**Modeling fibroblast cells movement**

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*Abstract***—Mathematical and Computational modeling are common approaches used successfully across many research fields. In this work we study the movement of fibroblast cells and how they contribute to the emergence of fibrosis. Traditional models usually focus on short time or spatial scale, often focusing on a specific migration mechanism. In contrast, we analyze the migration pattern caused by multiple mechanisms on large spatial and time scales. This approach allows us to optimize the costs and time of in-vitro experiments used to verify the in-silica results, while reproducing and proposing conditions to be explored in tissue engineering.**

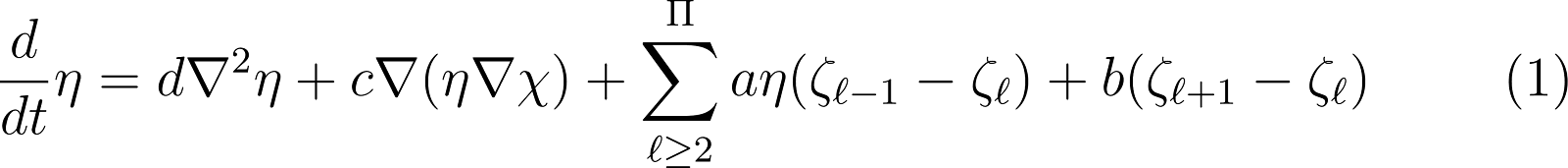
*Keywords***— Fibrosis, Fibroblast, Mathematical-Biology, Computational modeling.**

1. **INTRODUCTION**

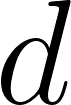
Fibroblasts are mobile cells, responsible for the production, remodeling, and repair of protein fibers. Hence, these cells are central during tissue homeostasis, by restoring and reshaping damaged fibers in the extracellular matrix (ECM) [1]. Dysregulation of mechanisms in both fibroblasts and the protein fibers in the ECM are often linked to the emergence of fibrosis, a condition characterized by accretion and deformation of protein fibers [2]. Motivated by the impacts of fibrotic diseases, we developed a mathematical and computational framework that models the central mechanisms that drive fibroblast movement, allowing us to explore with more detail the scenarios and conditions that drive high cell density commonly observed in early-stage fibrosis.

1. **METHODOLOGY**

Mathematical model. Our model is based on the principle that any variation in the density of fibroblast over time is due to the flux of fibroblast moving in and out of a small region, as shown below in equation (1).



Where () stands for the density of single fibroblast cells, () and () the coefficients of normal and chemical diffusion, () and () the rate of cluster aggregations and fragmentation, and () the cell cluster of size ().



The change in fibroblast density (n) is therefore defined as the fluxes that contribute to the various phenomena [3]. Here, we considered normal diffusion (Brownian motion), cell aggregation (Becker-Döring) and chemotaxis, depending on the stimuli or movement pattern observed on in vitro experiments.

In-silico model. The same mechanisms are explored computationally using a Markov Chain Monte Carlo approach to simulate representations of either homeostatic or fibrotic states. The in-silica model allows us to explore different conditions that lead to specific outcomes, such as fibrotic responses.

In-vitro experiments. HFL-1 (ATCC CCL-153) cells were seeded with a 0.15x 106 cells/ml density in a 10% FBS, 1% penicillin-streptomycin culture, and cultivated in 6-well place inside a Incucyte© S3 Live CEll Analysis System at 37˚C in a 5% CO2 atmosphere. Our target parameter during the image acquisition and image processing was to obtain the cells’ average displacement, its standard deviation, and the number of clusters with more than two cells.

1. **RESULTS**

A first analysis of the mathematical model reveals that normal diffusion dominates the first hours (6 hours). Cell aggregation, and chemotaxis, only exhibit effects in the fibroblast movements in a longer time scale (~24-48 hours). Note that for long time periods, cell aggregation dominates locally, depending on the experiment's initial density conditions.

1. **CONCLUSION**

Through modeling and simulation of cellular responses exposed to different conditions and stimuli, we are developing a framework which can be used to guide and optimize in vitro tissue models. Future work includes adding parameters directly associated to the cell-ECM which provide a complete set of parameters that can be used to guide studies related to the fundamental mechanisms behind fibrosis in a faster and more cost- effective fashion.

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**CONFLICT OF INTEREST**

The authors declare that they have no conflict of interest.

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