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Computational Modeling of Cell Behavior Driven by Growth Factor Release from Biodegradable Microcapsules

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Introduction

The study of **cell behavior** is essential for understanding fundamental biological processes and disease mechanisms, particularly in cancer, where cell differentiation, migration, and proliferation play critical roles. Differentiation, in particular, is highly influenced by biochemical signals such as growth factors, which regulate how stem or progenitor cells acquire specialized functions in response to their **microenvironment** [1].

Previous studies often rely on steady or static gradients of signaling molecules, assuming a constant concentration spatially and temporally, which fall short of replicating the complexity of the tumor microenvironment or tissue repair contexts [2].

In contrast, this study introduces a more realistic model where biochemical signal are released from **biodegradable microcapsules** over time. These microcapsules are designed with degradable shells, allowing precise control over the onset and rate of molecule release. This setup results in non-uniform, time-dependent concentration gradients, offering a better approximation of biological conditions. Moreover, the ability to modulate the release profile by altering microcapsule properties provides a powerful tool for targeted therapeutic strategies.

Methods

Mathematical models of diffusion-controlled system [3]**:**

$$\frac{\partial c}{\partial t} + \nabla \cdot (\mathbf{D}\,\nabla c) = 0,$$

$$\frac{\partial c}{\partial t} = -k\,c.$$

Validation of diffusion model [4]**:**

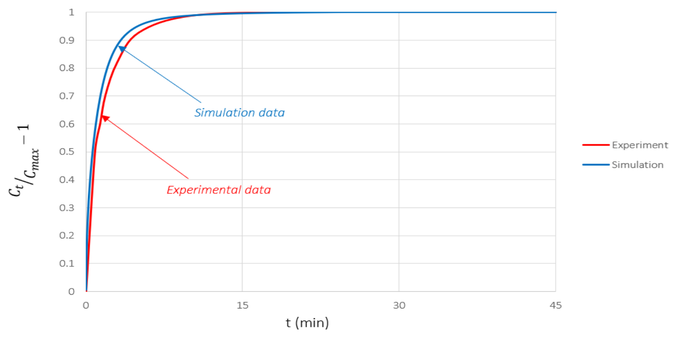

Figure 1. Model validation by reproducing diffusion results from Bielinski [4], using the same geometry and diffusion coefficients. The good agreement confirms the accuracy of our diffusion model.

Mathematical models of cell behavior [1, 2]**:**

$$\mathbf{F}_{trac}^{eff} + \mathbf{F}_{prot} + \mathbf{F}_{drag} = 0,$$

$$\mathbf{F}_{trac}^{eff} = (1-\mu_{chem})\|\mathbf{F}_{trac}\|\boldsymbol{e}_{mech} + \mu_{chem}\|\mathbf{F}_{trac}\|\boldsymbol{e}_{chem},$$

$$\mathbf{F}_{prot} = \alpha \cdot \|\mathbf{F}_{trac}\| \cdot \boldsymbol{e}_{rand}, \qquad \mathbf{F}_{drag} = 6\pi\, r\, \vartheta_f\, \mathbf{V}_{cell}.$$

$$\text{cell growth} = \begin{cases} 1 \text{ mother cell} \rightarrow 2 \text{ daughter cells} & \gamma_{prof}^{0} \le \gamma_{prof} \;\&\; MI = 1 \\ \text{no cell proliferation} & \text{otherwise} \end{cases}$$

$$\text{cell transmit} = \begin{cases} \text{MSC} \rightarrow \text{CAF} & \gamma_{dif}^{0} \le \gamma_{dif} \;\&\; MI = 1 \\ \text{no cell differentiation} & \text{otherwise} \end{cases}$$

