

From Diffusion to Cell Fate: Computational Design of Intelligent Porous Microcapsules

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Abstract

A multiphysics computational model is developed to predict cell fate regulated by porous microcapsules releasing biochemical signals within extracellular matrices (ECMs). Coupled diffusion-mechanobiological simulations reveal how membrane properties and capsule positioning influence cellular responses, enabling predictive optimization of tissue-regeneration strategies while reducing experimental trial-and-error.

Introduction

Mesenchymal stem cells (MSCs) play a major role in tissue engineering due to their capacity to regulate regeneration through differentiation and paracrine signaling [1,2]. Cellular processes such as proliferation, migration, differentiation, and apoptosis are strongly influenced by biochemical cues including growth factors [3]. Since burst release may induce adverse effects, sustained and localized molecular delivery is required to better reproduce natural tissue-healing processes [4,5].

Porous microcapsules have emerged as promising platforms for controlled biochemical transport. However, predicting how microcapsule properties influence cellular responses remains a major challenge. In this work, a multiphysics computational model is developed to investigate the coupled interaction between diffusion-controlled signaling and mechanobiological cellular responses within ECMs containing porous microcapsules. The model aims to predict how the microcapsule membrane properties and positioning regulate cell fate and tissue regeneration outcomes.

Methods

The proposed model couples molecular transport with mechanobiological cellular behavior to predict cell fate within ECMs containing porous microcapsules. Growth factor (GF) release from spherical porous microcapsules was modeled using

Fickian diffusion across the capsule core, porous membrane, and surrounding ECM. The membrane was treated as a porous barrier governed by:

$$\epsilon_p \frac{\partial c}{\partial t} + \nabla \cdot (-D_{eff,i} \nabla c) = 0,$$

where c is the GF concentration, ϵ_p is the porosity of the membrane and $D_{eff,i}$ is the effective diffusion coefficient that depends on membrane porosity and tortuosity, $D_{eff,i} = \frac{\epsilon_p}{\tau} D_m$, where τ is the tortuosity correction factor, and D_m is the membrane diffusion coefficient. Membrane porosity and thickness were considered the primary parameters controlling release kinetics.

Cell migration was governed by traction, protrusion, and drag forces coupled to biochemical signaling and adhesion strength [2]. Proliferation and differentiation were regulated using a maturation-index formulation dependent on biochemical and mechanical stimuli [2].

The diffusion model was implemented in COMSOL Multiphysics, while the mechanobiological framework was developed in Abaqus using user-defined subroutines. Parametric analyses were performed to evaluate the influence of membrane porosity, thickness, and capsule positioning on transport behavior and cell fate regulation.

Results and Conclusion

Validation

The diffusion model was validated against reference results reported by Bielinski and Kaoui [4]. Excellent agreement was obtained for concentration evolution across porous capsules, confirming the accuracy of the proposed diffusion formulation implemented in COMSOL Multiphysics.

Diffusion Tuning

Membrane porosity and thickness strongly influenced diffusion kinetics. Increasing porosity accelerated molecular transport by increasing

effective diffusivity, whereas larger membrane thickness delayed diffusion due to higher transport resistance. Figure 1 illustrates the combined influence of porosity and thickness on the characteristic steady-state diffusion time (t_{ss}). An empirical relationship was obtained from the numerical simulations:

$$t_{ss} = \alpha \epsilon_p^\beta \delta^\gamma,$$

where δ is the membrane thickness. α , β , and γ are constants that depend on the cell type. This expression enables predictive selection of membrane parameters for tissue-specific transport times without extensive experimental optimization.

Cell Fate Regulation

Three configurations were investigated to evaluate the influence of biochemical signaling on MSC behavior within osteogenic ECMs: without microcapsules, with a peripheral microcapsule, and with a centrally positioned microcapsule. In the absence of microcapsules, cell migration was mainly governed by intrinsic mechanical cues. Introducing a peripheral microcapsule generated localized biochemical gradients that redirected cell migration and moderately enhanced proliferation. The strongest cellular response was obtained for the centrally positioned microcapsule, where biochemical and mechanical stimuli acted synergistically, leading to accelerated differentiation and increased cell population. These results demonstrate the important role of microcapsule positioning in regulating cell fate and optimizing tissue regeneration outcomes.

Conclusion

The proposed multiphysics framework provides a predictive tool for investigating the coupled interaction between biochemical transport and mechanobiological cellular responses within porous microcapsule systems. The results demonstrate that membrane properties and capsule positioning critically influence diffusion kinetics and cell fate regulation, offering valuable guidelines for the computational design of bioactive tissue-engineering platforms.

Acknowledgements

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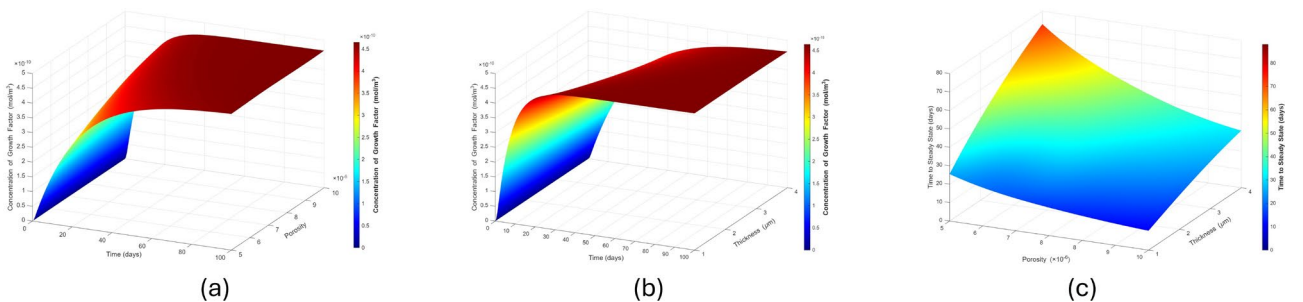


Fig. 1. Influence of membrane porosity and thickness on growth factor diffusion within the ECM: (a) effect of membrane porosity on concentration evolution, (b) effect of membrane thickness on diffusion dynamics, and (c) combined influence of porosity and thickness on the characteristic steady-state diffusion time.

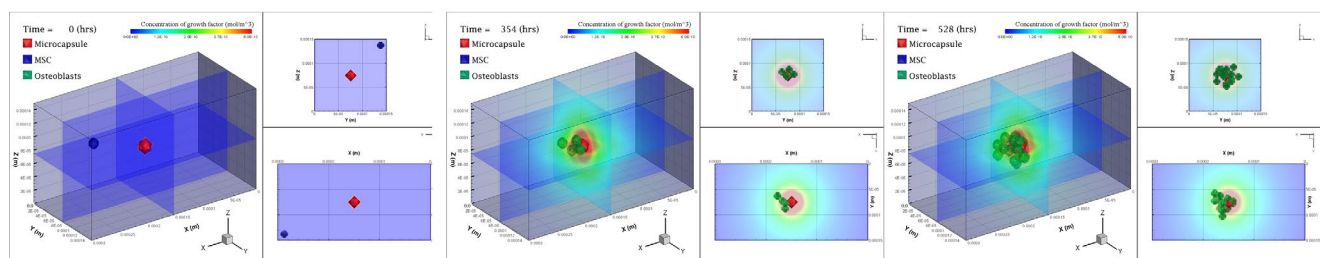


Fig. 2. MSC migration, proliferation, and differentiation under localized growth factor release for a centrally positioned porous microcapsule within the osteogenic ECM.