Mathematical Modeling of Invasive Carcinoma: Biomechanics of Small Groups of Cancer Cells

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Abstract. According to the latest research, cancer is a complex biological system that evolves over time and space. This means that cancer cells differ from each other in their functions in the tumor. They engage in various interactions with the microenvironment and compete for available nutrients to survive. The main problem of mathematical modeling in oncology today is the heterogeneity of a typical malignant neoplasm. In this work, we propose a chemomechanical model of the pattern formation of small groups of cancer cells of invasive carcinoma of a non-special type (IC NST). The model assumes that carcinoma is a heterogeneous formation, which consists of cells of different phenotypes performing different tasks to maintain the existence of the tumor. In the model, each cell is represented as a deformable polygon that changes its shape and size as the tissue develops. Numerical modeling implements various subtypes of IC NST structures. These patterns are compared with morphological structures identified in clinical studies.

1. Introduction

Cancer is the second most common cause of death in the world, with 9.6 million deaths from the disease in 2020 alone. It is worth noting that breast cancer is the most common malignant disease in women among various oncological manifestations. Moreover, over time, the incidence of breast cancer tends to increase, the reasons for which are actively discussed in the literature [1]. At the same time, there is still no direct cure for cancer, and all efforts are aimed mainly at the prevention and early detection of the disease. Thus, cancer is serious and dangerous. Fighting this ailment requires more and more material and intellectual resources.

Recent studies show that a tumor is a non-uniform accumulation of degraded cells that grows due to uncontrolled proliferation, as it was only recently thought. It is now reliably known that a tumor is rather a community of interacting cells that can form various structures of both invasive and non-invasive types [2, 3]. All structures can be divided into two types: multicellular, consisting of a large number of cells (N > 10), and small-celled, which are formed by a very small number of cells (up to one cell). In the literature, multicellular structures include solid, cribriform, papillary, micro-papillary, etc [2]. Small groups of cells include alveolar, tubular, trabecular structures, and single cells [3].

Most often, the tumor cannot be unambiguously differentiated. In all such cases, the term IC NST is used. Striking examples of this kind of tumor have been presented in [3]. The authors performed three-dimensional visualization, comparative genomic hybridization using laser microdissection, and microarray analysis of gene expression of various morphological structures. It was found that these structures were characterized by specific gene expression profiles and signaling pathways. Tumors significantly differed in the level of expression of genes responsible for the activation of the epithelial-
mesenchymal transition (EMT). Based on the results obtained, the authors of [3] proposed a working hypothesis for the emergence and evolution of IC NST structures in breast cancer.

As is known, collective cell migration plays a key role in morphogenesis, wound healing, and tissue renewal, as well as in the spread of cancer. EMT allows initiating the migration of both groups of cells and individual cells. This mechanism is activated whenever cell tissue requires intense movement. The migration of cell groups is described in [4]. There are two distinct types of cells participating in the migration: leading cells and the cells following it. The former one can activate the drag force. For successful migration of the entire group, the leading cell must not completely lose its adhesion bond with the rest of the cells following it. If this is the case, then the following cells are passively attracted in the direction of the resulting motion vector.

Let us note also the work [5], in which the authors distinguish the categories of collective invasion. Single-cell migration is defined as migration in which individual cancer cells invade tissue. This migration uses some strategies, depending on the extracellular matrix adhesion's rigidity, the contractility of the cytoskeleton, and the ability to reshape the extracellular matrix during migration. Multicellular cancer cell fluxes occur when individual cells are jointly driven by a chemokine or morphogen flux gradient and/or extracellular tissue structures. This type of migration can occur as a directed movement of cells moving individually, in multicellular streams, or small chains of cells. Collective migration and invasion of cell groups is the migration of a cohesive cell group. It occurs when connections between cells are maintained for long periods to attach to their neighbors during migration. The anterior edge generates traction, as described in [4], due to actomyosin-mediated protrusion and contractility. In this migration, intercellular adhesion is provided by adhesion systems.

