MODELLING THE APPEARANCE AND GROWTH OF CANCER FORMATIONS IN THE INTERACTIONS BETWEEN TISSUE CELLS

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Cancer development is a complex and dynamic problem, which cannot be described without the aid of mathematical models. The paper reviews a multistage model aimed at solving biomechanical problems. In the multistage modeling of solid avascular tumors, stochastic methods as Monte Carlo are also utilized as well as taking into account the impact of chemical interactions on the growth and nutrition of the cancer site. These include the mutual impact of proteins, the p53 gene and the vascular endothelial growth factor. Recently discovered molecular processes in the cells could be directly integrated into the model. This model could be used for numerical analysis of real tumor evolution with different initial and boundary conditions. Since the model involves the processes of gene regulation, it can be applied to the study of the effects of laser thermal therapy based on the protein-protein interactions, directly targeting the affected cells.

Many materials, including biological tissues and organs, appear homogeneous on a macroscopic level, but their structure on a meso-, micro-, and nano-level is predominantly heterogeneous, which determines their macroscopic behavior. The multistage modelling is based on: initially developing the tissue behavior on a "shallow" level and then transitioning to a "bigger" level while simultaneously keeping the information for the properties and mechanical reactions linked to the previous level. Eventually, a macro model of the studied object is obtained. The idea for multistage modeling was first applied to materials with internal structural heterogeneities, and subsequently, it has been transferred and applied to the research and developments in the field of composite materials.

The multistage modelling is utilized for solving such biomechanical problems as: examination of the growth processes, including the study of regeneration processes in the healing of fractures and wounds; study of the bone viewed as a nanocomposite material; analysis of the microstructure of soft tissues; hemodynamics of the cardiovascular system; biotribology; studies in the field of oncologic diseases.

Cancer growth is a complex and dynamic problem that cannot be quantitatively described without a mathematical model. The multistage models, applied to describing the progress of oncologic diseases, must consider the molecular basis of cancer and the complex nonlinear interactions between the cancer cells and the microenvironment which define the further course of the disease. The complexity in describing the cancer development lies in the investigation and mathematical de-scription on, at least, three levels: micro, meso and macro level: micro level, it should be accounted for the molecular and subcellular processes (genetic mutations, changes in the structure and functionality of the cyto-skeleton's components, biochemical signal); meso level, it is necessary to investigate the interaction of cells with each other. On this level, adhesion mechanisms as 'cell-cell' and 'cell-extracellular matrix' are present; macro level investigates processes occurring in the tissues (cancer growth as cell clusters, invasion, angiogenesis, nutrients supply, mechanical stress).

The main problem in developing successful mathematical models is establishing a connection between the micro and macro levels. Byrne and Chaplain propose a model approach, which establishes principles presented by Greenspan and are connected with the spherical stability of cellular states. It is assumed that the tumor is an incompressible fluid in which the cellular proliferation and death generates pressure gradients that stimulate the movement of cells. In multistage modeling of solid avascular tumors are used such probabilistic approaches as the Monte Carlo method. The impact of chemical reactions on the growth and nutrition of the cancer site should also be considered, as well as the mutual impact of proteins, the p53 gene and the Vascular Endothelial Growth Factor (VEGF).

MODELLING THE APPEARANCE AND GROWTH OF CANCER FORMATIONS IN THE COLLECTIVE INTERACTION BETWEEN TISSUE CELLS

One of the primary obstacles in modeling cancer growth (as well as biological systems) is the fact that the processes that occur are of different scales. On the lowest level, e.g. the cell's nucleus, these processes include the gene regulation and expression. From this level, a signal can induce cell regeneration, and in case of damaged genes, the cell can switch to disrupted and uncontrollable division. On the other hand, the processes of intercellular interaction (at the cellular level) are also a key factor in understanding the moment in which cancer emerges. In case of a healthy immune system, there is a considerable chance that the T lymphocytes would identify and destroy the cancer cells. Unfortunately, this mechanism is not 100% effective, so the risk of cancer development is significant.

We can conclude that every non-phenomenological modeling of the living tissue of the organism suggests the development of a dynamical model of many-cell interactions. The development of such models (individual-based models) is a complex task. However, recent advancements in this field as well as the evolution of computer technologies have enabled the realistic modeling of the functioning of living tissue. A multistage model for the emergence and growth of cancer in the epithelial tissue has been developed. Its significance lies in the fact that the epithelial tissue covers the surface of body cavities, mucosae of internal organs, gastrointestinal tract, respiratory system, and urogenital tract. Additionally, an important fact is that one of the most rapidly spreading carcinoma is the epithelial cancer. The model incorporates a primary chemo-mechanical model of epithelium migration, as well as a range of submodels which compose the various levels of describing the system. At the cellular nucleus level, previously studied molecular mechanisms for controlling the circadian rhythms of cells are utilized.

