FROM INDIVIDUAL CELLS TO COMPLEX TISSUES. AN IMMERSED BOUNDARY APPROACH

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Summary: We present a computational model of various tissues (such as epithelial sheets or tumor clusters) composed of different types of cells, which nevertheless allows us to focus on biomechanical processes of individual tissue components (such as cell proliferation or chemotactic migration). The discussed model is based on the immersed boundary method and couples the dynamics of separate elastic cells with continuous description of a viscous incompressible cytoplasm.

MODEL DESCRIPTION

Development of complex tissues depends on the behavior of separate cells, that form such a tissue and on communication with cell neighbors or surrounding microenvironment. Therefore, we propose a computational model which treats cells as individual entities, with their own elastic plasma membrane, fluid cytoplasm, point nucleus and partial cytoskeleton. However, this model also enables formation of cell clusters or cell sheets in which all cells act together as one complex tissue. Moreover, this model includes discrete sets of cell receptors which are used to sense signals from the surrounding microenvironment and to send signals to other cells. Based on these signals the cells can undergo different processes, such as cell growth, proliferation, apoptosis or migration toward the chemoattractants. The presented model is based on the immersed boundary method [1] and couples the dynamics of separate elastic cells with continuous description of a viscous incompressible cytoplasm. Applications of this model include several simulations of tumor related phenomena, such as the formation of early ductal carcinomas, an outgrowth of a capillary sprout in the early stage of angiogenesis and the transition of tumor cells from dormant into invasive, which occurs in the early stage of metastasis. Several computer simulation of such phenomena are presented.

Cell structure

The computational model of an individual eukaryotic cell includes the elastic plasma membrane modeled as a collection of boundary points connected by short linear Hooke's springs, the partial cytoskeleton represented by linear spring connections, the cell cytoplasm modeled as a viscous incompressible Newtonian fluid and the cell nucleus represented by a single point located inside the cell. Separate cells are joined together by adhesion links to form a tissue. Figure 1 shows a segment of such a complex tissue from a model of early ductal carcinoma.

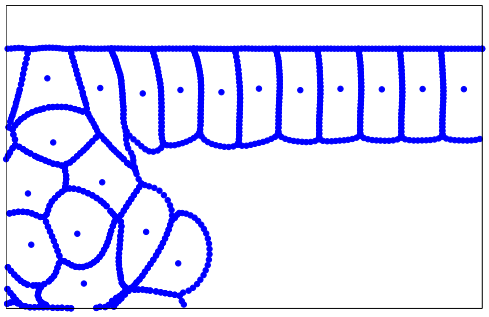

Figure 1: A segment of an early ductal carcinoma model containing different types of cells – a layer of epithelial cells (rectangles) and a cluster of tumor cells (ovals).

Main equations

The immersed boundary method captures interactions between elastic bodies (cell membranes) and a surrounding viscous incompressible fluid (cytoplasm). The fluid flow is influenced by forces generated by the immersed, elastic boundaries, as well as by sinks and sources of fluid distributed in the fluid domain, but at the same time the immersed bodies move at the local fluid velocity. The surrounding fluid, both inside and outside the cells is assumed to be of the same constant viscosity and density. In addition cell growth is modeled by tracking fluid sources located at the cells nuclei. The motion of the fluid is governed by the Navier-Stokes equations [1]:

$$\begin{cases} \rho\left(\frac{\partial \mathbf{u}}{\partial t} + (\mathbf{u}\cdot\nabla)\mathbf{u}\right) &= -\nabla p + \mu\Delta\mathbf{u} + \frac{\mu}{3\rho}\nabla s + \mathbf{f} \\ \rho\nabla\cdot\mathbf{u} &= s \end{cases}$$

Here, ρ is a constant fluid density, μ is a constant fluid viscosity, $\mathbf{u}$ is a fluid velocity field, p pressure, s fluid source distribution and $\mathbf{f}$ an external force density field.

The force density $\mathbf{f}$ captures the forces $\mathbf{F}$ generated by the elastic immersed boundaries of all cells as well as the adhesion or drag motility forces.

$$\mathbf{f}(\mathbf{x},t) = \int_{\Gamma} \mathbf{F}(l,t)\ \ \delta(\mathbf{x} - \mathbf{X}(l,t))dl$$

Here δ is the Dirac delta function and l is an Lagrangian parameter such as arc length. Γ is a finite collection of immersed boundaries of all cells. $\mathbf{X}(l,t)$ represents coordinates of the material points on Γ.

