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Do Cancer Cells Collaborate during Metastasis?

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Abstract. We consider a model for cell deformation and cellular forces that are exerted on the immediate environment. This model is applied to the transmigration of cancer cells through narrow, deformable channels. This migration process is an important and rate-determining mechanism during the metastasis of cancer.

Keywords: cell deformation, cell forces, cell migration, cancer metastasis

1 Introduction

Cancer is a disease that is characterized by cells that grow and proliferate in an uncontrollable way in a body part. The cells, commonly referred to as cancer cells, harm the surrounding tissue and organs. A region that contains a high density of cancer cells is usually referred to as a tumor. Furthermore, the cancer cells invade other parts of the body, where they proceed damaging other body parts and organs. For this reason, one may divide the development of cancer into roughly three stages: 1. nucleation, in which a certain cell phenotype mutates as a result of flaws in the DNA-program, resulting in cancer cells; 2. tumor growth, in which the cancer cells reproduce and form a growing tumor; 3. metastasis, in which cancer cells migrate from the tumor to other body parts. This migration proceeds through the blood stream, as well as through narrow channels to neighbouring organs. If cancer is left untreated, then in most cases cancer leads to death of the patient.

The first, nucleation stage, entails cells that divide and due to errors in DNA mutate to a different type of cell. In most cases, these mutated cells are cleared up immediately by the immune system, however, if they proliferate at a very high rate, then the immune system is not able to neutralize these cells. Then, these cells will proliferate unboundedly and a tumor results. This tumor grows and the cancer cells damage the healthy body parts in the immediate vicinity of the tumor. This damage may be inflicted from pressure forces that the cells exert, but also due to the chemokines that are secreted by the cancer cells. Subsequently, cancer cells will leave the tumor, migrate to other body parts and start colonies of cancer at other locations. The difference between a benign and invasive tumor lies in the fact that cancer cells are immobile or actively migrating to

other body parts. In most cases, skin tumors are benign since they mostly do not involve cancer cells that migrate to other body parts. On the contrary, most other cancers, such as lung cancer, intestinal cancer, or any other cancer in the abdomen, are metastatic (or invasive).

Mathematical models for biomedical processes like tumor growth, cancer metastasis, wound healing have been formulated in different scales. On the smallest, micro scale only the cell including its cytoskeleton, nucleus and membrane are considered. The cell is divided into the three aforementioned subdomains and the diffusion of chemicals and enzymes is simulated in connection to the deformation of the membrane and nucleus. Typically, this involves the solution of bulk-surface partial differential equations. On a larger scale the interaction between the cell and its environment is modelled. A limited number of cells may be taken into account, and then partial differential equations for the cell region, as well as for the regions around the cells are used in the modelling framework. On an even larger scale cells are treated as identical entities, which all have the same characteristics and same geometry. This framework makes the physics used to describe cellular behaviour a lot simpler, however, the framework allows large numbers of cells to be treated. If appropriate computing architecture is used, then millions of cells can be incorporated in this modelling type, which allows the treatment of organs. The aforementioned simulation frameworks are commonly referred to as agent-based models. The largest scale is fully macroscopic and this scale is based on systems of partial differential equations for cell densities, as well as for the mechanical balance. This scale is also referred to as the continuum scale.

The current short paper describes the modelling of the transmigration of cancer cells through deformable narrow channels. This process is of significance for cancer cells that enter the (small) blood vessels or that transmigrate through cavities in order to directly reach other body parts. The paper entails a summary of our earlier work, and therefore for more in-depth understanding, as well as the mathematical formulations, of our simulation studies, we refer to [1].