RESULTS

To calibrate the physical parameters representing the cells' morphology, cytological samples obtained from patients were studied. Figure 1 presents a microscopy images of flat epithelial cells. In Fig. 1(a) are shown healthy cells (larger), while Fig. 1(b) shows microscopy image of cancer cells (smaller with hypertrophic nuclei). The color images were converted to grayscale for this study. A histogram was constructed to plot the normalized pixel count as a function of the intensity of the pixels (Fig. 1(c)). This figure presents the intensity distribution of healthy cells (in orange) and the intensity distribution of cancerous cells (in blue) in the sample under study.

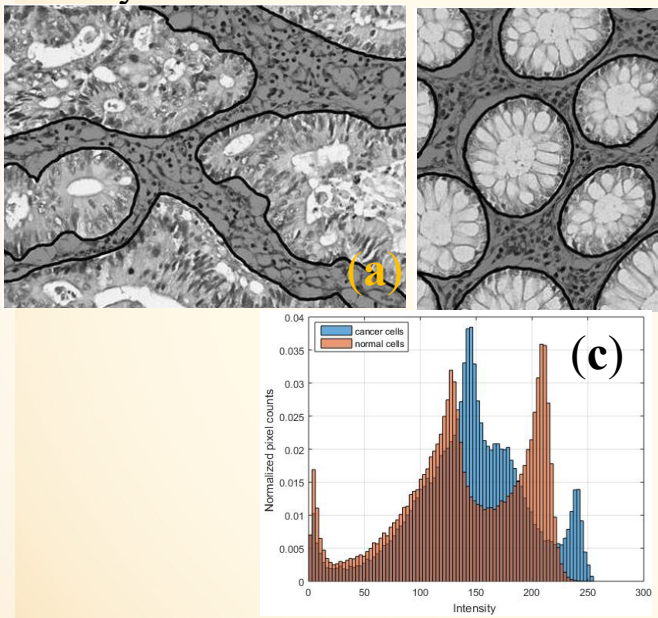


Fig. 1. Microphotography showing: a) – healthy epithelial cells, b) – cancer cell, which have smaller dimensions and hypertrophic nucleus; c) – normalized histogram of the intensity distribution of healthy and cancerous cells.

From Fig. 1b, it could be noted that the average size of the cancer cells is smaller. This can be attributed to the rise in the internal pressure and tightness of the tumor resulting from faster cell division. These results are obtained by direct measurements of cells from micrographs and are in accordance with the latest measurements of cell morphology acquired by the means of modern optical methods.

The model aims to simulate the growth and behavior of individual cells in epithelial tissue by representing them as polygons with varying numbers of vertices (as shown in Fig. 2). By computing the dynamics of these cells, we can gain insights into how local disruptions in circadian rhythms may lead to the transformation of healthy cells into cancerous ones.

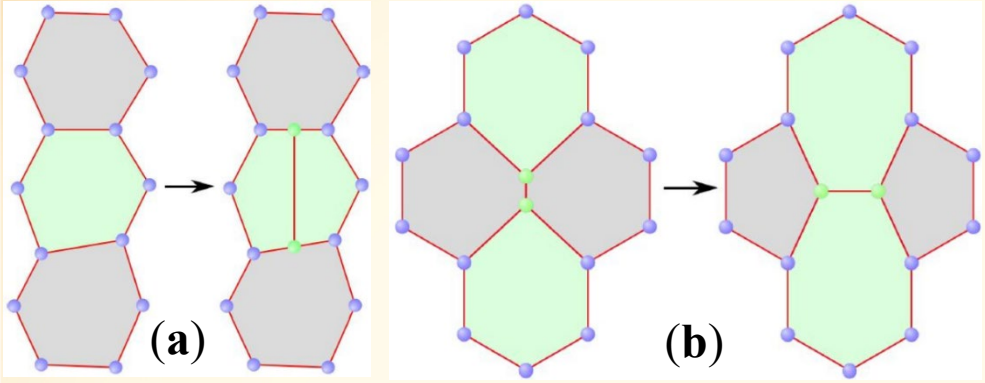


Fig. 2. Schematic representation of cell division; b) the process of intercalation of the cell in epithelial tissue.

The system is calibrated for the most probable hexagonal cell shape, but other shapes are also possible. Although real cells have more complicated shapes, no irregular shapes are observed when the perimeter varies greatly while keeping the cell surface area constant. Cells are in immediate contact, forming the continuous two-dimensional surface of the epithelium.

The model has a set of features which allow for simulating the behavior of real tissue:

- possibility of an increase in the total number of cells in the system as a result of their division when certain conditions for their evolution are met (Fig. 2a);
- possibility of the cells to migrate in the epithelium as a whole by the means of intercalation (Fig.2b);
- modeling the concentration dynamics of proteins which take part in regulating the vital functions of each cell in the cluster;
- exchange of signal molecules through the walls of neighboring epithelial cells.

