2. Semester report

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Title: *Computer simulations of neutrophil swarming and phagocytosis at various stages of inflammatory events*

1. Introduction

Our research aims at modelling and simulating two different biological processes: neutrophil swarming and phagocytosis.

With regard to the neutrophil swarming, during the last semester, we implemented an early version of a 2D model. we also started working on a 3D model [1] considering the secretion of two substances: (i) a diffusive ligand in the extracellular medium by neutrophils and (ii) an intracellular inhibitory molecule which prevents the synthesis of the ligand inside the cells.

Regarding phagocytosis, using CompuCell3D [2], we could simulate a simplistic version of the process in 2D. In that model, a macrophage moves as a random walker biased by chemotaxis due to secretion and diffusion of a chemoattractant from the pathogen/bacterium which was subsequently engulfed after their contact.

During the current semester, we have worked to improve the models to make them more realistic and to draw some quantitative insights from them.

2. Description of research work carried out in current semester

2.1.Neutrophil swarming

For simplicity and using an incremental approach, we decided to focus on a version of the model which does not consider the secretion of intracellular inhibitors.

The model considers two complementary aspects: the ligand dynamics and the cells' position update rules.

The ligand dynamics is governed by a diffusion equation with sources and sinks. We assume that the production of the ligands by a cell depends on the ligand concentration it senses and satisfies the Hill equation multiplied by a coefficient which represents the maximum production rate. Regarding the decay, we distinguish two classes of mechanisms that contribute to it: (i) the spontaneous decay due to regulatory processes to restore homeostasis in the tissue and (ii) the decay due to the chemical reaction happening between the ligands and the cell receptors. In the current state of the model, we have considered only the second class. But extension with the first class should be straightforward. For simplicity, we didn't include the saturation of the receptors in the current version of the model.

At each time step, the cells' position update rules consider (i) the persistency of the motion, (ii) some randomness and (iii) a chemotactic force which attracts cells in the direction of increasing gradients. In particular, the amplitude of the latter is considered to be proportional to the quotient of the chemoattractant gradient divided by the chemoattractant concentration sensed by the cell [3].

We set a no-flux boundary condition at the boundaries of the physical domain (tissue). For different parameter values, we could observe different behaviours of the cells and ligand dynamics as well. Interestingly, we had some instances of relay propagation of the ligands in the tissue.

2.2.Cell shape dynamics during phagocytosis

Our model to study the phagocytosis follows the Cellular Potts Model [4], the details of which are beyond the scope of this report.

The main variables we considered are $J_{X,Y}$ which denote the contact energy between X and Y, where X, Y take the values *Medium*, *Bacterium*, *Macrophage*.

The evolution of the system with respect to time is consistent with the transition probabilities guaranteeing that the microscopic changes in the configuration drive the system towards smaller energies.

From simulations that were carried out for specific preferred values of the surface and volume of the macrophage and a spherical bacterium, we could get the results below

