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MONTE CARLO UNCERTAINTY QUANTIFICATION IN MODELLING CELL DEFORMATION DURING CANCER METASTASIS

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Abstract: *During metastasis of cancer, cell migration plays a crucial role, which is normally accompanied by morphological evolution. To simulate cell deformation, we develop a phenomenological, computational model involving deformation of a cell as well as its nucleus. The migration of a single cell is orchestrated by a generic signal (e.g. a chemokine or a stiffness stimulus), the microvascular flow and stochastic processes, which are dealt with by using Green's Fundamental solutions, Poisseuille flow and a vector Wiener process, respectively. Moreover, due to the uncertainties in the input variables, Monte Carlo simulations are carried out to evaluate the correlations between various parameters and quantitatively predict the likelihood of vessel transmigration of one cell during cancer metastasis.*

1. INTRODUCTION

Cell migration takes place in many biomedical processes, which can be classified mainly into amoeboid movement and mesenchymal movement. Driven by external signals such as chemotaxis, durotaxis or tensotaxis, cell dissemination is crucially necessary to closing a wound opening for instance; conversely, it is detrimental during cancer metastasis. Therefore, the research on cell migration may provide a breakthrough for the pathology of many diseases.

Despite the fact that scientific research and medical technology have made significant progress on cancer inhibition and treatment during the past several decades, the global mortality rate caused by cancer has been rising along with emerging characters, i.e. disease diversity, complexity, and proneness of young patients. Thus, the input from various fields definitely needs to be enhanced. Mathematical modeling is capable of reproducing the situations that are beyond the scope of experiments. With proper validation and evaluation, mathematical models are able to provide avenues to understand cancer disease.

Cancer cells migrate typically attracted by chemokines [1] or the stiffness of substrate /extracellular matrix (ECM) [2]. However, due to the high inefficiency of cancer dissemination,

only less than 0.02% of the cells can form colonies at distant sites successfully [3, 4]. In spite of this inefficiency, cancer metastasis still causes around 90% of the deaths as a result of cancer mortality [5, 6]. Metastasis is a multi-step cascade. Generally, the cascade of a metastatic cell can be summarized by the following consecutive steps, 1) detachment of the primary tumor; 2) local invasion and intravasation; 3) survive transit in the blood /lymphatic vessels; 4) extravasation and colonization [7, 8]. To make the problem tractable, we aim at modeling the steps of intravasation and extravasation of a metastatic cell using a simplified formalism for cancer spread.

During cancer invasion, cells normally undergo transitions between two states of mesenchymal motion and amoeboid motion, respectively, involving degradation of the surrounding substrate /ECM by secreting proteinases MMP's [9, 10] and squeezing through preexisting sub-cell-size openings accompanied by the deformation of a cell and its nucleus [11]. In these two mechanisms, we solely consider the latter where a single cell migrates and deforms during cancer invasion with an independence of MMP's. Based on this scenario, a computational model is developed that also shows the interactions between the cell membrane and the nucleus surface during deformation. Furthermore, three unknown parameters are quantitatively analyzed by Monte Carlo simulations, which provides insight into the correlation between the metastatic rate and various input parameters. It is probably difficult to obtain these correlations from experimental (in-vitro and in-vivo) studies.

2. MATHEMATICAL MODEL

To mimic the cell cytoskeleton and the interaction between cell and its nucleus, a single cell is treated as a collection of parallel 30 nodal points on the cell membrane and nucleus surface, respectively. The corresponding parallel points are connected such that nucleus can move in coordination with cell cytoskeleton. The migration of each nodal point i on the cell membrane is considered as a result of the attraction from a chemokine /stiffness signal and a mechanical stimulus. The position of a nodal $\mathbf{x}_i(t)$ is determined by

$$d\mathbf{x}_i(t) = \beta \nabla c(t, \mathbf{x}_i(t))dt + \alpha \left(\mathbf{x}_i^n(t) + B(\phi)\hat{\mathbf{x}}_i - \mathbf{x}_i(t)\right) dt + u_z(r_i)dt + \eta_1 d\mathbf{W}(t). \quad (1)$$