There are many mathematical models of cancer development. A fairly complete overview of past works can be found in [6,7]. For example, a discrete approach to construct a mathematical model of tumor growth was applied in [8] where the authors demonstrated different forms of cell migration. In [9], a continuous-medium model of cancer invasion was proposed, which took into account the adhesion properties of cells by introducing special variables in the system of PDEs. Spatio-temporal dynamics presented by the authors are qualitatively similar to the growth of invasive malignant neoplasms, in particular, such as infiltrative breast cancer. The authors of this work investigated the forms of migration of multicellular structures (solid, cribiform, papillary) in [10]. We have shown the evolution of these structures, studied the dynamics of growth, as well as the composition and location of cells in a cancer society. Besides, we have provided the classification of cancer structures in terms of "complexity-entropy".

As for structures consisting of a small number of cells, their migration has received relatively little attention in the literature. As a rule, the interest of researchers is focused on the study of the invasion of individual cells. For example, work [11] considered tumor metastasis by individual cancer cells under the influence of enzymes affecting tissue remodeling as the main factor of invasive spread.

In this work, we propose a chemical-mechanical model of the formation of structures of small groups of cancer cells in epithelial tissue, focusing on the mechanisms of intercellular interaction.

2. Description of a mathematical model
There are several classifications of epithelial tissues. We consider a simple squamous epithelium, which allows us to consider this system to be quasi-two-dimensional. This assumption greatly simplifies the construction of a mathematical model.

The model includes the dynamics of individual cells represented at the very beginning of the evolution by regular hexagons. But the number of sides of a polygon is an individual feature of each cell and can change dynamically during its evolution. The system calibrates so that the most likely polygon shape is a hexagon, but the appearance of other types of polygons is quite possible [12]. The cells are tightly adjacent to each other such as in the natural epithelium.

As is known, to maintain life, a cell needs to consume nutrients that come from both the basement membrane and the nearest blood vessel. Having received the required amount of nutrients, the cell distributes its remains between neighbor cells. Although the transfer of nutrients in cells is a quite complicated process, the usage of intercellular diffusion is the simplest way to simulate the distribution of nutrients over the tissue. The equation for each cell can be written as follows:
The displacement of the nodes leads to the deformation of the cell. The vector of the mechanical force acting on the \( i \)-th node is determined by the gradient of potential energy (3) along the node’s radius vector. Thus, summing in term (1) is performed over all neighboring cells contributing to the total diffusion flux. The chemical signal \( C \) serves as a direct command to change the local mechanical properties of the tissue. In turn, cell mechanics (change in shape, division, intercalation) changes the signal formation conditions \( C \) and can weaken and enhance it. This is how the chemo-elasticity of the medium is formed.

To define two different kinds of cells, we introduce a state function \( Q \), which takes only two values to determine healthy and cancer cells: \( Q = 0 \) – healthy cell and \( Q = 1 \) – cancer cell. This makes it possible to mark cells and specify in the model two sets of values of control parameters. So we determine the totality of the chemomechanical properties of healthy and tumor tissue in the model. The key element of the model is the definition of carcinoma as a heterogeneous community of cells. The principal tool for identifying the phenotype of cells in a tumor is the cell’s EMT stage. Clinically, it can be determined by measuring level integrins’ expression [13]. In real tissue, the cell changes its phenotype and then begins to behave accordingly. In our model, this process determining by the cell’s position in the tumor and depends on its environment.

Let us denote the EMT index for the \( i \)-th cell as \( S_i \) and normalize its value so that the value \( S = 0 \) corresponds to the epithelial (E) phenotype, and the value \( S = 1 \) corresponds to the mesenchymal (M) phenotype. The intermediate values correspond to the mixed EM phenotype. The calculation of the index can be determined through the function of the state of the cell:

\[
S_i = \frac{1}{N_0} (N_0 - \sum_{j \text{adj}(i)} Q_j),
\]

where \( N_0 \) is the total number of cells around the cancer cell. The summation in (2) is carried out over neighboring cells. The expression in brackets (2) determines the number of healthy cells that are neighbors of the \( i \)-th cancer cell. Thus, the variable \( S \) determines the phenotype of the cancer cell. The numerical values of \( S \) are discrete because the number of neighbors of each cell always remains finite.

