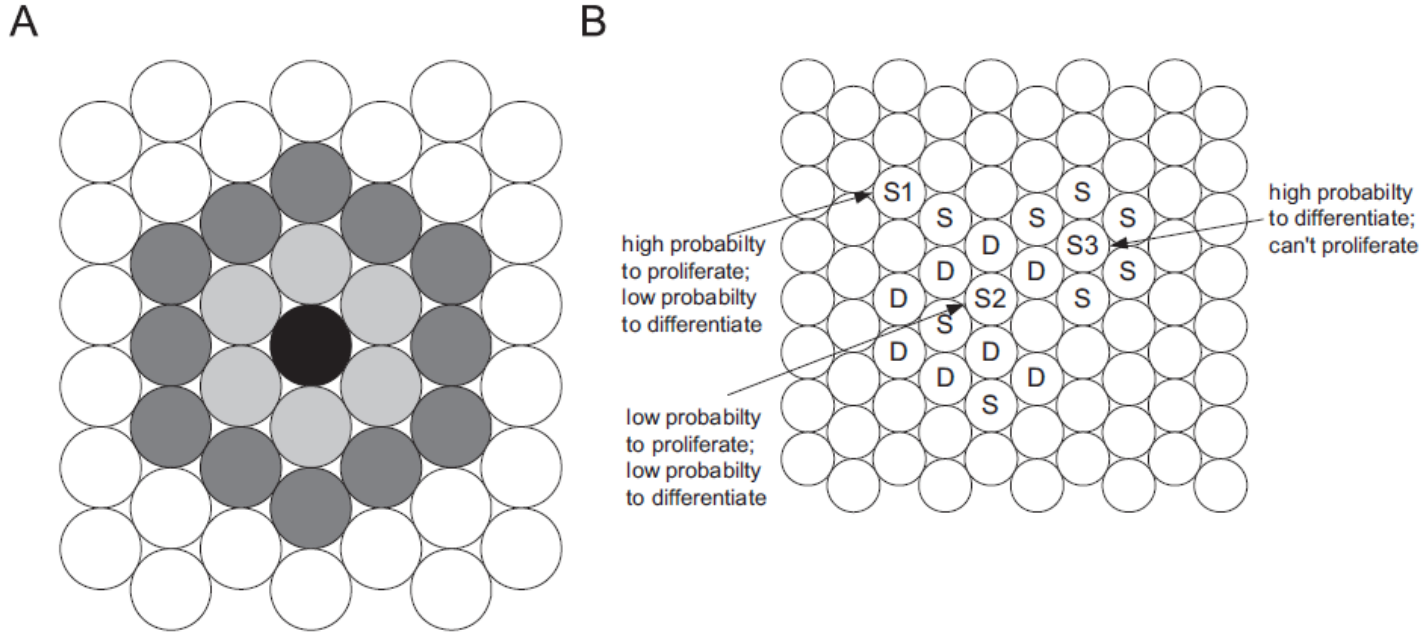

Fig. 1. An illustration of the CA structure, definition of neighborhood and CSC regulation. (A) The cells of the CA are circles tightly positioned on the plane. The six cells adjacent to a central (black) cell are first-degree neighbors (marked in light grey). The 12 second-degree neighbors are marked in darker grey. (B) Illustrative examples of CSC decisions. A CSC marked as S1 has only one stem neighbor (marked as S); therefore, it is not likely to differentiate and has a relatively high probability to enter the cell cycle. The CSC marked as S2 is mostly surrounded by DCs (marked as D); therefore, it also has low probability to differentiate, but also low probability to enter the cycle (having only one vacant adjacent site). The CSC marked as S3 is mostly surrounded by CSCs (marked by S) and thus has higher probability differentiate, but cannot enter cell cycle, until the adjacent DC dies.

Automata States

The model proceeds by discrete time steps. At a given time step, each automata cell contains either a single cell or a vacant space. The state of each automata at each time step consists of the following variables:

a) The type of automata cell (a non-cycling CSC, a cycling CSC, a DC, or an empty space);
b) The age (for a DC);
c) The stage of progression through the cell cycle (for a cycling CSC).

The initial state of the model comprises the states of all automata cells at time zero. To simulate the model, a random ordering on the set G is chosen. At each discrete time step, the automata cells undergo several sequential stages of processing according to the following rules.