2 The Mathematical Framework

This section only contains a qualitative description of the model. For a more exact and mathematical description, the reader is referred to [1]. The migration of cells is triggered and stimulated by possible combinations of the following cues: 1. haptotaxis: this is cell migration in extracellular matrix in the (positive or negative) direction of the gradient of a chemical. This chemical can be a chemokine serving as a growth factor, a nutrient, or oxygen, or even a toxic chemical, which the cell will avoid; 2. chemotaxis: cell migration in a fluid phase in the (positive or negative) direction of the gradient of a chemical; 3. random walk: unpredictable migration as a result of unknown local variations, such as density and orientation of collagen or extracellular matrix; 4. durotaxis: cell migration in the direction of increasing stiffness of the extracellular matrix; 5. electrotaxis: cell migration as a result of electric signals; 6. lumentaxis: cell migration that is determined by the intensity of light; 7. passive convection: which is caused by the mechanical deformation of the tissue. Cell deformation may also be caused by the aforementioned cues,

and additionally by the distribution of enzymes over the cell membrane. In the current study, we consider a cell that transmigrates through a narrow, deformable channel, see Figure 1 as a result of chemotaxis, random walk. The cell boundary is modelled as a set of nodal points and line segments. The nodal points, which are the vertices of the line segments, are connected to the centre of the cell. All connections are through springs. The formula for the movement of a nodal point on the cell boundary contains terms for chemotaxis (proportional to the gradient of a signaling chemical), surface tension (accounting for the separation of nodal points from the adjacent nodal on the boundary), cell stiffness (accounting for the separation of the nodal point from the cell centre), possible flow velocity and deformation velocity (displacements that are caused by traction forces in the substance in which the cell migrates). Further, it is accounted for in the model that the cells cannot migrate inward into obstacles. We refer to earlier papers [1] and [2] for the equations. The connection of nodal points on the cell membrane with neighbouring points on the cell membrane, and the physical contact between cells are the main innovations with respect to our earlier work [2], see Figure 2 for a schematic.

We limit the cues for cell deformation and migration to chemotaxis, random walk and passive convection. Cellular forces exerted by the cells onto the walls of the channel are incorporated, and deformation of the channel walls as well as of the tissue that surrounds the channel is incorporated. Cellular forces are modelled by a collection of pointwise Dirac delta distributions over the cell boundary. Since the tissue contains an extracellular matrix that partly consists of liquids by blood vessels and possibly cells, viscous properties are incorporated next to elastic properties. Since in many circumstances, cancer cells are able to (chemically) change their immediate environment, we model the displacements and deformation by the use of a morphoelastic framework, which allows modelling permanent deformations due to microstructural changes. Migration by focal adhesion onto the channel walls is modelled as well. Focal adhesion is modelled by a random process in which the likelihood of cell boundary attachment and detachment depends on the concentration of the chemoattractant and on the state at the previous time-step via a Markov Chain principle. More biological information on focal adhesion as a mechanism for cell migration can be found, among others, in [3]. We note that cells do not have to migrate through channels solely by means of focal adhesion of the integrins, but can also migrate by flowing and exerting contractile and protusive forces to the extracellular matrix [4]. For the modelling of the displacement of the solid material, we incorporate both displacements that are caused by forces and by microstructural changes through a morphoelastic mechanical framework. This morphoelastic framework introduces plasticity into the model, which makes it possible to model permanent displacements and deformation of solid tissues. A justification of the use of this framework is the ability of cancer cells to change the microstructure of their immediate environment through secretion of chemokines that react with the molecules of the immediate solid environment. Furthermore, cancer cells are known to exert forces to their immediate environment in order to facilitate invasion [6]. For the sake of illustration, we give the equation of motion of cell boundary points that are not in contact with (solid) obstables. Let i be the sequence number of the cell boundary point, see

