Modeling Cancer Metastasis by Using GGH Model in CompuCell3D

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CompuCell3D (CC3D) [1] is a friendly and free computational environment based on the Glazier-Graner-Hogeweg Model (GGH) [2]. CC3D is a powerful mathematical tool with efficient graphic interface to mimic dynamics of cellular structures. The GGH Model was initially developed to simulate cellular sorting by François Graner and James Glazier, but later upgraded by Paulien Hogeweg to include chemical effects.

The model utilizes a lattice in which the sites are labeled by integer numbers. Connected sites with the same label represent cells (a grain, a biological cell, a foam bubble, etc.). These cells have definite properties, e.g., an energy associated with their interfaces, volume, and surface area. For biological cell we may also include some behaviors in the model, for example, the response to an external chemical field, or chemotaxis.

The mathematical representation for the system’s free energy can be written as,

$$ E = \sum_{S} \sum_{\langle S \rangle_n} J(\tau, \tau') [1 - \delta_{S,S'}] + \sum_{S} \lambda_{\text{surf}}(S) [a(S) - a_{\text{target}}(S)]^2 + \sum_{S} \lambda_{\text{vol}}(S) [v(S) - v_{\text{target}}(S)]^2 + \sum_{S} \lambda_{\text{chem}}(S) C_s, $$

where, the first term represents interfacial energy and the sum is made over all $s$ lattice sites and over their $n^{th}$ first neighbors $\langle s \rangle_n$, $J(\tau, \tau')$ is the interfacial energy between cells $S$ and $S'$ which have type $\tau$ and $\tau'$, respectively, and $\delta_{S,S'}$ is the delta function which is equal 1 for $S = S'$, and 0 otherwise. The second and third terms represent surface area and volume fluctuations around desired or expected target, with the sums made over all $S$ cells, and the $\lambda$’s are constraints for volume $v(S)$, surface area $a(S)$. The fourth term is a constraint for affinity to a chemical field of concentration $C_s$, and $\lambda_{\text{chem}}$ is its constraint, enabling us to simulate chemotaxis.

The simulation dynamics follows Metropolis algorithm with Monte Carlo method [3]. It consists in randomly choosing a pair of sites in a lattice, usually a square (as in Figure 1) or hexagonal, and proposing a change of one upon another different neighbor site (as a membrane fluctuation): if this exchange reduces the total energy of the system ($\Delta E < 0$), then it is accepted; on the contrary ($\Delta E \geq 0$), it will only be accept it with small probability given by $\exp(-\Delta E/T)$, where $T$ represents temperature, in our simulations it means membrane fluctuations, or cell motility. With this method, we have minimization of energy, so that the system is always going to derivate to minimal states of energy.

Figure 1 – Example of a square lattice with 2 different types of cells (yellow and red) [1].
With these complex interactions, we can analyze the behavior of either an individual cell or cell aggregates. In addition, with CC3D, we are able to integrate chemical fields, chemotaxis, and growth factors secretion and absorption, to simulate mitosis, morphogenesis and cellular adhesion, i.e., development in general.

All this together allow us to model in vitro the typical events underlying cancer proliferation and metastases such as vascularization, segregation, and others well-known hallmarks of cancer as outlined in Ref. [4].

Why cancer? Because cancer is not a single disease, but a complicated set of diseases with bad consequences for the patient, relatives, friends, and even for the society. The treatment is usually expensive, invasive, and not completely effective. Cancer evolution is very complex and has a strong dependence with the microenvironment which surrounds it, resulting in enormous differences between one and another tumor, and their treatments also have different ways.

Aiming understand the invasiveness of cancer cells, we have been constructing a robust simulation model to mimics the process by which those cells become metastatic (i.e., process like epithelial to mesenchymal transition EMT [5], metalloproteinase secretion, and changes in cellular adhesion), as well as the mechanisms controlling their proliferation (3D view is showed in Figure 2).

Figure 2 – Tridimensional simulation view made in CompuCell3D. The sequence shows the evolution of a tumor in a cellular medium, the vascularization, necrosis and EMT creating mesenchymal cells.

Using this model we have been studying some hypothesis to explain how this transition occurs and what are the factors influencing this process, as follow:

1. The EMT occurs instantaneous and randomly for any cell at any time, and mesenchymal cells are expelled out of tumor by pressure;
2. The EMT occurs instantaneous and randomly for any cell at any time, and mesenchymal cells are chemotacted by nutrient concentrations;
3. The process occurs gradually, as a randomly gain or loss of motility (by expression of metalloproteinase, up or over regulated), carried like an error in mitosis process which is not repaired, once the repair mechanisms in cancer cells don’t work. By Natural Selection, cells with high adhesion goes to inside the tumor, where there is low nutrients concentration, and became necrotic, when ones with low adhesion goes outside tumor.

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[1] www.compucell3d.org;