In the case of modeling the migration of small groups of IC NST, the potential energy of epithelial tissue is defined by the following equation:

\[
E = \frac{1}{2} \sum_{\alpha \beta} \eta (A_{\alpha} - A_{\beta})^2 + \sum_{\alpha \beta} \mu_{\alpha} L_{\alpha}^2,
\]

where \( \eta \) is the coefficient of elasticity. This parameter is responsible for maintaining the original cell area \( A_0 \). The summation in (3) is carried out over all cells of the system under consideration. The sum of the second term is carried out according to the number of sides of the cell where

\[
\mu_{\alpha} = \mu_0 - \beta C_i.
\]

Here, \( \mu_0 \) and \( \beta \) are parameters. As is known, the cancer cells can synthesize protein [14], which contributes to the softening of healthy tissue during migration and invasion of cancer cells. Let us denote the concentration of this protein expressed by the malignant cell as \( C_i \). The second term in equation (4) directly affects the value of the coefficient \( \mu_{\alpha} \), which is responsible for maintaining the average cell perimeter. Thus, the second term in expression (3) adaptively depends on the conditions, in which the cell is. In the case of a local decrease in the coefficient \( \mu_{\alpha} \), the probability of spontaneous expansion of the cell under the influence of external forces increases. And this, in turn, stimulates the intercalation and self-movement of cancer cells.

Epithelial tissue evolves through the movement of cell nodes. The vector of the mechanical force acting on the \( i \)-th node is determined by the gradient of potential energy (3) along the node’s radius vector. The displacement of the nodes leads to the deformation of the cell.
Since the cellular environment is viscous and dissipative, the most correct approach to modeling the movement of cells in epithelial tissue is to use the apparatus of Aristotle's mechanics [10,12]. In this case, the forces directly determine the speed of movement of the body. With this remark in mind, the equation for the offset of the cell nodes will look like this:

$$\mathbf{v}_i = \frac{d\mathbf{r}_i}{dt} = K F_i H(|F_i| - F_0),$$

(5)

where $H$ stands for the Heaviside function, $K$ is the coefficient motility, $F_0$ is the critical force, below which the node remains stationary. Any local motion in the medium begins if the external force exceeds a certain threshold $F_0$. This is a necessary condition to avoid fluidity and give the cell tissue more general stability and a certain inertness.

The important property of tissue is the ability of cells to divide. This mechanism guarantees the possibility of tissue growth. We assume in the model that the probability $p$ of cell division depends on the number of its sides:

$$p = p_0 q^{n-6},$$

(6)

where $p_0$ and $q$ are the problem parameters. The probability distribution is designed in such a way that the division of cells with a large number of sides would be preferable. In this case, the hexagon remains the most advantageous form of the cell. After the act of division, the new cell is recorded into the cell registry and begins its evolution in tissue. At the same time, it inherits from the mother cell the instantaneous values of chemical and mechanical fields at the time of division. Thus, the algorithm closely mimics the properties of mitotic cell division.

Another important property of the epithelium is the intercalation process. It is necessary to weaken the excess instantaneous stresses that arise locally in the vicinity of a given cell [15]. The simplest intercalation algorithm can be written as follows:

$$p_{\text{int}} = \begin{cases} 1, & l < l_0 \\ 0, & l \geq l_0 \end{cases}.$$  

(7)

Algorithm (7) is triggered if the bridge between the cells becomes less than the critical value $l_0$. The mechanisms of proliferation and intercalation allow the cell to change dynamically its size and shape by changing the number of vertices of the polygon and moving the vertices under the influence of external forces. Thus, each cell in the model undergoes several chemomechanical influences, under which it evolves with the entire system.

The mathematical model described above can be classified as a complex system of interacting elements capable of evolving. The model is discrete in the sense that it includes the individual dynamics of individual elements. It can reproduce both continuous-medium behaviors, as well as group effects of the collective behavior of elements.
Figure 1. Evolution of small cellular groups celled structures IC NST. Frames show the function of the state of cells at times (a) 100; (b) 200; (c) 300; (d) 400; (e) 500; (f) 600. The values of parameters used in the simulation: mechanics of tissue \( \eta = 4.5, \mu_0 = 0.2, \beta = 0.01, \)
\( A_0 = 2.598, F_0 = 0.01, K = 1.0; \) diffusive exchange \( \alpha = 1.0, G = 1.0, \beta_C = 0.02; \)
intercalation and division: \( I_0 = 0.01, p_0 = 0.0002, q = 1.4, p_0^{\text{cancer}} = 0.001, E_0 = 10.0. \)

3. Dynamics of small groups of cancer cells.
Let us formulate the initial conditions for the numerical simulation. Healthy cellular tissue, which consists of 1560 cells, contains 12 cancer cells at random.