The first term in Equation 1 takes care the chemokine or stiffness attraction, where we use Green's Fundamental solutions to deal with an imaginary point source. Here, β and c represent a nodal point's response to external signals and the intensity of the signal, respectively. Taking the cell cytoskeletal dynamics into account, the second term is used to model the interaction between cell and nucleus, where α stands for cell deformation relaxation and $B(\phi)$ is a two dimensional rotation matrix. Within a small blood vessel, flow of blood is modelled by means of Poisseuille flow with the velocity $u_z(r_i)$. Moreover, due to the random nature of cell movement, $d\mathbf{W}$ simulates random local deformation, which is a vector Wiener process with independent samples from a normal distribution. Analogously, the stochastic differential equation of motion for a nodal on the surface of nucleus is given by

$$d\mathbf{x}_i^n(t) = \alpha^n \left(\mathbf{x}_c(t) + B(\phi)\hat{\mathbf{x}}_i^n - \mathbf{x}_i^n(t)\right) dt - \alpha \left(\mathbf{x}_i^n(t) + B(\phi)\hat{\mathbf{x}}_i - \mathbf{x}_i(t)\right) dt + \eta_2 d\mathbf{W}(t), \quad (2)$$

where α^n denotes the deformation relaxation of the nucleus, and thereby the migration of a nodal point on nucleus surface is restricted by the cell mass center (the first term in Equation 2)

and the outer boundary (the second term in Equation 2). For more information, we refer to our other two works [12, 13].

With respect to our above-mentioned two previous studies, we have incorporated a steady blood fluid flow. Since we are assuming a slow flow in the capillary-sized vessel, it is natural to consider a laminar flow. Note that we only consider a component in the axial direction of the blood flow velocity to simplify the phenomenon. Considering the pressure-induced Poisseuille flow, the solution reads as

$$u_z(r) = -\frac{\partial p}{\partial z} \cdot \frac{R_t^2}{4\mu} \cdot (1 - \frac{r^2}{R_t^2}), \quad in\ \Omega_b, \tag{3}$$

where, p, μ and R_t denote the pressure, viscosity of fluid and half width of the blood vessel. Within the vasculature domain Ω_b, the distance between one nodal point and vessel boundary r decides the axial velocity of the nodal point, which gives a parabolic profile. This straightforward phenomenological treatment of the blood flow can also be found in [14]. We note that the current formalism is two-dimensional and that real world situations are three-dimensional. In a three-dimensional setting a cell is able to migrate around a venule and hence it is able to reach a location behind a small blood vessel without having to be transported through a vessel. The current simulation should be considered as phenomenological in the sense that the current model provides a formalism that can be used to use the following chain: (1) transmigration of (cancer) cells through a vessel, (2) transport through the small blood vessel to a remote location, and (3) the subsequent transmigration through a vessel wall, triggered by an external signal, to exit the blood vessel. Finally, the cell can possibly colonize through possible successful proliferation in its environment. This is one of the scenarios in which a cancer can spread from one tumor to different locations in the body of an organism.

3. RESULTS

There are preexisting pores and fiber-like tracks in the substrate /ECM, and thereby cells are able to penetrate through them without destroying their surroundings [15]. Based on available literature, parameters have been chosen listed in Table 1 and more input values with corresponding sources are provided in [13].

We model the intravasation of a metastatic cell through a preexisting pore in endothelium, where the exact underlying mechanism is still poorly understood. Some studies suggest that cell intravasation is regulated by tumor-stromal cell interactions [16], biochemical factors (like tumor necrosis factor alpha TNF-α) or other cell-cell communications [17]. Therefore, we assume that a cancer cell is attracted to translocate into the bloodstream by a biochemical signal (see Figure 1 (a) and (b)). Due to the flow of microfluid in the vessel, the migrating cell is advected at a velocity whenever subject to the flow. Note that there is no slip on the vessel wall, hence the blood velocity is zero on the vessel boundaries. To visualize the blood flow, some imaginary particles indicated in red color have been plotted in Figure 1, which have no influence on the migrating cell. Subsequently, the cell is capable of moving towards the emitting source (chemokine or stiffness) to complete the extravasation in Figure 1 (d). Once the source is engulfed, the cancer cell is no longer mechanically deformed and hence the cell (and also its nucleus) returns to its equilibrium circular shapes which has been described in more detail in

