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

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Abstract

Among other stimuli, cell behavior is also regulated by biochemical signals such as growth factors, pharmaceutical agents. Unlike previous models assuming steady gradients, we model the time-dependent release and diffusion of growth factors from degradable microcapsules. Drug diffusion is modeled using Fick's law with spatially varying diffusivity. The model is validated against previous experimental studies and offers a realistic framework to study localized, controlled drug release and its effect on cell movement.

Introduction

The study of cell behaviour is crucial in understanding fundamental biological processes and disease mechanisms, particularly in cancer, where the movement of malignant cells is closely linked to metastasis and therapeutic resistance. For example, cell migration is not just random, but it is highly regulated by external cues, especially biochemical signals like growth factors, pharmaceutical agents, influencing cell directionality, speed, and survival [1].

While previous studies have provided valuable insights into these mechanisms, they often rely on steady or static gradients of signaling molecules, assuming a constant concentration spatially and temporally. Such assumptions, while simplifying analysis, fall short of replicating the complexity of the tumor microenvironment or tissue repair contexts, where signal concentrations can significantly be fluctuated over time [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. The release of biochemical substances from the microcapsules was modeled using Fick's diffusion theory [3]. Fick's first and second laws were employed to describe the transport of solutes across the microcapsule membrane and cell Extracelular Matrex (ECM) [3]:

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

where c is the solute concentration in the bulk and $\mathbf{D}$ is the diffusion coefficient. Degradation was implemented using a first-order kinetic expression, allowing temporal control over the initiation of release [3]:

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

where k is the degradation rate. This formulation enables simulation of dynamic concentration profiles as a function of both time and space.

Mathematical models of cell migration. Cell migration is modeled by accounting for mechanical interactions between the cell, the ECM, and neighboring cells. Traction forces generated by actin-myosin contractility are transmitted to the ECM via focal adhesions, and their magnitude is modulated by internal stresses, adhesion strength, fibronectin concentration, and the availability of surface receptors [1, 2].

The effect of induced biochemical substances on cell-ECM adhesion is included by regulating receptor availability based on their local concentration. This captures the enhanced adhesion

and motility triggered by biochemical signaling [1, 2].

In addition to traction forces, stochastic protrusion forces resulting from actin polymerization and hydrodynamic drag forces opposing cell movement are considered. The overall migration behavior results from the balance between these driving and resisting forces. Consequently, we can write the force balance as bellow [1, 2]:

$$\mathbf{F}_{trac} + \mathbf{F}_{prot} = \mathbf{F}_{drag}.$$

In addition, cell proliferation and differentiation are governed by a time-dependent Maturation Index, representing the progression of the cell cycle dependence on both mechanical and chemical stimuli [1]. The cell cycle completion is influenced by internal cell deformation and biochemical signals. Mechanical cues are quantified through strain energy on the cell membrane, while biochemical levels adjust the cell's responsiveness, enabling a dynamic, environment-sensitive cell proliferation and/or differentiation [1, 2].

Validation of diffusion model. To validate the diffusion model, we reproduced the experimental results presented by Bielinski (2021) by setting the model parameters to insulin diffusion [4]. By successfully reproducing these results in our implementation (Figure 1), we confirm the reliability and accuracy of our diffusion modeling approach.

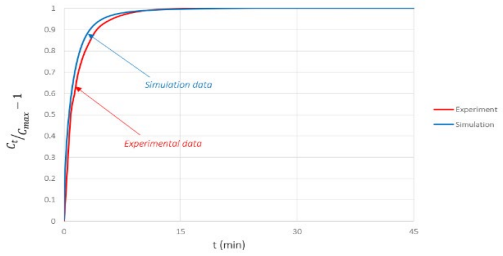
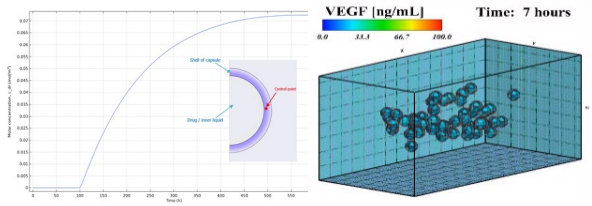


Figure 1. Model validation by reproducing diffusion results from Bielinski [4], using the same geometry and diffusion coefficients. The good agreement confirms the accuracy of our diffusion model.

Results and conclusions

This study investigates the impact of vascular endothelial growth factor (VEGF) on the behavior of multiple myeloma cells (MMCs). Here VEGF is gradually released from drug-loaded microcapsules over several days, incorporating a controlled release delay (Figure 2a). Unlike previous models with fixed VEGF concentrations, this approach captures spatially and temporally varying VEGF diffusion within the ECM. The results demonstrate significant changes in cell behavior in response to time-dependent VEGF release compared to a steady chemical gradient. As VEGF accumulates near the microcapsules, cells generate stronger traction forces and migrate toward these regions. This leads to central cell aggregation, increased cell-cell adhesion, and reduced internal deformation due to clustering. Overall, the simulation reveals that gradual and delayed VEGF release can effectively guide MMC proliferation and differentiation, highlighting the model's potential for studying drug–cell interactions in dynamic tissue environments (Figure 2b).



(a) (b)

Figure 2. (a) the VEGF concentration and (b) the effect of VEGF release on the cell behavior.

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References

[1]. Pau Urdeitx, S. Jamaleddin Mousavi, Stephane Avril, Mohamed H. Doweidar. *Computational modeling of multiple myeloma interactions with resident bone marrow cells*. Computers in Biology and Medicine, 2023, vol. 153.

[2]. S. Jamaleddin Mousavi, Mohamed H. Doweidar, *Three-dimensional numerical model of cell morphology during migration in multi-signaling substrates*, PLoS One 10 (3) (2015) e0122094.

[3]. Crank, J. *The Mathematics of Diffusion*. 2nd ed. Oxford: Oxford University Press, 1975.

[4]. Bielinski, C., and Kaoui, B. *Numerical method to characterise capsule membrane permeability for controlled drug delivery*. Biomechanics and Bioengineering Laboratory, Université de Technologie de Compiègne, CNRS, France, November 3, 2021.