

Agent-Based Model of Radiation-Induced Lung Toxicity

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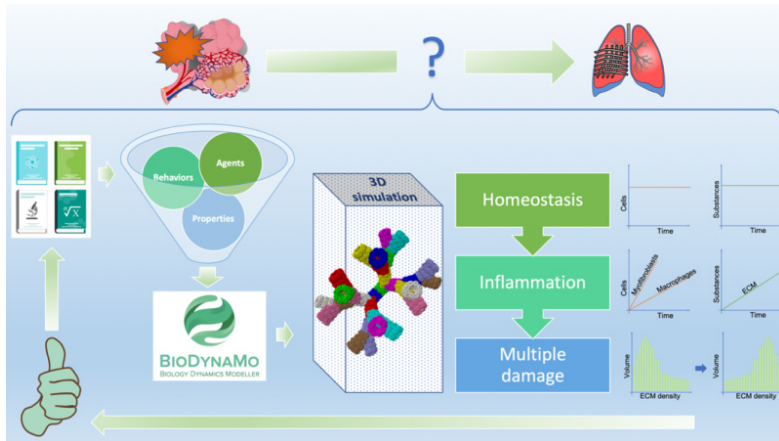
Project Term
2021 - 2022

Clusters
Lichtenberg Cluster Darmstadt

Additional Software
BioDynaMo

Institute
Institute for Condensed Matter
Physics

University
Technische Universität Darmstadt



Introduction

Understanding the pathophysiology of lung fibrosis is of paramount importance to elaborate targeted and effective therapies. Interestingly, similar pathways have been reported for both idiopathic pulmonary fibrosis and radiation-induced lung fibrosis (RILF). Individuals suffering from the disease, the worldwide incidence of which is growing, have poor prognosis and a short mean survival time. Mathematical and computational models can shed light on key underlying pathological mechanisms, shorten the time needed for clinical trials, parallelize hypotheses testing, and improve personalized drug development. Agent-based modelling (ABM) has proven to be a reliable and versatile simulation tool, whose features make it a good candidate for recapitulating emergent behaviours in heterogeneous systems, such as those found at multiple scales in the human body. We implemented a 3D agent-based model of lung fibrosis using a novel simulation platform, namely, BioDynaMo (BDM), and proved that it can qualitatively and quantitatively reproduce published results. Furthermore, we provided additional insights on late-fibrosis patterns through ECM density distribution histograms. Our model recapitulates key intercellular mechanisms, while cell numbers and types are embodied by alveolar segments that act as agents and are spatially arranged by a custom algorithm. Finally, our model may hold potential for future applications in the context of lung disorders, ranging from RILF to COVID-19 and inflammatory diseases (such as asthma or chronic obstructive pulmonary disease).

Methods

The model was implemented with BDM 1.0, an open-source software simulation platform that allows users to build and run multi-scale simulations. The elements of the simulation, i.e., the

simulation space, the entities inside it, and the interaction rules, are encoded in the C++ language and simulations can be carried out on common laptops and cluster nodes. ABMs are aimed at simulating systems of many interacting entities. Their intrinsic nature thus makes cluster nodes very well-suited architectures for ABM simulations as they can strongly benefit from multiple cores as well as multithreading.

In BDM, discrete time is marked by simulation time steps and agents are instances of the Agent class. Variability between agents from different populations can be emphasized by defining custom attributes, which altogether define the state of an agent, whereas agent-agent and agent-environment interaction rules are wrapped in behaviours. Behaviours, in turn, are executed for each agent at every time step when certain conditions are satisfied.

Results

The final goal of our project is the mechanistic simulation of RILF. As a first stage (phase 1 of the project), we developed a 3D agent-based model of the idiopathic pulmonary fibrosis which shares multiple mechanisms with RILF.