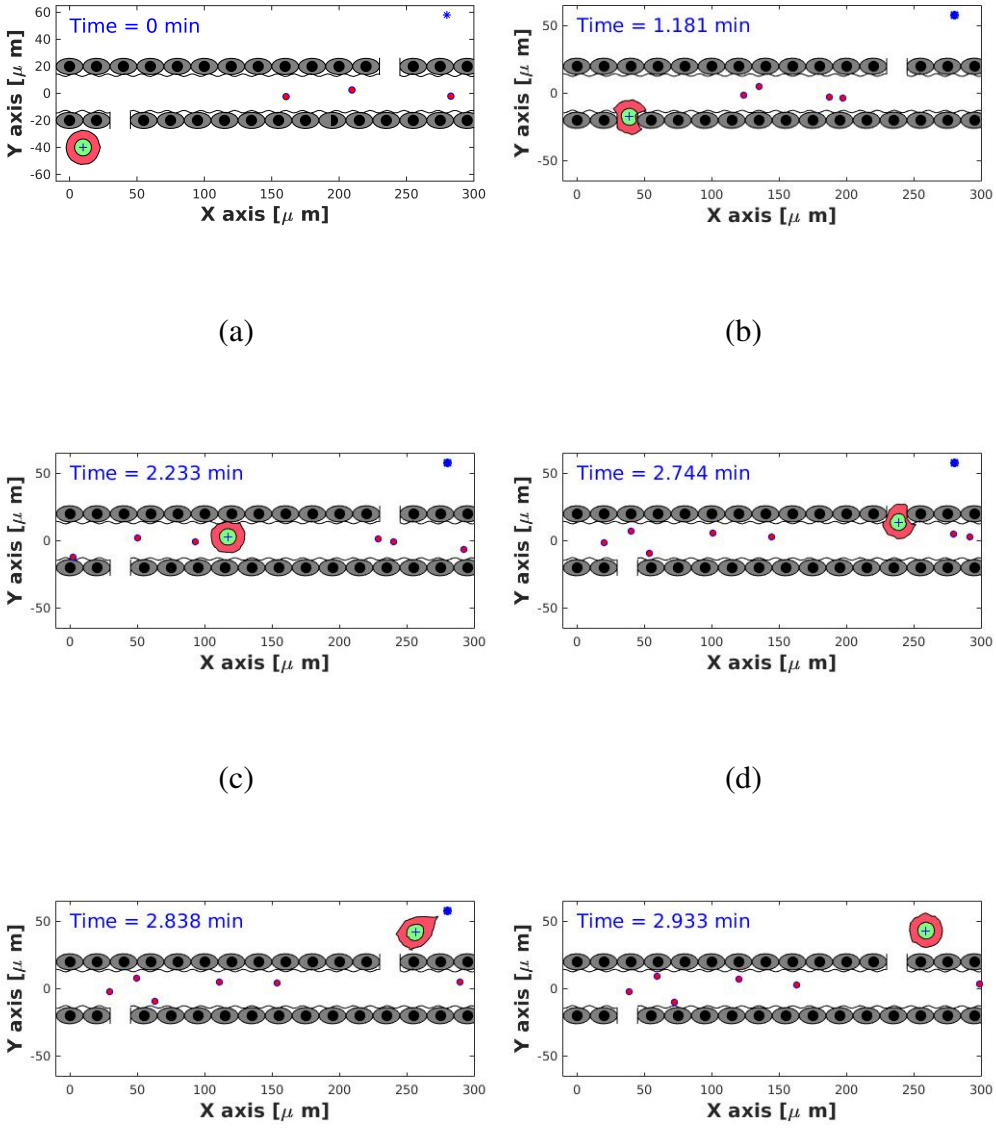


Figure 1. Consecutive snapshots of one cell during intravasation and extravasation of a blood or lymphatic vessel in a 2D simulation. The migrating cell, nucleus and the vessel are visualized by red, green and grey colors, respectively. A blue asterisk denotes any type of sources.

Table 1. **Parameter values**

Constant	**Notation**	**Value**	**Unit**
Radius of a cell	R	12.5	μm
Radius of a nucleus	R_c	6.25	μm
Half width of the vessel	R_t	14	μm
Cell deformation relaxation rate	α	250	min^{-1}
Nucleus deformation relaxation rate	α^n	2500	min^{-1}
Mobility of points on cell membrane	β	60	min^{-1}
Pressure difference	dp	1	$kPa/100\ \mu m$
Viscosity	μ	0.1	$Pa \cdot s$
Time step in 2D	Δt	0.0001	min

