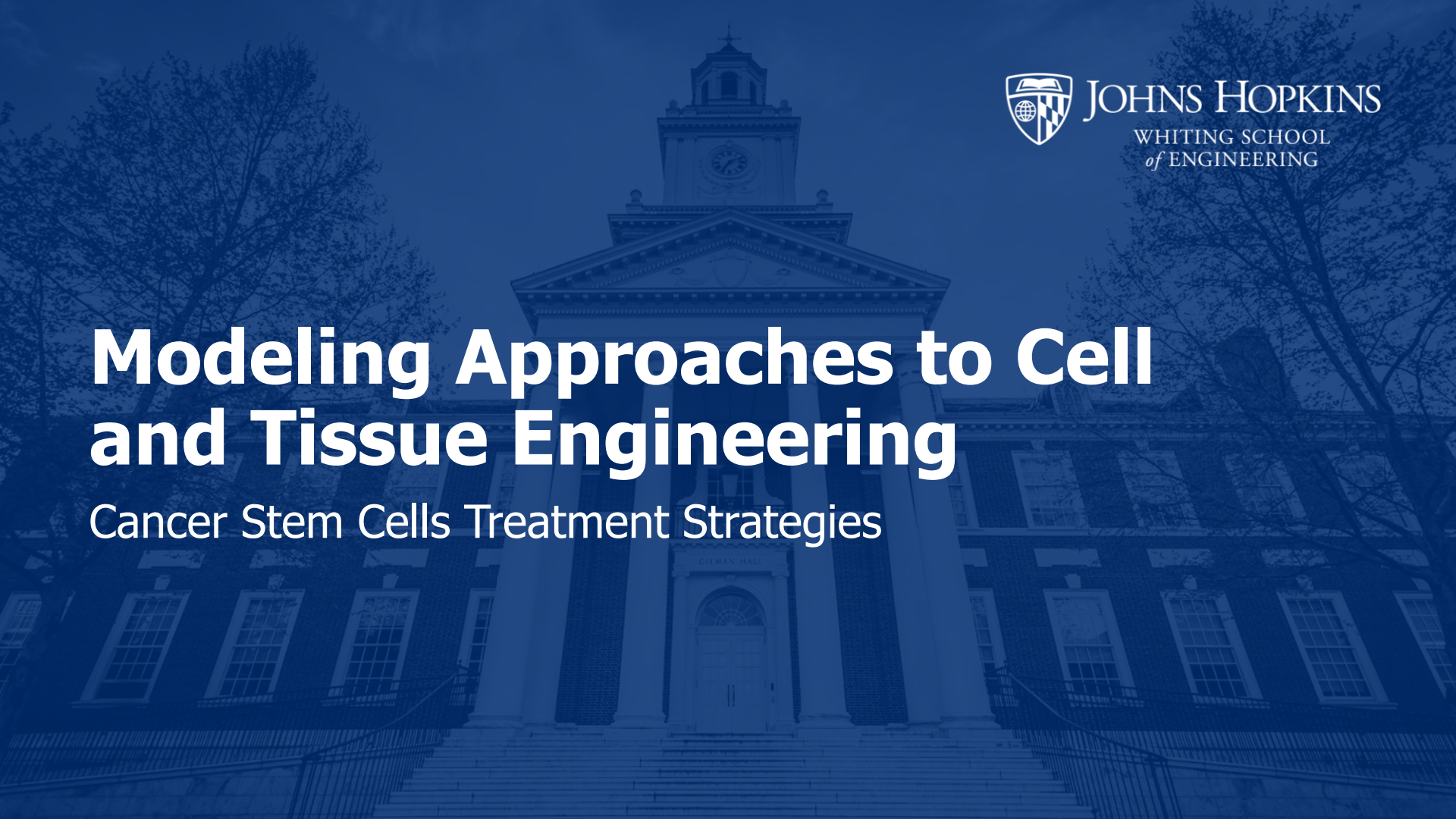


Modeling Approaches to Cell and Tissue Engineering

Cancer Stem Cells Treatment Strategies

Cancer Stem Cells Treatment Strategies

Alexander A. Spector

1. Main groups of cell and parameters of the model of tumor growth
2. Dependence of numbers of cells in different groups on model parameters
3. Dependence of microscopic growth rate of the tumor on model parameters
4. Simultaneous effect of differentiation rate and cancer stem cell proliferation rate
5. Optimal tumor treatment
6. Lessons from computational models

