PhD proposal F/H MATHEMATICAL MODELING OF BIOLOGICAL TISSUE ARCHITECTURE

1. PHD ADVISORS

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2. CONTEXT OF THE CALL

This PhD proposal is in the frame of an application to the Inria - Inserm call 'Santé Numérique' (https://pro.inserm.fr/theses-inserm-inria-sante-numerique-2024). We are looking for candidates with a mathematical background, with a strong interest for biological applications and interdisciplinary work.

3. SCIENTIFIC AND MEDICAL CONTEXT

Tissue regeneration is defined as the ability of damaged tissue or organ to regain its normal architecture and functionality after injury. The evolutionary loss of regeneration capabilities and their limitation throughout mammalian life represent a fundamental issue in biology. Indeed, tissue repair in adult mammals is associated with the formation of fibrotic scars, impairment function and, ultimately, organ dysfunction. Tissue regeneration in adult mammals is a major medical challenge.

Using an original model based on massive resection of subcutaneous adipose tissue (AT) in adult mice, we previously demonstrated that tissue repair results from an emerging process based on simple local mechanical interactions between cells and the extracellular matrix (ECM), and that modifying the ECM in the initial stages of repair is sufficient to guide tissue reconstruction towards regeneration or scarring. This significant result could not have been achieved without the development of a 2D agent-based model to study AT morphogenesis and a tissue repair model based on this initial model. AT displays a lobular like structure and each lobules is composed of clusters of round cells (adipocytes) separated from each other by septa composed of ECM fibers. Specifically designed for AT, the agent-based model represents round cells as 2D spheres interacting via mechanical interactions with fibers represented as segments, forming a dynamically connected network through crosslinking. This initial model has thus been a key element in identifying putative targets that have been later in vivo validated for inducing the regeneration of lobular-shaped tissue in adult mammals. However, biological tissues can present cylindrical forms such as muscle bundles, blood vessels, excretory ducts or round forms such as the acini of glandular structures. Cell shapes also differ depending on the organs.

The goal of this PhD is to study the mechanisms of the emergence of spatio-temporal structures within biological tissues, by the development of a realistic mathematical and computational model of tissue morphogenesis. The aim is to better understand the role of the various physical and behavioural parameters which control and modulate the emergence of tissue architectures, and demonstrate that for all biological tissue, morphogenesis and repair is the result of an emerging process mostly driven by simple mechanical interactions between a few sets of agents. This challenge will be tackled in the frame of an already established collaboration between two research teams with complementary competences MAMBA/MUSCLEES (Inria Paris) on the mathematical side and RESTORE (Inserm, Toulouse) on the biological side) . As described previously, our

previous work only focused on the emergence of lobular structures of round cells in aligned fiber networks as observed in adipose tissues. In this PhD, we propose to develop a multiscale theory for interacting particle systems composed of different types of agents, focusing on the role of the shape of the individual agents in the global architectures of the whole system and test the generalization of our previous findings and conclusions.

In the first phase, we will study the system at the microscopic scale and extend the model of [1] for anisotropic cells. In order to ensure the biological relevance of our approach, the agent-based model will be systematically confronted to experimental data collected by our biological partner on different tissues (muscles, tendons, epidermis), and each model hypothesis will be tested experimentally. In this part, the PhD candidate will develop the conceptual models, numerically implement the model and perform simulations, and develop innovative sensitivity analysis methods to better understand how the different model parameters control the model outputs described by a set of quantifiers (shape and number of cell and fiber structures, size distributions, ECM connectivity etc). According to the software competences of the PhD candidate, the implementation of the model in a user-friendly interface for the biologist partner may be envisioned, enabling biologists to interface ‘in-silico’ with ‘in-vivo’ experiments to identify the different parameters leading to regeneration in different tissues.

The second phase of the PhD will be devoted to the derivation of the agent-based model into a continuum model, using tools from kinetic theory. The main challenge lies in the fact that individuals have different shapes, breaking the usual assumption of identical particles needed for mean-field limits. The resulting continuum model will provide a large-scale ‘synthetic tissue’ model, i.e. a large-scale counterpart of the agent-based synthetic tissue model described in the preceding sub-segment. It will serve for the investigation of large-scale effects in general tissue homeostasis and repair.

4. SCIENTIFIC PARTNERSHIP

This multi-disciplinary PhD will be conducted in the context of a collaboration between Inria Paris and RESTORE, Toulouse (www.restore.fr). The Inria team (MAMBA/MUSCLEES) will be represented by the PhD advisor D. Peurichard and the RESTORE team (GOT-IT, Inserm) will be represented by L.Casteilla. The collaboration between the two partners is well-established and fruitful, and the contributions of the both advisors are perfectly complementary. Indeed, D. Peurichard team (Inria Paris) has established expertise in the development of rule-based models and derivation of macroscopic models, and L. Casteilla team (RESTORE) is expert in tissue development, regenerative medicine and imaging. The new approaches and methods proposed in this project will represent not only a fundamental step in our understanding of biological tissue and their changes over time opening new avenue for innovative regenerative medicine therapies, but will also tackle important challenges in the mathematical field.
This established collaboration has led to the supervision of several theses and the publication of several papers.

[1] Peurichard D, Delebecque F, Lorsignol A, Barreau C, Rouquette J, Descombes X, Casteilla L, Degond P. Simple mechanical cues could explain adipose tissue morphology. J Theor Biol. 2017 Sep 21;429:61-81. doi: 10.1016/j.jtbi.2017.06.030. Epub 2017 Jun 23. PMID: 28652001.

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Chassonnery P, Paupert J, Lorsignol A, Séverac C, Ousset M, Degond P, Casteilla L, Peurichard D. Fibre crosslinking drives the emergence of order in a three-dimensional dynamical network model. R Soc Open Sci. 2024 Jan 31;11(1):231456. doi: 10.1098/rsos.231456. PMID: 38298399; PMCID: PMC10827420.

Pacary A, Peurichard D, Vaysse L, Monsarrat P, Bolut C, Guissard C, Lorsignol A, Planat-Benard V, Paupert J, Ousset M, Casteilla L. A computational tissue repair model identifies an early transient decrease in fiber cross-linking that unlocks regeneration in adult mammals. NPJ regenerative medicine, in revision

5. CONDITIONS FOR PHD REALISATION

We seek for candidates with a mathematical background, preferably already familiar with asymptotic methods and PDE analysis, and with programming competences (python, Matlab, C++). The PhD candidate will be hosted at the LJLL where he/she will benefit from the rich scientific landscape. The candidate will be given all necessary equipment (laptop, access to computing servers, hard-drives) for model development/analysis and a budget for missions (travels/participation to conferences/workshop/seminars). Several visits to RESTORE, Toulouse (from few weeks up to 3 months according to the needs of the projects) will be organized to meet the INSERM partner and discuss the advancements of the project.

6. HOW TO APPLY

To apply, candidates should send the following documents by email to diane.a.peurichard@inria.fr and jenny.paupert@inserm.fr

Documents:

- CV
- Cover letter
- License and Master’s notes
- Recommendation letters (if relevant)