The description of mechanical properties of epithelial tissues should be extended with the description of the processes of gene regulation occurring within the cell nucleus. Therefore, it is necessary to compute the entire chain of chemical reactions. In living cells, there are thousands of reactions occur concurrently within the nucleus. A specific molecular mechanism responsible for the circadian rhythm of cells has been created. Figure 3 shows two model schemes for gene regulation, which are developed and studied by the authors. (a) is a model of the auto-repressive gene x which regulates the synthesis of its corresponding protein X by a negative feedback with delay τ. (b) is a model of two interacting genes x and y, which stimulate the synthesis of the corresponding proteins X and Y by a positive feedback with delay τ. Indeed, the delay in the processes of transcription and translation is assumed one of the factors contributing to the remarkable stability of the circadian rhythms of animals and plants.

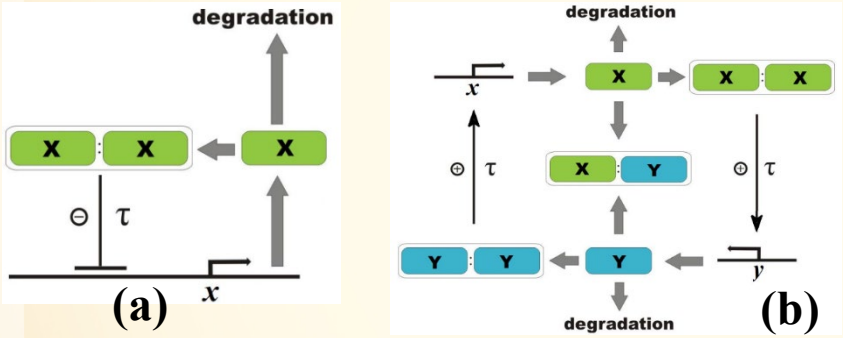
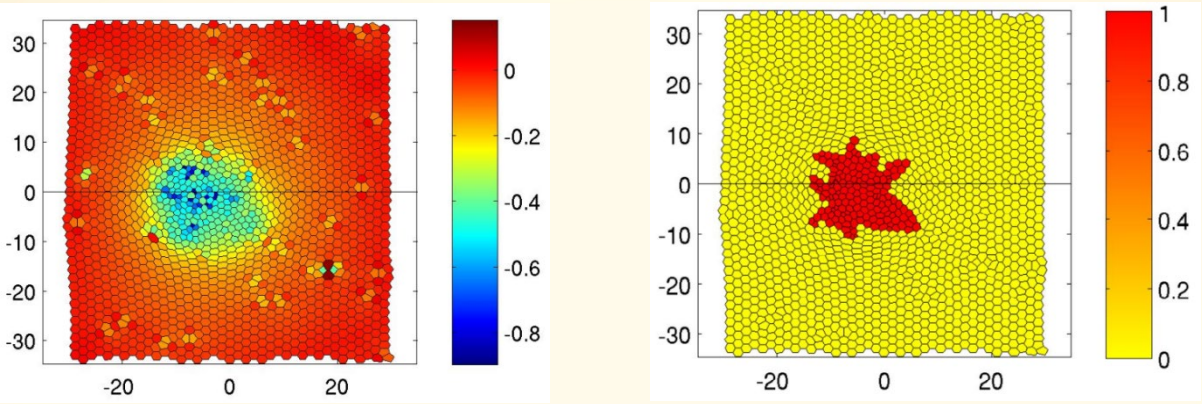


Fig. 3. Schematic representation of the molecular mechanism responsible for sustaining the circadian rhythm.

Synchronization of rhythms on a tissue level during protein signal exchange is thought to lead to the formation of spatial models. As a specific mechanism linking disrupted circadian rhythms with cancer has not yet been identified, a phenomenological model of cell transformation to a cancerous state is proposed. For each cell, the magnitude of the dephasing is calculated, which is the sum of the differences between the oscillations of one cell and the oscillations of its neighboring cells. The probability that a cell will transform into a cancerous one is highest for the cell with maximum value of the dephasing.

This means that a cell which oscillates out of phase with its neighboring cells is exposed to the highest risk of degeneration. In this way, a feedback in the system is established between the processes in the nuclei and the mechanics of the individual cells as well as their groups.



(a) **(b)**

Fig. 4. Example for computing the spread of invasive carcinoma in epithelial medium of more than 1600 cell.

Figure 4a shows the distribution of cells in the medium based on the difference between their surface area A and the average size A_0. Figure 4b displays the distribution of cells based on their state, with 1 indicating cancer cells and 0 indicating healthy cells. It can be observed that, on average, cancer cells are smaller due to mechanical limitations.

In conclusion, it can be stated that the model has the potential to be generalized to the three-dimensional case and is structurally stable. The amount of epithelial cells that is involved in the evolution of tissues is solely limited by the computational capabilities of the utilized system. The model's design allows for easy incorporation of newly discovered molecular processes, which can be applied to numerically analyze the evolution of real tumors under different initial and boundary conditions. Since the model integrates the processes of gene regulation, it can also be used to study how thermal laser therapy influences tumor development based on the protein-protein interactions that act directly on the abnormal cells or groups of cells.

THANK YOU

FOR YOUR ATTENTION