CA Structure

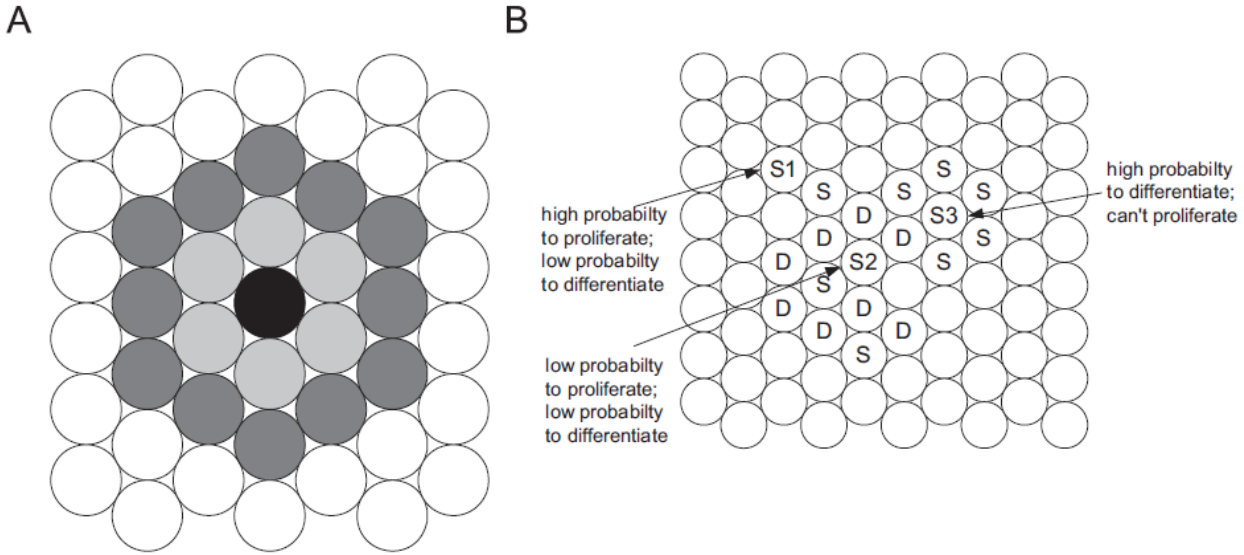


Fig. 1. An illustration of the CA structure, definition of neighborhood and CSC regulation. (A) The cells of the CA are circles tightly positioned on the plane. The six cells adjacent to a central (black) cell are first-degree neighbors (marked in light grey). The 12 second-degree neighbors are marked 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.

Cellular Automata – Computational Cell, CSC – Cancer Stem Cells (Cycling and Non-Cycling), DC-Differentiated Cells

- **The information associated with CA:**
  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 probability of differentiation:** $$p_d = p_{\max} - \frac{a^m (p_{\max} - p_{\min})}{a^m + (den(A))^m}.$$

- **The probability of entering cell cycle:** $$p_c = 1 - (1 - p_0)^n = np_0 + o(p_0),$$

- **The density of differentiating non-cycling CSC cells:** $$den(A) = N_1 + \frac{N_2}{2k},$$

N_1 and N_2 are the first and second-degree neighbors of the A-cell (gray and black circles in Fig. 1A)