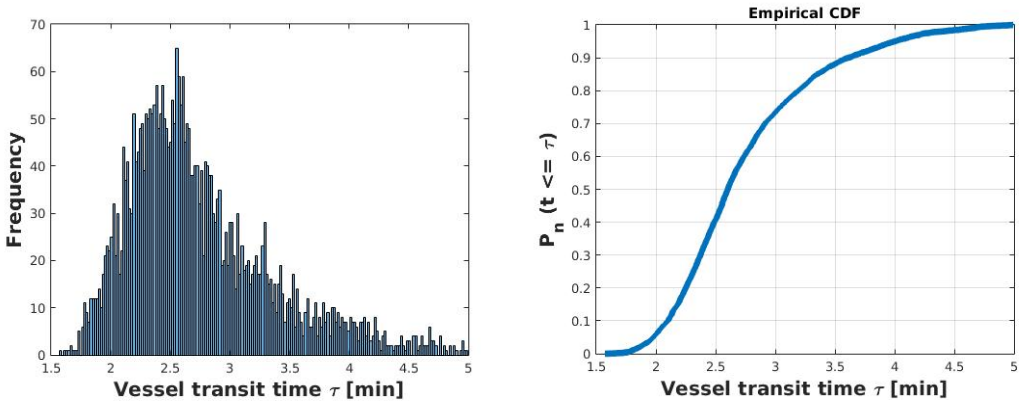
[13]. As a conclusion, our model phenomenologically shows that the circular shapes of the cell and its nucleus interactively evolve according to the stiff barrier during the cell metastasis.

To draw any quantitative conclusions from the model, Monte Carlo simulations have been carried out to evaluate the uncertainties among the input variables on the vessel transit time of one cell during cancer metastasis τ. The input parameters are the radius of a cancer cell R, the radius of microvessel R_t and the cell deformation relaxation rate α. According to experimental results, the MMP-independent cell migration arrests if the pore size is below 10% of the nuclear cross section [10]. Since we choose the radius of the nucleus, R_c, to be half of the radius of cell R in our model, we investigate the cell transit time by sampling on the R value (which is the equilibrium radius of the cell) such that intravasation fails if the cell is too big. By equation 3, it is clear that the velocity of blood is influenced significantly by the vessel radius R_t, and thereby we evaluate the impacts of R_t on the cell transit time τ. Furthermore, the cell deformation relaxation parameter α is sampled to show the relation between the cell deformation relaxation and the cell transit time. We sample each parameter from a normal distribution with 5000 simulations (see Table 2) such that the Monte Carlo error is sufficiently small. Based on our simulation results, the cell stucks out of the blood vessels (like Figure 1 (b)) during a relatively long time. Therefore, we assume that the cell fails to reach the other part of the body through the vessel if the transit time satisfies $\tau > 5$ min. By analyzing the output data, there are 1496 out of 5000 failures, and thereby the success rate of cell transit during cancer metastasis is 70.08% in our simulations. In Figure 2, we present two diagrams: (a) is a histogram of 3504 successful samples showing the distribution of the cell transit time τ and (b) is the corresponding cumulative probability distribution function (CDF), where the x-axis denotes the cell transit time τ and the y-axis, represents the frequency of occurrence and the probability $P_n\ (t \leq \tau)$ given that cell penetrates to the other part of the body. In fact, Figure 2 (b) shows $P_n\ (t \leq \tau$ | cell has penetrated). It is a conditional probability, given by $P_n\ (t \leq \tau$ | cell has penetrated) = $P_n\ (t \leq \tau \cap$ cell has penetrated) / P_n (cell has penetrated). Since we have that $P_n\ (t \leq \tau \cap$ cell has penetrated) = $P_n\ (t \leq \tau)$, (because $P_n\ (t \leq \tau \cap$ cell has not penetrated) = 0), we have $P_n\ (t \leq \tau)$ = $P_n\ (t \leq \tau$ | cell has penetrated) * P_n (cell has penetrated), where P_n (cell has penetrated) $\approx$ 0.70. Furthermore, the slope of the CDF curve in Figure 2 (b) represents the probability density and thereby any probability P_n can be integrated within an time interval.

On the other hand, it is also possible to estimate the time at which for instance 95% of the successfully metastasizing cells have reached the other side of the vessel within a time of 4 min. To compute the likelihood that the cell penetrates within a certain time, one has to multiply the conditional probability from Figure 2 (b) by the probability of successful penetration, which is about 0.70.