The sources ($S^+ > 0$) of fluid are defined only at the finite collection of cell nuclei Ξ with coordinates $\mathbf{Y}_k(t)$ and sinks ($S^- < 0$) are taken at the boundaries $\mathbf{X}(l,t)$ of growing cells, so that

$$s(\mathbf{x},t) = \sum_{k\in\Xi} S^+(\mathbf{Y}_k,t)\ \ \delta(\mathbf{x} - \mathbf{Y}_k(t)) \quad + \quad \int_{\Gamma} S^-(l,t)\ \ \delta(\mathbf{x} - \mathbf{X}(l,t))dl$$

The material points of immersed boundaries $\mathbf{X}(l,t)$ and cell nuclei $\mathbf{Y}_k(t)$ are moved at the local fluid velocity. Here, R denotes the whole fluid domain.

$$\frac{\partial \mathbf{X}}{\partial t} = \mathbf{u}(\mathbf{X}(l,t),t) = \int_R \mathbf{u}(\mathbf{x},t)\ \ \delta(\mathbf{x} - \mathbf{X}(l,t))\ d\mathbf{x} \qquad \text{and} \qquad \frac{\partial \mathbf{Y}_k}{\partial t} = \int_R \mathbf{u}(\mathbf{x},t)\ \ \delta(\mathbf{x} - \mathbf{Y}_k(t))\ d\mathbf{x}$$

Cell processes

Each cell in this model can sense signals from the surrounding microenvironment and signals sent by its neighboring cells through the receptors located on the cell surface. Based on these signals the cell can undergo different processes, such as growth, proliferation, apoptosis or migration toward the chemoattractants. Here, we give more details only about one of these processes, but mechanisms of all other processes are discussed in our presentation.

A few snapshots of the computer simulation of the multistep process of cell cycle are presented in Figure 2. We include all mechanical phases of cell cycle, but we do not model chromosome replication. We start the process of cell growth and division with introducing two point sources inside the cell, that correspond to two sets of sister chromatids (Figure 2a). The fluid created by both sources causes the cell growth by pushing cell boundaries and by increasing cell volume (Figure 2b). The sources are inactivated when the cell doubles its volume. At this time, the contractile ring is created by attaching the contractile forces on the opposite sites of the cell boundary (Figure 2c). This causes division of the cell into two daughter cells of approximately equal volumes and with their own nuclei (Figure 2d).

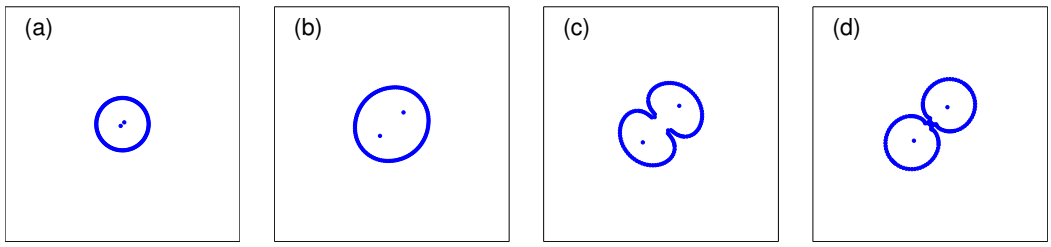

Figure 2: Four main phases of cell growth and division – (a) nucleus division, (b) cell growth, (c) formation of a contractile ring, (d) cellular division which results in formation of two daughter cells.

CONCLUSIONS

The presented technique can be applied in modeling the development of complex tissues composed of various types of cells. It allows us to focus on biomechanical processes of individual cells and on communication between neighboring cells, however it also enables the formation of cell clusters and cell sheets that act together as one tissue. Applications of this model include several computer simulations, such as formation of an early carcinoma or outgrowth of a capillary sprout in the early angiogenesis.

References

[1] Peskin C.S.: The Immersed Boundary Method. *Acta Numerica*, 1-39, 2002.