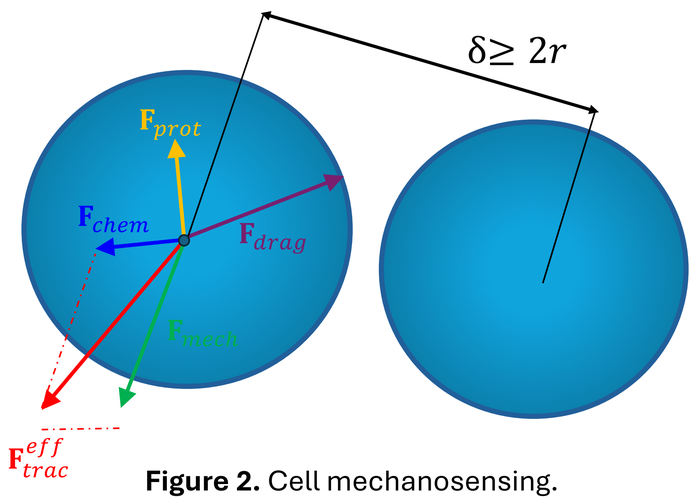

Figure 2. Cell mechanosensing.

Results and conclusions

This study investigates the impact of vascular endothelial growth factor (VEGF) on the behavior of multiple myeloma cells (MMCs). VEGF is gradually released from drug-loaded microcapsules over several days, incorporating a programmed release delay. Unlike previous models with fixed VEGF levels, our approach captures both spatial and temporal variations in VEGF diffusion within the extracellular matrix (ECM).

The simulation results show that MMCs respond dynamically to the evolving VEGF gradient. As VEGF accumulates near the capsules, the cells generate stronger traction forces and migrate toward these regions. This directed migration leads to central aggregation, increased cell–cell adhesion, and reduced internal deformation due to clustering. Over time, as VEGF diffuses throughout the ECM, the cells continue to follow regions with higher VEGF concentration.

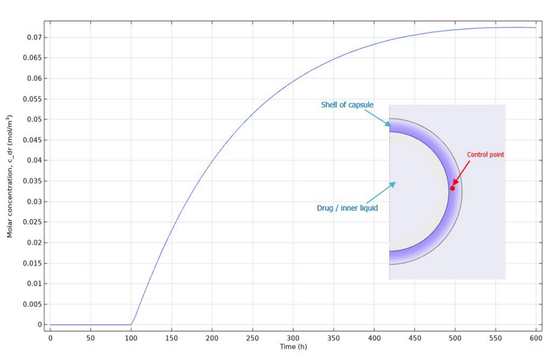

Figure 3. Controlled release profile of VEGF from biodegradable microcapsules over time.

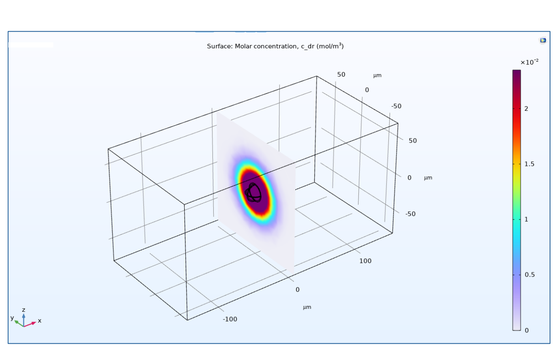

Figure 4. release of VEGF, microcapsule located in the middle of ECM.

The model demonstrates that gradual and delayed VEGF release can effectively modulate MMC proliferation and differentiation. These findings highlight the importance of spatiotemporal signal dynamics and underscore the model's potential for exploring drug delivery strategies in evolving tissue microenvironments.

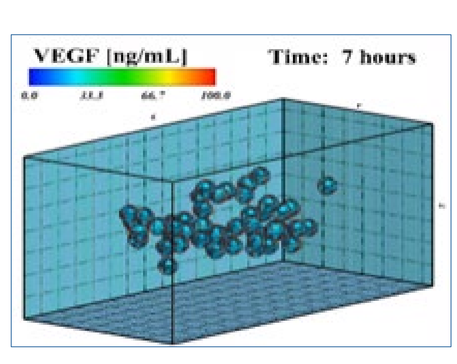

Figure 5. Simulated multiple myeloma cell behavior in response to VEGF gradients.

Acknowledgements

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