Table 2. **Sample values**

-	R	R_t	α
Value	$N \sim (12.5, 5^2)$	$N \sim (16, 5^2)$	$N \sim (250, 50^2)$
Unit	μm	μm	min^{-1}



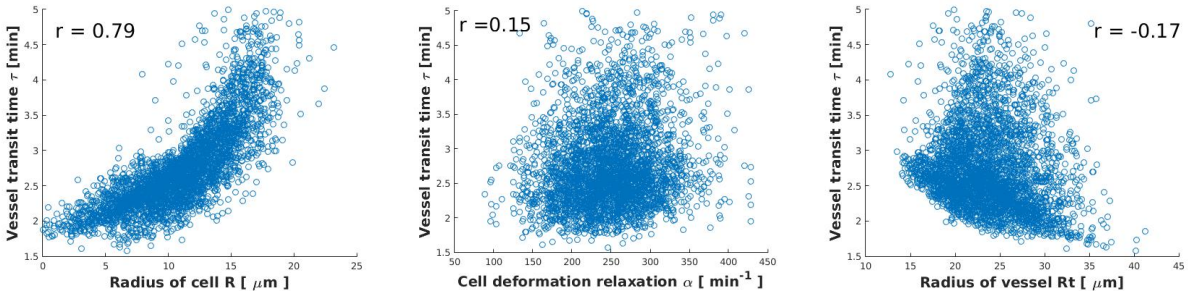
(a) (b)

Figure 2. The histogram (a) and CDF plot (b) of the vessel transit time of one cell during intravasation and extravasation.

Regarding the correlations between the cell transit time τ and three variables R, R_t and α, Figure 3 shows the scatter plots with corresponding correlation coefficient. Note that there is a significantly positive linear correlation between the cell transit time τ and cell radius R with correlation coefficient r equals to 0.79. This result is consistent with a biological experiment that the migrating cancer cells with relatively big radius fail to penetrate a blood or lymph vessel [10]. Conversely, the radius of vessel R_t shows a negative linear correlation with the cell transit time τ in Figure 3 (c). As R_t increases, the flow velocity increases slightly which probably accelerates the cell metastasis resulting in a shorter time τ. Moreover, the cell deformation relaxation rate α shows no significant correlation with the cell transit time τ in current scenario.

4. DISCUSSION AND CONCLUSIONS

We developed a phenomenological model for chemico-mechanically induced cell and nucleus deformation during cancer spread in 2D and we combined the model with Monte Carlo simulations. Taking a generic signal into account, the emitting source has been incorporated such that it allows a simple treatment using Green's Fundamental solutions. Next to the signal,



(a) (b) (c)

Figure 3. Scatter plots to show the dependence of the cell transit time τ on (a) the radius of cell R, (b) cell deformation relaxation rate α, and (c) the radius of vessel R_t.

the interaction between the cell membrane and its nucleus proceeds via the deformation relaxation of the cell's cytoskeleton, which is dealt with using a collection of springs. In contrast to our previous works, a steady blood flow is taken into account using Poisseuille flow, where the bloodstream is treated as an incompressible fluid. To determine the positions of one cell and its nucleus, we use an IMplicit–EXplicit (IMEX) time-integration method to update the positions such that the linear parts are treated using an Euler backward scheme, whereas the nonlinear parts are treated in a forward Euler method. As we expected, the migrating cell and nucleus are able to deform extensively in the confined spaces. Our model is likely to benefit the further understanding of cancer spread mechanisms and thereby the model is likely to be helpful for preventing the deterioration of early cancer lesions.

Most parameters are taken from literature, due to the variations of parameters, the quantification of the propagation of uncertainty in the data is crucially important. To this extent, we carry out Monte Carlo simulations to estimate likelihoods of vessel transmigration of a single cell during cancer metastasis. In our simulation, the likelihood of a cancer cell transmigration is 70.08%. To metastasize successfully through constrained openings without ECM degradation, the sizes of the migrating cell and its nucleus are dominating comparing with other two input parameters. Furthermore, the speed of the microfluid negatively affects the cell's transmigrating time, and hence positively the cell's penetration rate.