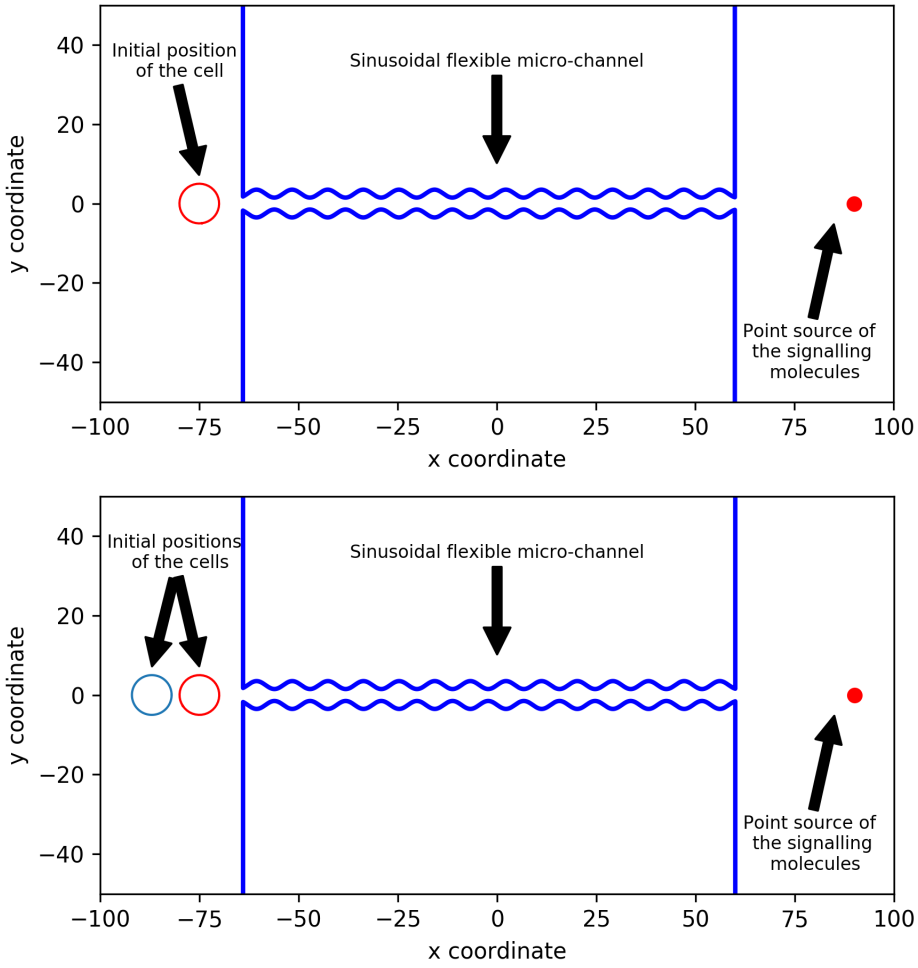

Fig. 1: Initial setting for both cases (1–top, 2–bottom), from [1]

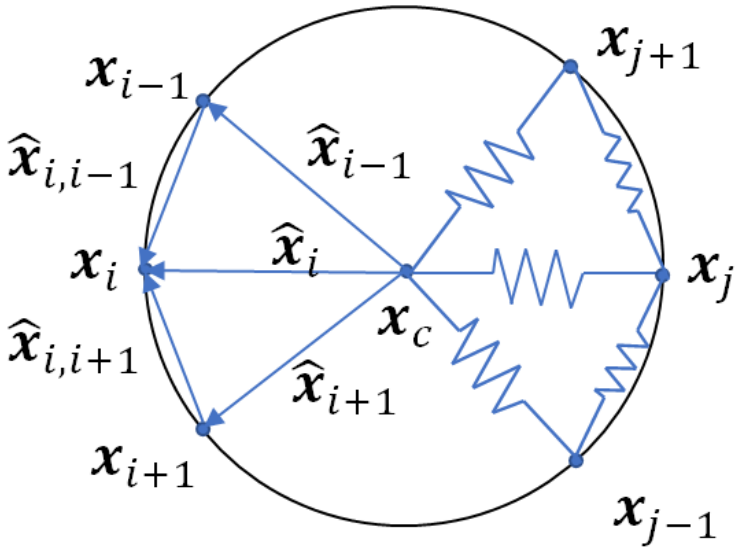

Fig. 2: A schematic of the distribution of the nodal points. The equilibrium shape is maintained by a collection of springs, from [1]

