Analysis and modelling of the dynamics of pathogen-host interactions through force microscopy and image-based mechanobiology

Proposé par : Jean-Christophe Olivo-Marin
Directeur de thèse : Jean-Christophe Olivo-Marin
Unité de recherche : Institut Pasteur, BioImage Analysis Unit, CNRS UMR 3691
Domaine : Sciences et technologies de l'information et de la communication

The aim of this thesis is to propose methods that are based on 3D imaging data to measure and quantify biological forces in a non-invasive and non-direct manner. Over the last few decades, it has indeed become increasingly evident that mechanical forces are essential to many biological processes, giving rise to the blooming field of mechanobiology [1]. Until recently, biological forces were mostly measured using probes such as cantilevers or micropipettes which require direct contact, and are mostly limited to 2D. To gain higher insight into cells and tissue inner working, physiologically relevant and imaging friendly 3D settings have been developed and are now enabling image-based mechanobiology. This new enabling technology requires however an integrated and robust framework to relate imaging data to physical quantities.

To this end, we will take a data assimilation approach that combines image processing functionals that describe deformations within images (i.e. registration problems such as optical flow) with physical models that explain the observed deformations and whose parameters we want to measure (e.g. biological forces). Since it is common that only approximate descriptions of biological materials are available, the measurements will have to account for the errors introduced by surrogate models. This approach has been formulated previously in our laboratory as a Bayesian PDE-constrained inverse problem [2]. This thesis will develop further the previous method in two main directions:

1. Extend its application from linear to viscoelastic models that better reflect the polymeric nature of biological materials. This will require accounting for non-linearities, for instance combining the Finite Element Method with Newton's method; and dealing with time-dependent domains, for example via arbitrary Lagrangian-Eulerian methods.
2. Develop mathematical strategies that allow regularising the Bayesian inverse problem with edge-preserving priors, which are typically non-linear and thus too computationally expensive to implement under the current PDE-constrained framework.

Moreover, to extract relevant and well-conditioned data from the acquired images, we will pursue additional work in 3D filtering and segmentation along the lines of our previous studies [3].

We will apply this general method to study the mechanobiology underlying two kinds of host-pathogen interactions. First, we will study *Toxoplasma gondii*, a parasite that infects metazoan cells by squeezing in through gaps smaller than its nucleus [4]. We wonder whether the mechanical stress undergone by the nucleus has an effect on DNA transcription. To study this effect, we will image the 3D deformation of the nucleus and link it to a viscoelastic model to extract the stress within. Second, we will study the effect of intestinal contractions on the invasion of the parasites *Shigella flexneri* and *Entamoeba histolytica*. It has been shown that periodic contractions in colon models increase the infection rate [5], but we ask whether the entry points of these parasites correlate with zones of maximum mechanical stress. In this case, we will image the 3D movement of the colon model and link it to a viscoelastic model to extract the surface stress.

Références

[1] « Forces in cell biology », *Nature Cell Biology*, **19**, 579 (2017), https://www.nature.com/articles/ncb3552

[2] Boquet et al., « BioFlow : a non-invasive, image-based method to measure speed, pressure and forces inside living cells », *Scientific Reports* **7**, 9178 (2017), https://www.nature.com/articles/s41598-017-09240-y

[3] Meniel et al., « Denoising of microscopy images : A Review of the State-of-the-Art, and a New Sparsity-Based Method», *Trans. Image Processing*, **27**, 3842-3856 (2018), https://ieeexplore.ieee.org/abstract/document/8327626

[4] A. Barragan & L. D. Sibley, « Transepithelial Migration of *Toxoplasma gondii* Is Linked to Parasite Motility and Virulence», *J. Exp. Med.*, **195**, 1625-1633 (2002), https://rupress.org/jem/article-lookup/doi/10.1084/jem.20020258

[5] Grassart et al., « Bioengineered Human Organ-on-Chip Reveals Intestinal Microenvironment and Mechanical Forces Impacting *Shigella* Infection », *Cell Host & Microbe*, **26**, 435-444 (2019), https://www.sciencedirect.com/science/article/pii/S1931312819304160?via%3Dihub