As far as we know, our model is the first description considering the interactive deformation between a cell and its nucleus during cancer metastasis. The full model is presented in more detail in [13]. For the current conference proceedings we extended the model in [13] with the laminar flow of blood through a small blood vessel. Although the current formalism is very elementary in the incorporation of the migratory path of cancer cells through the blood stream, it does provide a first incentive to include realistic complex migration of cancer cells in the wake of metastasis. Our model is expected to predict the microenvironmental behavior of the cell and nucleus and to complement biological experiments as well as clinical trials for researching cancer metastasis inhibition and new drug developments.

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References

[1] Christine L Chaffer and Robert A Weinberg. A perspective on cancer cell metastasis. *Science*, 331(6024):1559–1564, 2011.

[2] Sonbula Massalha and Daphne Weihs. Metastatic breast cancer cells adhere strongly on varying stiffness substrates, initially without adjusting their morphology. *Biomechanics and Modeling in Mechanobiology*, pages 1–10, 2016.

[3] Toni Celià-Terrassa and Yibin Kang. Distinctive properties of metastasis-initiating cells. *Genes & development*, 30(8):892–908, 2016.

[4] Keith J Luzzi, Ian C MacDonald, Eric E Schmidt, Nancy Kerkvliet, Vincent L Morris, Ann F Chambers, and Alan C Groom. Multistep nature of metastatic inefficiency: dormancy of solitary cells after successful extravasation and limited survival of early micrometastases. *The American journal of pathology*, 153(3):865–873, 1998.

[5] Thomas N Seyfried and Leanne C Huysentruyt. On the origin of cancer metastasis. *Crit Rev Oncogenesis*, 18(1-2):43, 2013.

[6] Gaorav P Gupta and Joan Massagué. Cancer metastasis: building a framework. *Cell*, 127(4):679–695, 2006.

[7] AF Chambers, AC Groom, and IC MacDonald. ā dissemination and growth of cancer cells in metastatic sites, ā nat. *Rev. Cancer*, 2:563ā, 2002.

[8] L Kopfstein and G Christofori. Metastasis: cell-autonomous mechanisms versus contributions by the tumor microenvironment. *CMLS-Cell Mol Life S*, 63(4):449–468, 2006.

[9] Tea Kalebic, S Garbisa, B Glaser, and LA Liotta. Basement membrane collagen: degradation by migrating endothelial cells. *Science*, 221(4607):281–283, 1983.

[10] Katarina Wolf, Mariska Te Lindert, Marina Krause, Stephanie Alexander, Joost Te Riet, Amanda L Willis, Robert M Hoffman, Carl G Figdor, Stephen J Weiss, and Peter Friedl. Physical limits of cell migration: control by ecm space and nuclear deformation and tuning by proteolysis and traction force. *J Cell Biol*, 201(7):1069–1084, 2013.

[11] Peter Friedl, Katarina Wolf, and Jan Lammerding. Nuclear mechanics during cell migration. *Current opinion in cell biology*, 23(1):55–64, 2011.

[12] Jiao Chen, Daphne Weihs, and Fred J Vermolen. A model for cell migration in non-isotropic fibrin networks with an application to pancreatic tumor islets. *Biomechanics and modeling in mechanobiology*, pages 1–20, 2017.

[13] Jiao Chen, Daphne Weihs, Van Dijk Marcel, and Fred J Vermolen. A phenomenological model for cell and nucleus deformation during cancer metastasis. *Biomechanics and Modeling in Mechanobiology*, (Under review), 2018.

[14] FJ Vermolen, MM Mul, and A Gefen. Semi-stochastic cell-level computational modeling of the immune system response to bacterial infections and the effects of antibiotics. *Biomechanics and modeling in mechanobiology*, 13(4):713–734, 2014.

[15] Colin D Paul, Panagiotis Mistriotis, and Konstantinos Konstantopoulos. Cancer cell motility: lessons from migration in confined spaces. *Nature Reviews Cancer*, 17(2):131, 2017.

[16] Carlos P Huang, Jente Lu, Hyeryung Seon, Abraham P Lee, Lisa A Flanagan, Ho-Young Kim, Andrew J Putnam, and Noo Li Jeon. Engineering microscale cellular niches for three-dimensional multicellular co-cultures. *Lab on a Chip*, 9(12):1740–1748, 2009.

[17] Ioannis K Zervantonakis, Shannon K Hughes-Alford, Joseph L Charest, John S Condeelis, Frank B Gertler, and Roger D Kamm. Three-dimensional microfluidic model for tumor cell intravasation and endothelial barrier function. *Proceedings of the National Academy of Sciences*, 109(34):13515–13520, 2012.