Dependence of Cell Population

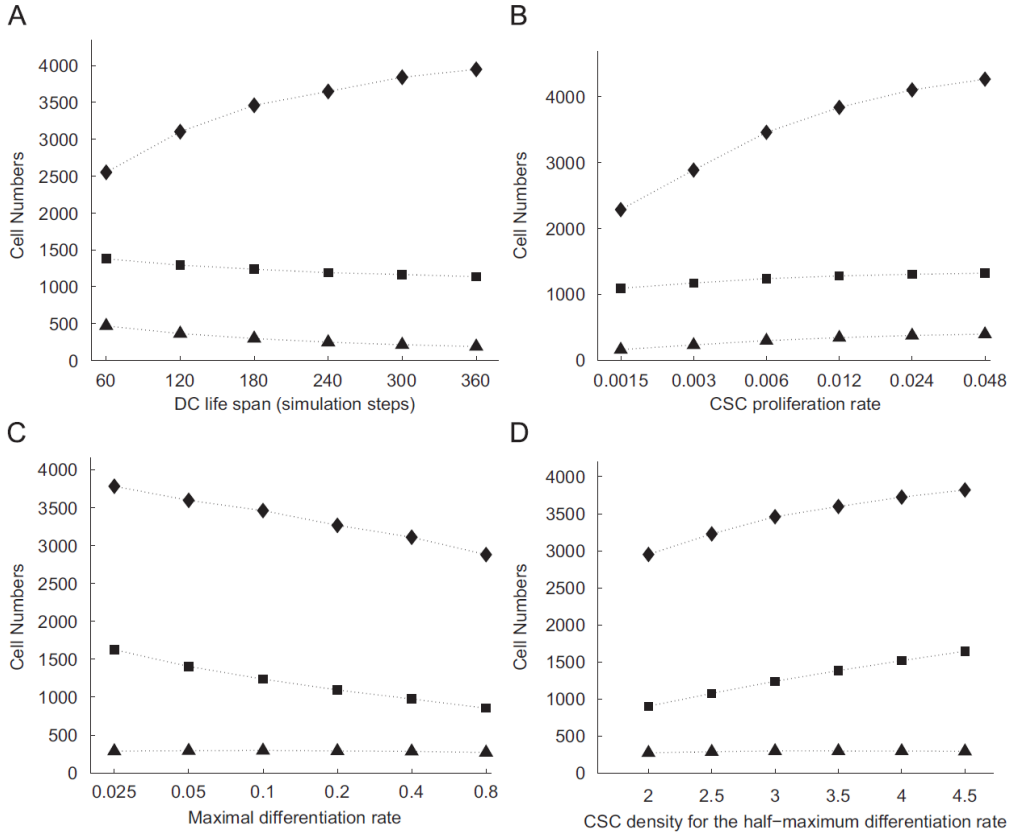


Fig. 5. Dependence of cell populations in the quasi-steady state on model parameters. The cell numbers at the quasi-steady state are plotted as a function of different values of DC lifespan (A), CSC proliferation rate (B), maximal differentiation rate (C), and CSC density giving the half-maximal differentiation rate (D). All other parameters were set at baseline values. Total cell number is represented by rhombuses; total CSC number – by triangles.