Figure 2, then

$$d\mathbf{x}_j = \omega_s(S(\Omega_c,\mathbf{x}_j))\frac{\nabla c_S(\mathbf{x}_j,t)}{\gamma+||\nabla c_s(\mathbf{x}_j,t)||}\,dt + C_c\,\left(\mathbf{x}_c(t)+\mathbf{B}(\phi)\hat{\mathbf{x}}_j-\mathbf{x}_j(t)\right)\,dt + C_m\,\left(\mathbf{x}_{j-1}(t)+\mathbf{B}(\phi)\hat{\mathbf{x}}_{j,j-1}-\mathbf{x}_j(t)\right)\,dt + C_m\,\left(\mathbf{x}_{j+1}(t)+\mathbf{B}(\phi)\hat{\mathbf{x}}_{j,j+1}-\mathbf{x}_j(t)\right)\,dt + \mathbf{v}\,dt+\mathbf{v}_s\,dt.$$

The first term on the right-hand side accounts for haptotaxis, and the second term accounts for a spring force as a result of the cell centre. The third and fourth terms account for spring forces to the immediate neighbouring points on the cell boundary. The last two terms account for possible flow velocity and the displacement velocity in case that the cell migrates through a gel. This absolutely does not complete the mathematical description of the model, the reader is referred to [1] for more information regarding the model equations.

3 Results

We study simulations in which two (or three) cells that transmigrate through the channel with permanently deformable channel walls are considered. Two different cases are considered in our simulation studies: case 1: two cells are released one after another, where the first cell, the leading cell, transmigrates on its own through the channel. Once the cell has left the channel, the second cell, follower cell, is released to transmigrate through the channel. In some of the simulations, this is followed by a third cell; case 2: the first and second cells are released simultaneously adjacent to each other, see Figure 1, to transmigrate through the channel. Case 1 reflects the case that the first cell 'widens' the channel so that the second cell can migrate more easily. Case 2 reflects the case that the second cell pushes the first cell through the channel. The second case was not considered in [2]. The model contains a random component as a result of random walk, which is modelled through a vectorial Wiener process, as well as randomness for focal adhesion depending on the concentration of the chemo-attractant, which is modelled by sampling from exponential distributions. Furthermore, since many of the input parameters for the cancer cells are unknown, we assume statistical distributions (normal and lognormal) for the input parameters, see [1]. Hence a simulation run merely represents a sample from a multivariate statistical distribution, where the chosen distributions for the input parameters can be regarded as prior distributions. As a result, the velocity of the cells over time, as well as the transmigration times follow posterior statistical distributions. These posterior distributions have been estimated using the Monte Carlo-based sampling with respect to the input parameters. In this sense the common approach follows a Bayesian principle. The simulation results are presented in Figure 3, where the cell velocity is shown as a function of time for both cases. Furthermore, the average velocity has been presented in Table 1. Since the mechanism of focal adhesion impacts the transmigration velocity, it is important that the channel is not too wide, otherwise focal adhesion cannot occur. Furthermore, a very thin channel is disadvantageous as well since the cell can only be deformed up to a maximum deformation. From Figure 3 and Table 1, the following is observed: In case 1, the follower cell migrates faster

than the leading cell. Hence, this mode by plastic widening of the channel as a result of microstructural changes accelerates transmigration of cancer cells. However, the relation is not monotonic since too wide a channel will inhibit focal adhesion and, thereby, cell migration. In case 2, both the follower cell and the leading cell benefit from each other since the follower cell 'pushes' the leading cell through the cavity, which accelerates transmigration. Using Wilcoxon's Statistical Test, the model significantly favours the hypothesis that the transmigration of multiple cells benefits from collaboration. This conclusion is in line with the experimental outcomes in [6,7].

