GRADUATE SCHOOL on Cancer, Ageing, Rejuvenation

EUR CARe PhD program pre-proposal 2022

(2 pages maximum)

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AIM: Artificial Intelligence to analyse Mechanobiological properties of cancerous cells.

AIM aims at awakening force spectroscopy and mechanobiological properties to statistically and medically relevant information. We rely on our innovative method for automating force measurements (by AFM) that generates massive data on at least 1000 cells[1–3]. Biophysical analyses and machine learning methods will be adapted to extract mechanobiological information from the large amount of data generated.

The mechanical properties measurement of living cells by AFM has brought important knowledge in mechanopathology. By performing thousands of measures on a few cells, this method has laid the foundation for mechanopathology. Unfortunately, the statistical limitations of the method prevent both to answer mechanopathology questions involving populations of cells and to transfer the technique to medical laboratories.

In AIM we will apply our recent development to prostate and breast cancer models with cell lines ranging from normal cells to carcinoma. The work will be carried out in 3 steps, first, data acquisition on prostate and breast cancer cell lines (respectively PC3; 957 E; PNT1A and SKBR3, MCF7; MCF10A; from the less to the more invasive) then, their study by automatic learning algorithms. Finally, we will confront our method with a mixed cell population. The objective is to automatically classify the cells as a function of their aggressiveness, according to their mechanical properties.

The collected data will be analyzed by machine learning algorithms to create classes based on biophysical parameters known in advance and then according to an unsupervised process, with the aim of discovering new biophysical markers hitherto ignored in mechanopathology.

The driving hypothesis is that the analysis by automatic learning, without a priori, of large quantities of mechanobiological data, will lead to the emergence of signals, hitherto ignored by a priori biophysical analyses (elasticity, adhesion, dissipation etc). Our objective is therefore to demonstrate the statistical ability of our method to investigate specific mechanical signatures of breast and prostate cancerous cells. This will serve as a demonstrator of the possibility of separating cells using machine learning algorithms on the basis of their biophysical properties in a heterogeneous cell population.

Mechanopathology must disentangle the mechanome which represents the intricacy of mechanobiological markers and to do this we need to change the paradigm of Bio-AFM measurements by automating them and analyzing them by machine learning. This ensemble constitutes an epistemological rupture whose repercussions are not entirely predictable.

The PhD student will be supervised by E. Dague, LAAS-CNRS, expert in applying AFM to living cells, and Adrian Martinez-Rivas, researcher at the Computer Science Research Center of the National Polytechnic Institute (CIC-IPN) of Mexico. Adrian and Etienne have developed during the last 5 years a productive collaboration firstly based on the development of AFM automation algorithm (3 publications and 1 patent, one international PhD cotutelle funded by Mexico) and now moving towards artificial intelligence analysis of mechanobiology data.

The student will benefit from this active collaboration and is welcome for a stay of 3-6 months at CIC-IPN to learn, develop and adapt the machine learning algorithms to mechanobiology.

Describe in 50 words max for each how this project fits the 3 defining criteria of the CARe graduate programme:

1) Relation to CARe topics of Cancer, Ageing and/or Rejuvenation

The project addresses the cancer theme and proposes to study the mechanobiological properties of cancer cells using an original approach. The mechanobiological measurements will be the basis of the artificial intelligence work aiming at classifying the cells according to their degree of aggressiveness.

2) Multidisciplinary aspect

The project is inherently interdisciplinary. The main theme of cancer is obviously related to biology, Atomic force microscopy comes from physics, our approach to automate AFM is based on algorithmic, and the machine learning classification of mechanobiology data is part of artificial intelligence.

3) International and/or industrial aspect(s)

The PhD will be co-supervised by Adrian Martinez-Rivas, researcher at the Computer Science Research Center of the National Polytechnic Institute (CIC-IPN) of Mexico and Etienne Dague, LAAS-CNRS. Etienne and Adrian collaborated thanks to an ECOS-Nord Grant 2016-19 (Nano-palpation for diagnosis) and are currently collaborating in the ANR project autobiotip (ANR-20-CE42-0017).

5 keywords in line with EUR CARe

Cancer, Bioengineering, mechanobiology-pathology, artificial intelligence, Interdisciplinarity

5 references of the teams, highlighting the co-signatory students: (the supervisors are underlined, **the PhD student** appears in bold)

1. Martinez-Rivas A., Dague E., **Pro-Coronado S.** and Gonzalez-Quijano, K. **2019**
Process by atomic force microscopy for massive physical and mechanical analysis of materials, biomaterial arrays and structures. Patent WO2019112414 A1 ; Date de publication 2019-13-06

2. Proa-Coronado S., Severac C., Martinez-Rivas A., and Dague E. **2020**
Beyond the paradigm of nanomechanical measurements on cells using AFM: an automated methodology to rapidly analyze thousands of cells. **Nanoscale Horizons,** 5, 131-138, https://pubs.rsc.org/en/content/articlelanding/2020

3. Severac C., **Proa-Coronado S.**, Formosa-Dague C., Martinez-Rivas A., and Dague E. **2021,**
Automation of bio-atomic force microscope measurements on hundreds of *C. albicans* cells **Journal of Visualized Experiments** 170, e61315, doi:10.3791/61315

4. Camacho-Fernández C., González-Quijano G.K., Séverac C., Dague E., Gigoux V., Santoyo-Salazar J. and Martinez-Rivas A. **2021,**
Nanobiomechanical behavior of Fe3O4@SiO2 and Fe3O4@SiO2-NH2 nanoparticles over HeLa cells membranes. **Nanotechnology,** 32, 38, 385702 https://iopscience.iop.org/article/10.1088

5. Martinez-Rivas A., Formosa-Dague C., Carrillo K., Mijoule V., **Thomas-Chemin O.**, Lelann M-V., Séverac C., Dague E.
Convolutional neural network based deep learning to classify nanobiomechanical data of cells,
manuscript in preparation