Automata Stages

At each stage, all automata cells are processed one after the other, according to the predetermined order. In the first stage, each cell is processed for the decision of DC death; each DC that dies is replaced with an empty space. Next, each cell is processed for the decision of CSC differentiation; each CSC that differentiates is replaced with a DC. Then, each cell is processed for the decision of non-cycling CSCs to enter the cell cycle. The ability of a CSC to enter the cell cycle is contingent on the availability of a neighboring empty space into which the CSC will later be able to divide. Then, every cyclinging cell that has reached the final step of the division stage of the cell cycle turns into two non-cycling CSCs. When a CSC divides, one of the two daughter cells remains in the site of the original CSC, and the other moves into a neighboring empty site. In order to prevent the same site from being occupied by two newborn cells, when a CSC enters the cell cycle, one of its empty neighboring automata cells is randomly chosen to be reserved for each of the daughter cells. All other CSCs subsequently consider the reserved automata cell to be non-empty, and thus they are unable to divide into it. In the final stage of processing, the counters for the ages of DCs and for the cell cycle progression of cycling CSCs are increased by one.

CSC Differentiation & Proliferation Decision Processes

The CSC differentiation and proliferation decision processes are formally implemented in the model as follows.

CSC differentiation decision: If A is non-cycling CSC in our model, we calculate the weighted number ("density") of CSCs in its neighborhood:

$$den(A) = N_1 + \frac{N_2}{2k}$$

Where N1 is the number of first-degree CSC neighbors of A, i.e., neighboring automata cells occupied by CSCs; N2 is the number of second-degree CSC neighbors, i.e., the automata cells that are neighbors of A's neighbors (but are not A's first-degree neighbors) and are occupied by CSCs; k is the damping coefficient that reduces the effect of the second-degree neighbors.

Probability of the Cell to Differentiate

Then, the probability p_d of the cell A to differentiate at the current time step is determined by a sigmoid-like function:

$$p_d = p_{\max} - \frac{a^m \left(p_{\max} - p_{\min}\right)}{a_m + \left(den\left(A\right)\right)^m}$$

Here $p_{\min}$ is the minimal probability of differentiation (reached when the number of neighboring CSCs is zero), $p_{\max}$ is the maximal probability of differentiation (reached when the number of neighboring CSCs is infinite), hereafter termed "maximal differentiation rate", a is the CSC density in the neighborhood that gives the probability $0.5\left(p_{\min} + p_{\max}\right)$, and m is function steepness. In this work, $p_{\min}$ was set to zero and m to 5.

CSC Decision to Enter the Cell Cycle

CSC decision to enter the cell cycle: The probability of a non-cycling CSC to enter the cell cycle at a given time step is calculated as follows:

$$p_c = 1 - (1 - p_0)^n = np_0 + o(p_0)$$

Where n is the number of vacant automata cells in the neighborhood of a given cell, calculated similar to den(A), and is a parameter, representing the basic probability to enter the cell cycle (i.e., the probability to enter the cycle when only one empty neighboring automata cell is available), hereafter referred to as the "proliferation rate". As noted, upon the decision of a cell to ent the cell, cycle one of its adjacent empty automata cells is chosen randomly to be reserved for one of its future daughter cells.