Dependence of the Macroscopic Growth

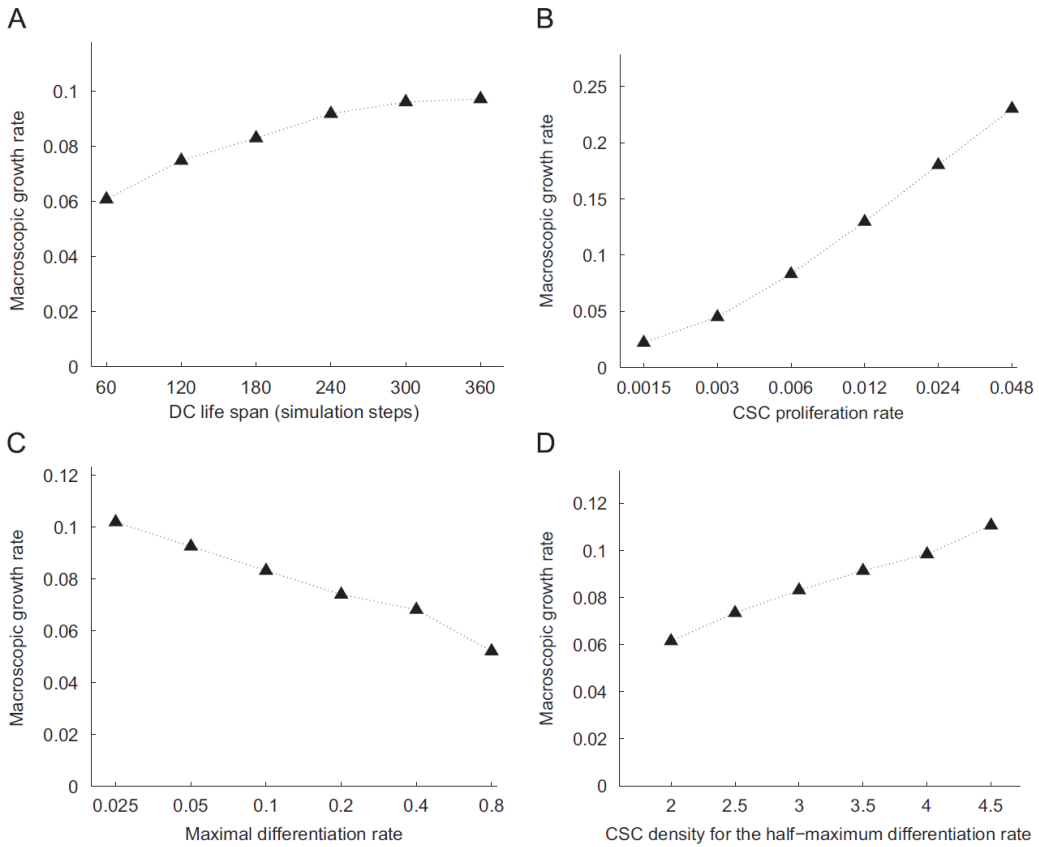
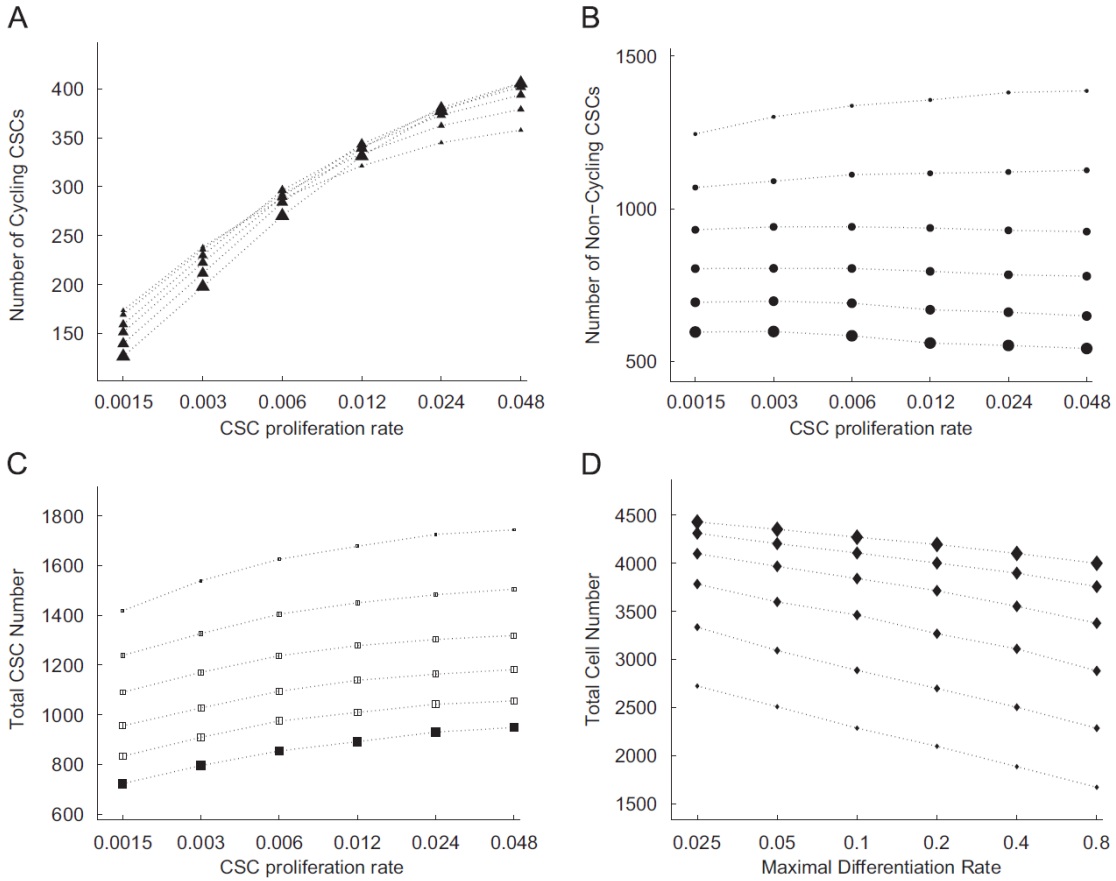