We initially run our model without damaged cells and adjusted the parameters so that both the number of simulated cells and the concentration of the diffusing substances agreed with the homeostatic conditions reported in the literature. We then repeatedly expanded the population of damaged alveolar epithelial cells to match the experimental results from previous models and explore most extreme situations in which alveolar ducts are fully depleted from healthy cells. For each degree of damage we also reported ECM distribution histograms and looked for possible correlations. Finally, we performed a sensitivity analysis on the main parameters and identified the parameters that most affect the model outputs.

Discussion

Our ABM of lung fibrosis can successfully mimic the findings reported by previous studies. To the best of our knowledge, this is the first 3D agent-based model of lung fibrosis which supports both substance diffusion and extracellular pathways on a geometrical framework that reflects morphometric data.

Accordingly, it may be employed as a starting point and easily extended for further use in the context of lung diseases (such as COVID-19 and asthma) by implementing additional layers of complexity, both on smaller and larger spatial scales as well as multiple sources of damage. Our multi-level damage approach might be of interest for simulating radiation-induced injuries as cells irradiated at different doses experience varying amounts of damage. Moreover, the possibility to easily implement interpatient variability by changing the acinar structure, the density of alveolar ducts, the cell damage sensitivity, and the number of cells makes it well suited for studies of personalized medicine and the clinical testing of drugs.

Figures

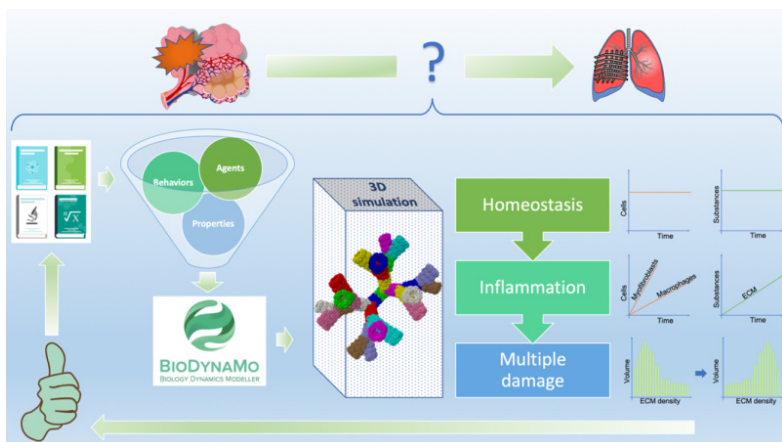


Figure 1: Project overview, mechanistic modelling of radiation-induced lung injury.

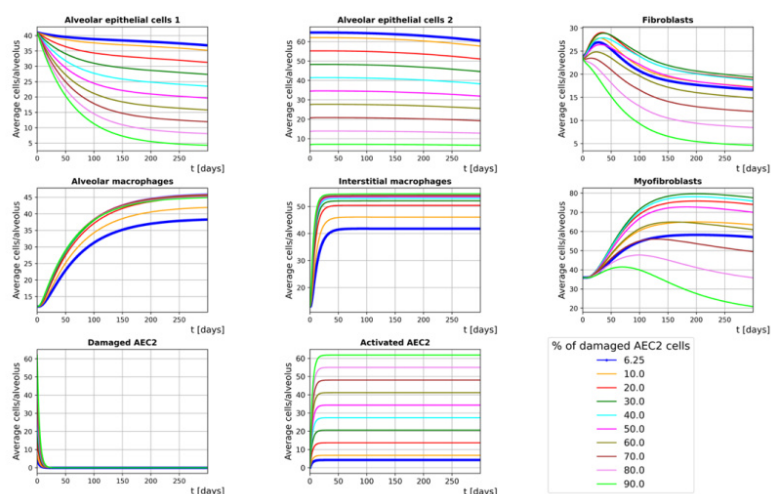


Figure 2: Time evolution of the simulated cell types.

Publications

Cogno, N.; Bauer, R.; Durante, M.: "A 3D Agent-Based Model of Lung Fibrosis", *Symmetry*, 14, 90, 2022 <https://doi.org/10.3390/sym14010090>

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