Cell Decisions in the Model

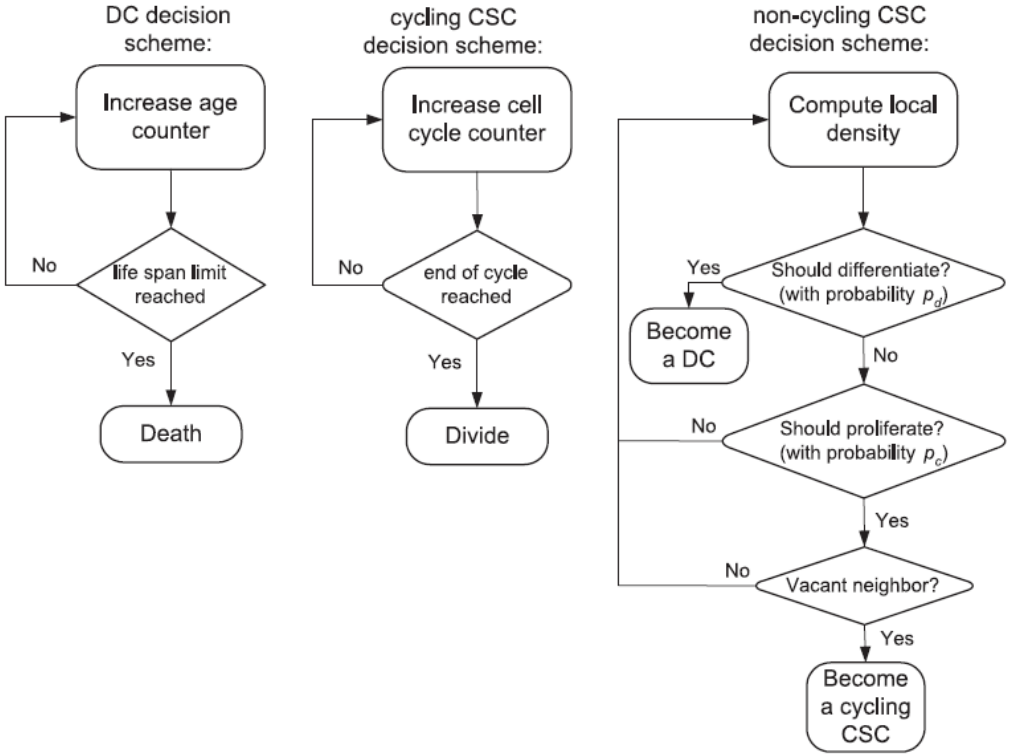

Fig. 2. A flowchart of cell decisions in the model. We summarize the decision taken by each type of cells (Differentiated Cells (DC), cycling Cancer Stem Cells (CSC), non-cycling Cancer Stem Cells (CSC)) during the automata run. The scheme is repeated at each time step for each cell.

List of Parameters and Initial Conditions

List of parameters and initial conditions	Baseline values
Lifespan of DC (hours)	90
Damping coefficient for the second degree neighbors, k	2
Basic probability of entering cell cycle	0.006
Maximal differentiation rate	0.1
Numbers of CSC neighbors giving the half-maximal differentiated rate	3
Initial cell number	100
Initial percentage of DC	30
Size of subsquare of initial cell distribution	20 x 20
Minimal and maximal age of initial DC subpopulation (as a fraction of DC lifespan)	(0;1)