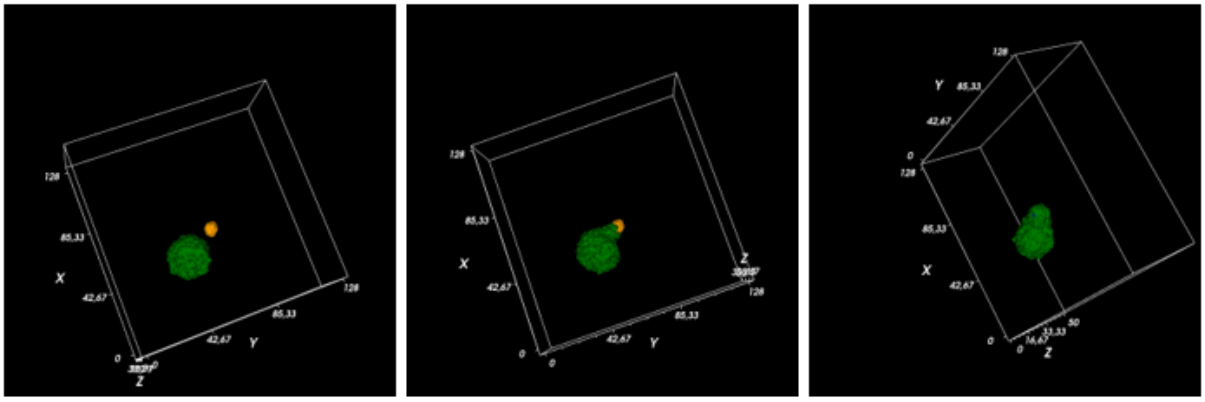

Figure 1: An engulfment sequence

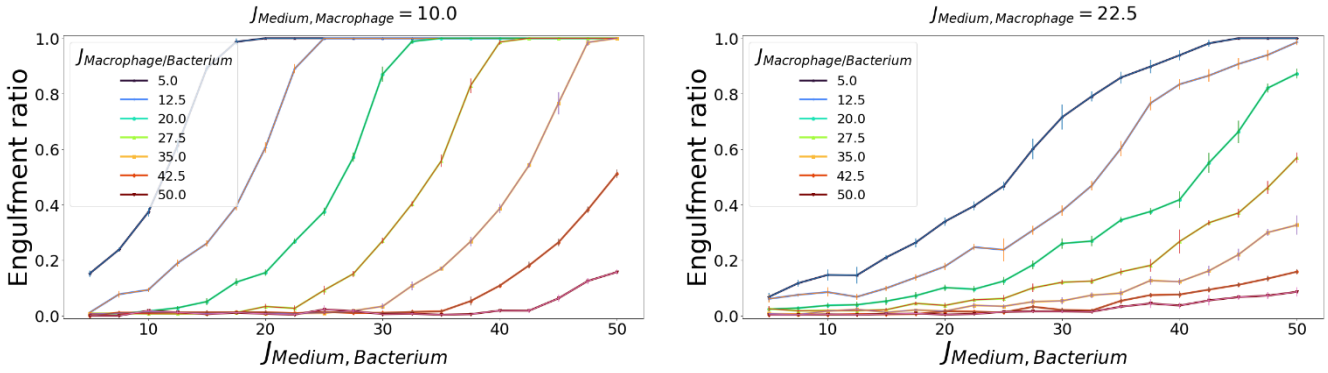

Figure 2: Engulfment ratio – the proportion of bacterium engulfed. Each data point results from 7 simulation runs. The error bars denote the SEM.

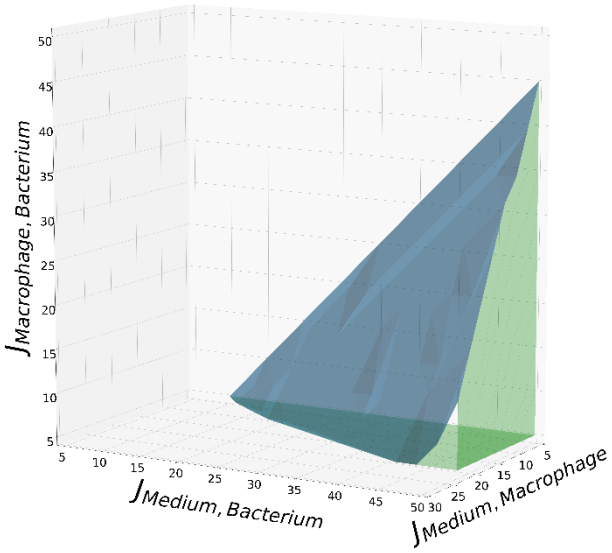

Figure 3: Phase diagram for the engulfment ratio

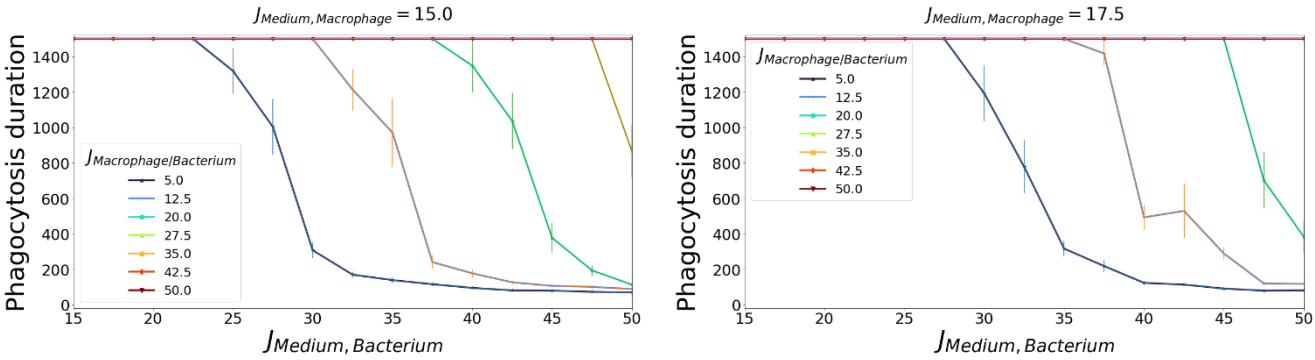

Figure 4: Engulfment duration. Each data point results from 7 simulation runs. The error bars denote the SEM.

3. Studies in current semester

During this semester, I enrolled to four courses: *Biophysics I* (biophys1f20ex) from the department of Physics, *Molecular and biophysical mechanisms of cell motion* (FIZ/3/071E) and *Graphs in the bioinformatics* (FIZ/3/063E) from the Doctoral School of Physics and *Receptors, signalling, cell-cell communication* (BIO/06/11E) from the Doctoral School of Biology.

4. Conferences in current semester

I attended and presented a poster on the topic cell shape dynamics of phagocytes during phagocytosis at the European Phagocyte Workshop which took place in Visegrad, Hungary in on 20 – 23 March 2024.

References

1. Strickland J, Pan D, Godfrey C, Kim JS, Hopke A, Degrange M, Villavicencio B, Mansour MK, Zerbe CS, Irimia D, Amir A, Weiner OD. Self-extinguishing relay waves enable homeostatic control of human neutrophil swarming. bioRxiv [Preprint]. 2023 Jun 28:2023.06.27.546744.
2. M. Swat, Gilberto L. Thomas, Julio M. Belmonte, A. Shirinifard, D.Hmeljak, J. A. Glazier. Multi-Scale Modeling of Tissues Using CompuCell3D. Computational Methods in Cell Biology, Methods in Cell Biology 110: 325-366 (2012).
3. Herzmark P, Campbell K, Wang F, Wong K, El-Samad H, Groisman A, Bourne HR. Bound attractant at the leading vs. the trailing edge determines chemotactic prowess. Proc Natl Acad Sci U S A. (2007 Aug 14). doi: 10.1073/pnas.0705889104.
4. J. A. Glazier, F. Graner. Simulation of the differential adhesion driven rearrangement of biological cells. Physical Review E, 47(3), 2128-2154 (1993)