Fig. 6. Dependence of the macroscopic growth rate on model parameters. We show the macroscopic growth rate as a function of DC lifespan (A), CSC proliferation rate (B), CSC maximal differentiation rate (C) and CSC density giving the half-maximal differentiation rate (D). In each case, all other parameters we set at baseline values. The dependence of macroscopic growth rate on model parameters is similar to that of total cell density; see Fig. 5.

Dependence of Cell Population Sizes



Dependence of cell population sizes on simultaneous effects of differentiation rate and CSC proliferation rate.

Optimal Tumor Treatment

- The CSC hypothesis suggests that an efficient anticancer treatment should eliminate as many CSCs as possible (both cycling and non-cyclng), while "non-stem" (i.e., differentiated) tumor cells will eventually die out even without intervention.
- Different forms of therapy, implemented by varying the values of model parameters, affect tumor growth rate and cell population sizes. Three biologically important observations emerged.
- First, accelerated death of DCs (represented in the model by decreased lifespan) decreased the number of DCs, but increased the number of cycling CSCs (see Fig. 5A).
- Second, decreasing the proliferation rate of CSC causes lower number of cycling CSCs, but the number of non-cycling CSCs remained unchanged (see Fig. 2B).
- Third, promoting differentiation (either by increasing maximal differentiation rate or by increasing CSC sensitivity to their density) decreased the maximal number of non-cycling CSCs but did not decrease the numbers of cycling CSCs and DCs (Fig. 2C,D).
- These results suggest that for a wide range of parameters, neither inhibition of proliferation alone nor induction of differentiation alone suffices to reduce the CSC number.
- However, the combination of two strategies can effectively minimize both populations of CSC and the total number of cancer cells (Fig 4).

Insights from Computational Models

- Our results provide new insight into some of the disappointing outcomes of clinical trials targeting CSCs. Owing to the low efficacy of cytotoxic therapy on this cell population, research efforts have been invested in the development of differentiation therapy.
- Yet clinical trials with differentiating agents as mono- therapy have failed so far to show clinical benefit despite promising results in vitro. We demonstrate that under a wide range of biologically plausible conditions, differentiation therapy is expected to be ineffective when used alone to eradicate a CSC population, and is only effective in combination with antiproli-ferative agents.
- Although it may seem unsurprising that the two treatment approaches are synergistic in eradication of CSCs, our results are notable in showing that combination therapy is a necessary condition for successful cancer treatment