Model State Simulation Examples

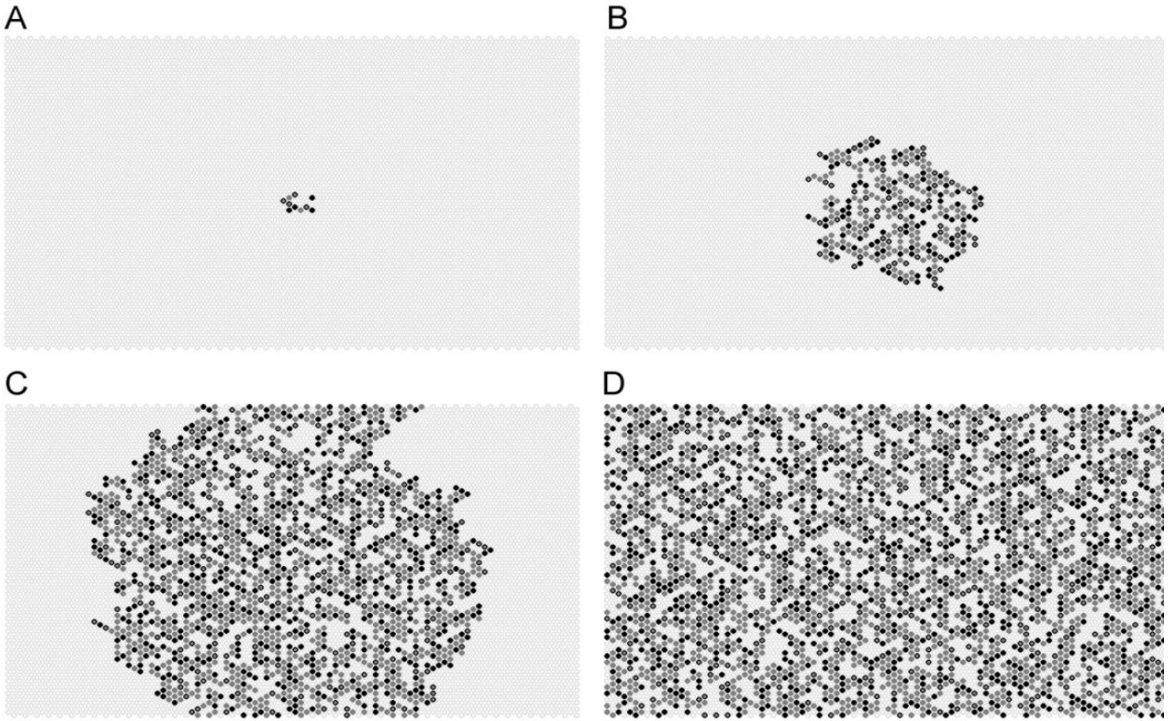

Fig. 3. Examples of model state during the simulation. We show four representative examples of the CA state during the simulation run. Vacant automata cells are marked in yellow, DCs are marked in grey, non-cycling CSCs are represented by black circles, while cycling CSCs are shown as grey circles with a black rim. (A) Initial composition of the model; several cells are present, among them cycling and non-cycling CSCs. (B) Early stages of growth; the colony is small and expands outwards. (C) During later phases, the colony grows more slowly, but still has room to expand. (D) At the final stage, the whole CA is filled and the expansion stops.

Representative Example of Simulation Results

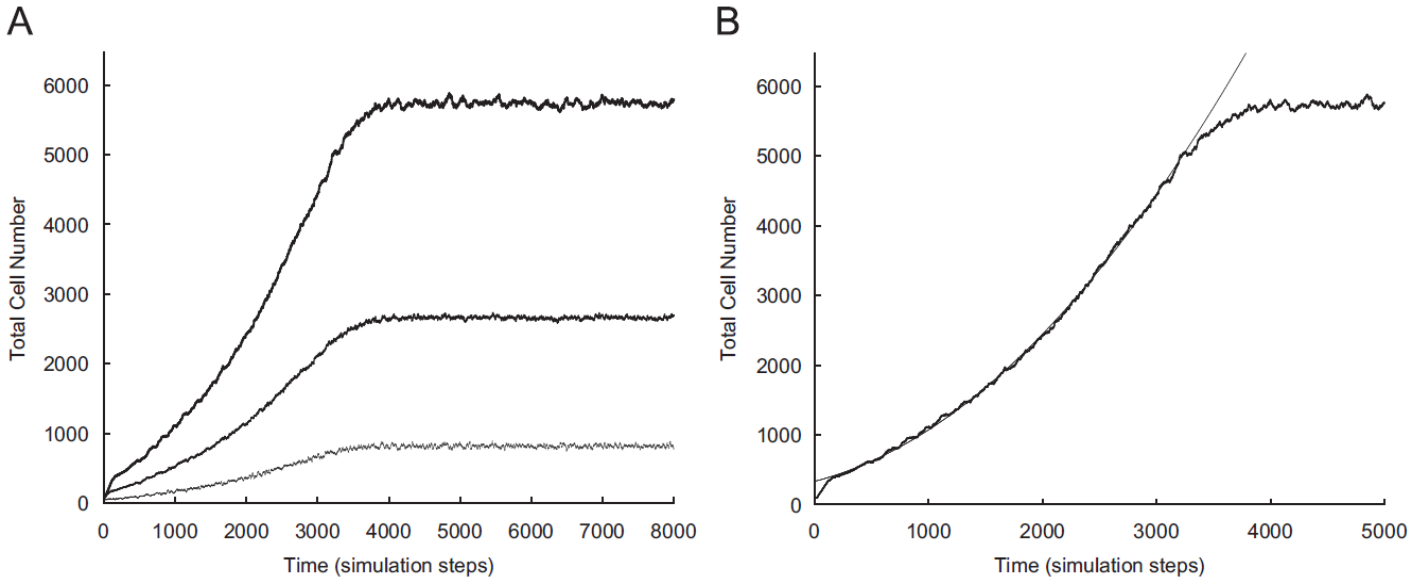

Fig. 4. A representative example of simulation results, showing cell population growth under regular conditions. Initially, 100 cells were seeded in a 20 x 20 subsquare of the automata. The initial conditions and parameters were set at baseline values (see Table 1). (A) The top curve shows the total number of cells. The intermediate curve shows the total number of CSCs. The bottom curve shows the number of cycling CSCs. The number of cells increases progressively up to a quasi-stead state, where small fluctuations around the threshold are observed. Three places can be distinguished; initial variable growth, and decelerated growth up to saturation. (B) The intermediate phase of the cell population growth is well approximated by a parabola (shown by the thin line). The leading coefficient of this parabola is referred to as the "macroscopic growth rate" and is considered as a macroscopic characteristic of the population growth.