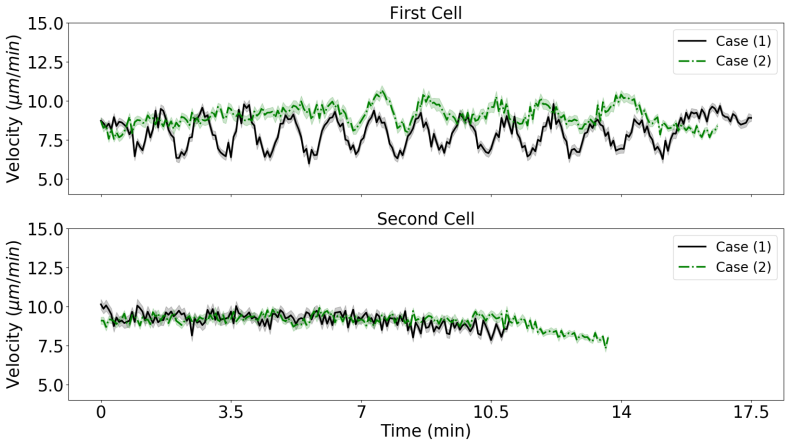

Fig. 3: Average velocity of 50 runs of simulations at every time step for Cell 1 and Cell 2 in both cases, from [1]

Average Velocity $(\mu m/min)$	**Cell 1**	**Cell 2**	**Cell 3**
Case (1)	3.99	4.59	4.52
Case (2)	4.48	4.46	NA

Table 1: Duration time of the cells penetrating through the channel

The simulations that we present mimic the *in-vitro* experiments where cells penetrate through narrow, rigid channels. The main difference is that the channels in the experimental studies are rigid. Our previous modelling study involved such rigid channels [5]. We believe that the current model innovation may initiate new experimental studies with deformable channel walls. Deformable channel walls are probably closer to reality since during metastasis, the cancer cells migrate through deformable walls of (small) blood vessels in order to get into the blood stream. Although it seems straightforward from an intuitive point of view that a first cell that widens the channel facilitates faster

migration of subsequent cells through the channel, our study is, as far as know, the first computational framework that attempts to quantify the extent that cancer cells benefit from each other in migrating from one region to another region.

4 Conclusions

The model predicts that collective cell transmigration enhances the process of transmigration and hence metastasis of cancer is enhanced by collective cell migration.

References

1. Peng, Q., Vermolen, F.J., Weihs, D.: Physical confinement and cell proximity increase migration rates and invasiveness: a mathematical model of cancer cell invasion through flexible channels. J. Mech. Behav. Biomed. Mater., 142, 105843 (2023), https://doi.org/10.1016/j.jmbbm.2023.105843
2. Peng, Q., Vermolen, F.J., Weihs, D.: Predicting the efficacy of stalk cells following leading cells through a micro-channel using morphoelasticity and a cell shape evolution model. In: Tavares, J.M.R.S., Bourauel, C., Geris, L., Vander Slote, J. (eds) Computer Methods, Imaging and Visualization in Biomechanics and Biomedical Engineering II. CMBBE 2021. Lecture Notes in Computational Vision and Biomechanics, vol 38. Springer, Cham. https://doi.org/10.1007/978-3-031-10015-4_10
3. Bershadsky, A.D., Kozlov, M.M.: Crawling cell locomotion revisited. Proc. Nat. Acad. Sc., 108 (51), 20275 – 20276 (2011), https://www.pnas.org/doi/full/10.1073/pnas.1116814108
4. Lämmermann, T., Bader, B.L., Monkley, S.J., Worbs, T., Wedlich-Söldner, Hirsch K., Keller, M., Förster, R., Critchley, D.R., Fässler, R., Sixt, M.: Rapid leukocyte migration by integrin–independent flowing and squeezing. Nature, 453, 51–55 (2008), doi:10.1038/nature06887
5. Peng, Q., Vermolen, F.J., Weihs, D.: A formalism for modelling traction forces and cell shape evolution during cell migration in various biomedical processes. Biomech. Model. Mechanobiol., 20, 1459 – 1475 (2021), https://link.springer.com/article/10.1007/s10237-021-01456-2
6. Merkher, Y., Weihs, D.: Proximity of metastatic cells enhances their mechanobiological invasiveness. Ann. Biomed. Eng. 45 (6), 1399–1406 (2017).
7. Tulchinsky, M., Weihs, D.: Computational modeling reveals a vital role for proximity-driven additive and synergistic cell-cell interactions in increasing cancer invasiveness. Acta Biomater. 163, 392-399 (2022)