Each cancer cell initiates a linear flow of protein around itself, softening healthy tissue [14]
\[
J^{(0)} = \alpha L_x (C_0 - C_i).
\]
Here \( C_0 \) is maximum value of synthesized protein. In the model, we assume that this protein is constantly reproduced, and its value \( C_0 \) in the cancer cell does not decrease. The act of intercalation is performed by that edge of the cancer cell, which has the smallest energy (9), calculated by the product of the second term in equation (3):
\[
p_{\text{int}} = 1, \quad \min_{\ell \in \Omega} \left( \mu L^2 \right).
\]
Thus, cancer cells weaken the attachment of healthy tissue cells to each other and it is energetically more favorable for them to intercalate in the direction of the protein gradient. This leads to the gradual convergence of cancer cells. It should also be borne in mind that in the course of their movement, cells are capable of the mitotic division at they reach a certain level of potential energy
\[
p_{\text{div}} = H(E - E_0)p_0^{\text{cancer}} q^{E-6}.
\]

The biggest change in the energy of a cell occurs with an increase in its size. Thus, larger cancer cells divide more intensively according to equation (10).

Figure 1 presents the results of numerical simulation of the dynamics of such a system. The evolutionary development of the structure of a small cell group of IC NST is shown at regular intervals.

Let us discuss the obtained results of the numerical simulation. We can see in Figure 1a (circled) two trabecular structures that are formed by one row of cancer cells. This is very similar to trabeculae seen in real histological specimens. Trabecular structures are short, linear assemblies consisting of one or two rows of small cells [14]. Figure 1b shows the merging of two trabecular structures and the appearance of a new trabecula consisting of three cells. Besides, we can see that the rate of division of other cancer cells has noticeably grown. In Figure 1c, we can notice several alveolar structures (squared), which
usually consist of clusters of tumor cells of a round shape or slightly irregular shape. It also closely resembles the structures observed on histological sections of real tumors presented in the work [14]. Also, this frame demonstrates the emergence of new trabecular structures. Figure 1d shows the enhanced growth in the number of cancer cells. At this point, a wide variety of different cancer structures consisting of small groups of cancer cells has appeared in the tissue. At the same time, groups begin to unite in various combinations and it becomes difficult to identify specific types of structures. Nevertheless, we still can distinguish individual trabecular structures here. It is clearly seen that the alveolar structures are the center of the growth of carcinoma because around them the greatest growth of cancer cells is observed. The frames shown in Figures 1e and 1f illustrate the formation of the IC NST since the identification of a specific final structure becomes impossible. Here, we can observe only clusters of cancer cells giving rise in future a solid structure characterized by the presence of cells with the E phenotype (Figure 2).

Throughout the process illustrated in Figures 1a–f, the number of malignant cells with the S = 1 phenotype increases by about 1.5 times (see Figure 2), which is typical for IC NST. The authors of [16] call such a manifestation the formation of metastatic seeds because such single cells have a high potential for a further appearance of metastasis.

![Figure 2. Distribution of cells by index S in time.](image)

### 4. Conclusion

We discuss the methodology for constructing a discrete mathematical model of the evolution of the small groups of cancer cells. Small groups or even individual cancer cells are the most dangerous formations, as they provoke the occurrence of metastases even if the main tumor is removed. The model is constructed for a quasi-two-dimensional cellular medium, in which a polygon deformable in real-time formally describes the dynamics of a cell with individual behavior. The behavior of a cell depends on the place that the cell occupies in the medium in general and in the tumor in particular, and the properties of its immediate environment. Within the framework of the suggested model, we gave examples of numerical simulations of the movement of both single cancer cells and small tumor cell groups under the influence of the chemo-mechanical field of epithelial tissue.

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