A cellular automata to simulate the growth and death of a cell culture

Motivation: The term “cell culture” is generally referred to the process by which some cells, often derived from multicellular organisms or tissues, or tumoral cell lines, are grown under controlled conditions outside of their natural environment. This system is very useful for different applications, for example to study physiological phenomena, or for the production of some useful molecules, or for testing the toxicity of some compounds. The life of the cells in culture is conditioned by many elements. Apart from physical factors such as pH and temperature, the growth of a cell culture is conditioned by its density: cells compete for the nutrients and growth factors available and die when they are exhausted. Moreover, dead cells release in the medium some toxic factors that, in their turn, can lead the surrounding cells to death. Additionally, the presence of exogenous toxic factors in the medium can induce cell death We present a cellular automata developed in order to reproduce the growth of a cell culture of a particular human cell line, Caco-2, derived from human colorectal adenocarcinoma cells. The cellular automata has been developed in order to reproduce the phenotype of Caco-2 cells, their cell cycle with all phases, and the influence of 4-nonylphenol (4-NP), an environmental pollutant, on this model system.

Methods: The cellular automata developed is a grid whose dimensions reproduce a cell counting Burker chamber. Two matrices have been used to take into account, respectively, the global duration of the cellular growth and the phase of the cell cycle for each cell. Two vectors are also introduced to take into account the length of each phase and their variability range. A shuffling algorithm is used to distribute the starting cells on the chamber, then the algorithm starts by assigning a variable lag phase before reproducing the start of the cell cycle with the entering of the cells in G1 phase. All the following phases of the cell cycle are characterized by a fixed length (in minutes) + 10% variability. The cell death is described by a logarithmic function that is influenced by different factors: culture density, cellular senescence, presence of dead cells in the environment of each cell, introduction of a toxic substance. The application was developed in a stand-alone manner and has been written in Java using the OpenGL library integrated in Java.

Results The application is made by an intuitive GUI to set several parameters useful for the simulation (see Figure, panel A). In order to highlight the different cell cycle phases, different colors were attributed to each phase. The cellular automata is evolving in the space and in the time reproducing the four steps of the cell cycle (G1, S, G2, M). The evolution of the simulated cell growth reproduces the phenomena present in a real Caco-2 cell culture. (Abstract truncated at 3,000 characters - the full version is available in the pdf file)

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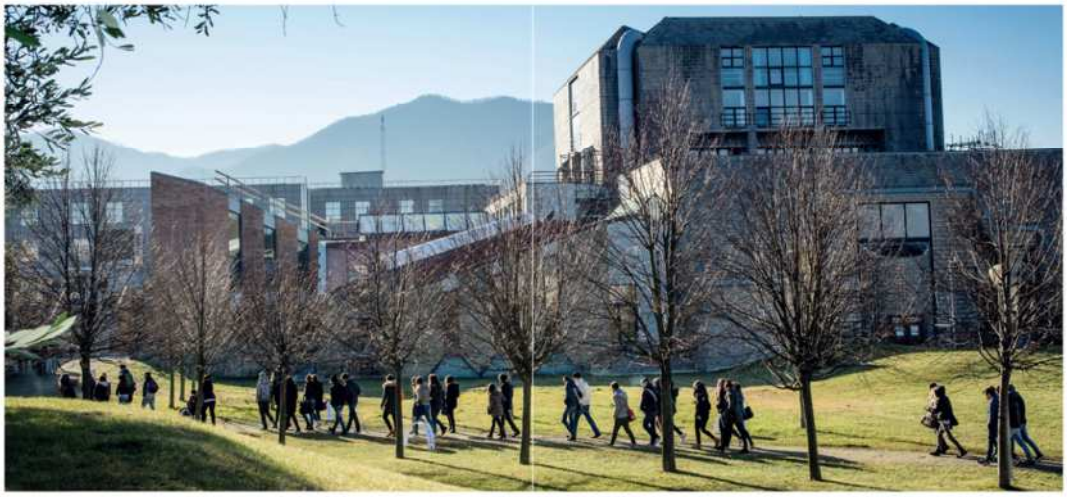

ABSTRACT BOOK

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A cellular automata to simulate the growth and death of a cell culture

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Motivation

The term "cell culture" is generally referred to the process by which some cells, often derived from multicellular organisms or tissues, or tumoral cell lines, are grown under controlled conditions outside of their natural environment. This system is very useful for different applications, for example to study physiological phenomena, or for the production of some useful molecules, or for testing the toxicity of some compounds.
The life of the cells in culture is conditioned by many elements. Apart from physical factors such as pH and temperature, the growth of a cell culture is conditioned by its density: cells compete for the nutrients and growth factors available and die when they are exhausted. Moreover, dead cells release in the medium some toxic factors that, in their turn, can lead the surrounding cells to death. Additionally, the presence of exogenous toxic factors in the medium can induce cell death.
We present a cellular automata developed in order to reproduce the growth of a cell culture of a particular human cell line, Caco-2, derived from human colorectal adenocarcinoma cells. The cellular automata has been developed in order to reproduce the phenotype of Caco-2 cells, their cell cycle with all phases, and the influence of 4-nonylphenol (4-NP), an environmental pollutant, on this model system.

Methods

The cellular automata developed is a grid whose dimensions reproduce a cell counting Burker chamber. Two matrices have been used to take into account, respectively, the global duration of the cellular growth and the phase of the cell cycle for each cell. Two vectors are also introduced to take into account the length of each phase and their variability range. A shuffling algorithm is used to distribute the starting cells on the chamber, then the algorithm starts by assigning a variable lag phase before reproducing the start of the cell cycle with the entering of the cells in G1 phase. All the following phases of the cell cycle are characterized by a fixed length (in minutes) $\pm$ 10% variability. The cell death is described by a logarithmic function that is influenced by different factors: culture density, cellular senescence, presence of dead cells in the environment of each cell, introduction of a toxic substance.
The application was developed in a stand-alone manner and has been written in Java using the OpenGL library integrated in Java.

Results

The application is made by an intuitive GUI to set several parameters useful for the simulation (see Figure, panel A). In order to highlight the different cell cycle phases, different colors were attributed to each phase.

The cellular automata is evolving in the space and in the time reproducing the four steps of the cell cycle (G1, S, G2, M). The evolution of the simulated cell growth reproduces the phenomena present in a real Caco-2 cell culture. Cells initially grow slowly, but after about 32 h their growth becomes exponential until a confluence of about 80% is reached (in about 72 h) (see Figure, panel B). Then, the negative effect of senescence and culture density becomes predominant and all the cells die after about 120 h.
Analogously, the introduction of 4-NP produces different effects depending on the initial density of the cell culture: the number of dead cells is higher at high 4-NP concentration and the effect is more pronounced if the initial cell density is lower (see Figure, panel C). The results are consistent with those obtained experimentally.
In conclusion, we have developed a cellular automata able to correctly reproduce the behavior of a Caco-2 cell culture, also in the presence of a toxic substance. This application can be modified in the future in order to simulate the behavior of other cell lines and/or different stress conditions to be applied.

Figure: