GENERATION OF A TUMOR MODEL

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Abstract

The physical environment of living cells and tissues, and more particularly their mechanical interaction with it, plays a crucial regulatory role in their biological behaviour such as cell differentiation, apoptosis, proliferation, tissue growth, remodelling, tumor growth, etc. However, the way that mechanical forces at the cellular level (i) influence the cell functions and (ii) govern the behaviour of cell assemblies as well as their development, remains unclear and hard to model.
First of all, we investigate a tissue growth model. The model is generated with PhysiCell [1, 2].

Computational model

Each agent is of the state S(t) at time *t,* Macklin *et al.*. The possible states are [Q, P, A, H, N, C, M]. They are as follows: Q is the quiescent state. The cells in the Q state can become proliferative P, apoptotic A, and motile M. Cells in each of the states can become hypoxic H. The H cells can become necrotic N or come back to their previous states. The N cells can be replaced with calcified debris C. The signalling protein networks to regulate the transitions Q to P, Q to A and to M are according to Macklin et al. as well [4]. Cell cycle models for regulation of P to Q transitions are according to Zhang et al. [5]

Flow of the program

1) Update biochemical microenvironment for cell-based secretions, uptake, reaction-diffusion, for current cell positions

2) For the fixed cell positions and chemical substrate fields run the cell processes for each cell

a) Update cell parameters – indentify the phenotype

b) Advance the cell cycle, death

c) Evaluate the cell's volume (sub-volumes)

3) Update the position of each cell based on calculated forces

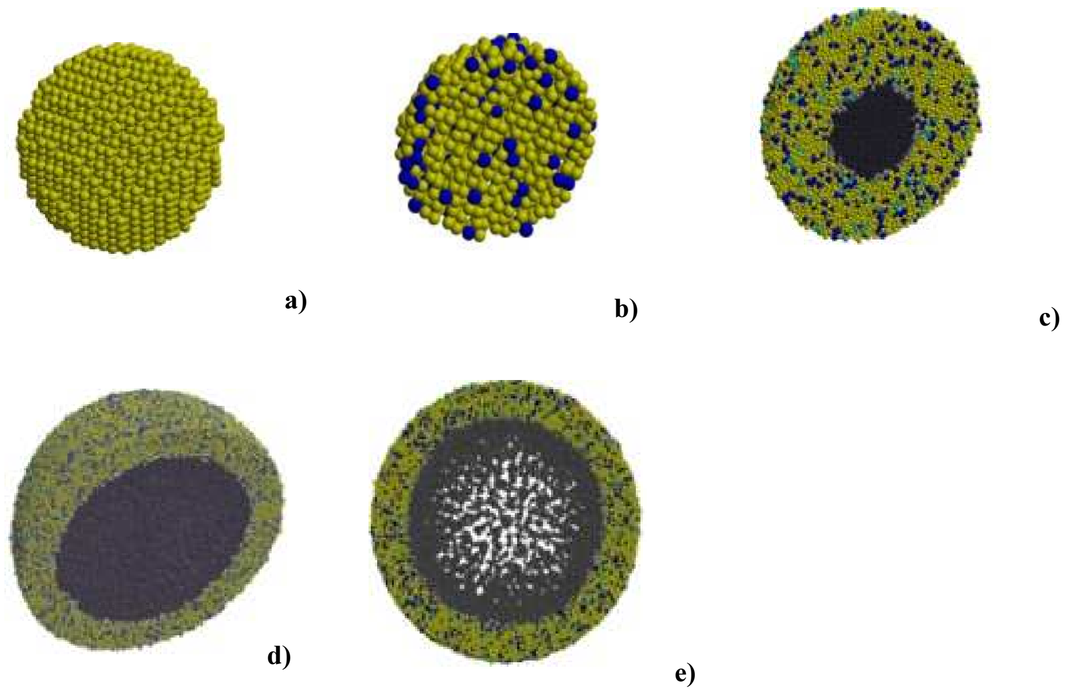
4) Update the time

The biochemical environment is defined by a vector of reaction-diffusion equations:

$$\frac{\partial \boldsymbol{\rho}}{\partial t} = \mathbf{D}\nabla^2\boldsymbol{\rho} - \boldsymbol{\lambda}\boldsymbol{\rho} + \mathbf{S}\left(\boldsymbol{\rho}^* - \boldsymbol{\rho}\right) - \mathbf{U}\boldsymbol{\rho} + \sum_{cells\ k} \delta\left(\mathbf{x} - \mathbf{x}_k\right) W_k \left[\mathbf{S}_k\left(\boldsymbol{\rho}_k^* - \boldsymbol{\upsilon}\right) - \mathbf{U}_k\boldsymbol{\rho}\right]$$

$$\frac{\partial \boldsymbol{\rho}}{\partial t} = diffusion - decay + bulk\ \ source - bulk\ \ uptake + sources\ and\ \ uptake\ by\ \ cells$$

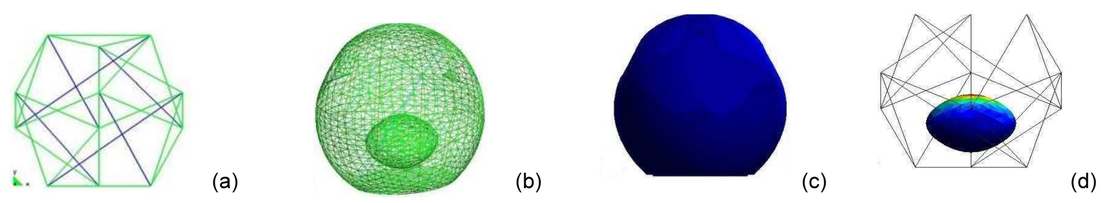
Here, **x**_k is the k_th cell's position, W_k is its volume, **S**_k is its vector of source rates, **U**_k is its vector of uptake rates, and ρ^* is the vector of saturation densities (the densities at which the cells stop secreting). Likewise, **D** and $\boldsymbol{\lambda}$ are the vectors of diffusion coefficients and decay rates, **S** is the bulk supply rate, and **U** is the bulk uptake function.



Tumor growth model

Using the PhysiCell paradigm we build the tumor growth model taking into account cell transitions, cell cycles according to cell line MCF7. We create a group of N cells (2346, green) in Fig (a). The subsequent steps are given in Figs (b), (c) and (d).
In this case, the states of the cells are S(t)=[C, A, N]. They can be cycling C and be A and N. The C cells cycling according to MCF7 cell line [3]. The N dead cells are shown in Fig. (c) and (d) in the middle of the spheroid. The core of the cells cluster is surrounded by viable ring. The final number of cells after 36 days is 505220, Fig (d). We may see internal structure of the necrotic core due to cells degradation, (e).

Next step – mechanical model [7]



The simplest CSK (a), Finite element model (b), Deformed model (c), View of the cytoskeleton and nucleus (d).

We should replace every cell with its mechanical model. In fact, we can make it with only a part of the tumor. The response of the tumor cells will be obtained using numerical models. The physical properties of tubulins, actin filaments, cortex and membrane are taken from the literature, for example, Mofrad and Kamm [6]. Further, the response of the cells is verified with the available up to date literature.

Remark

We generated all elements for building up agent-stress model of a tumor.

References:

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