Post doc subject: **A Multi-agent System of the Cell Membrane: Auto-assembly and Particle/ion Interaction**

Post doc Advisors:

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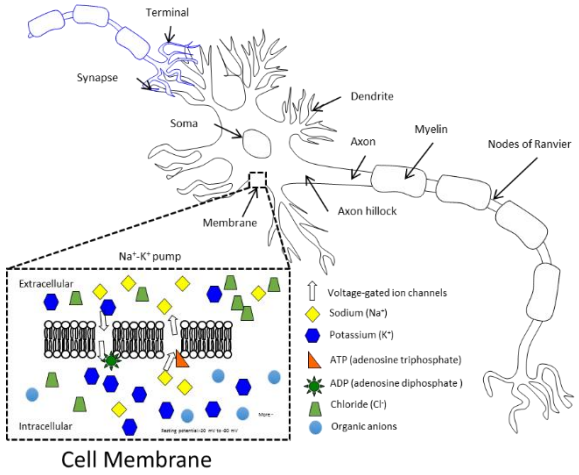
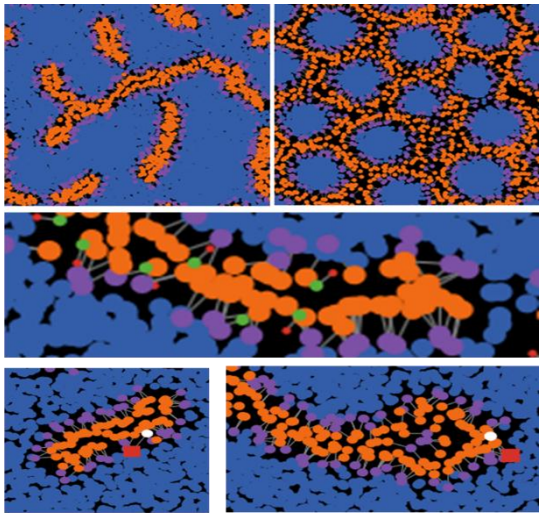
This proposal relates to the theme 3.1 (Optimized design of technological SoSs - Multi-level and multi-physical optimization of a set of complex systems) of the Labex MS2T.
Post-doctoral duration: 12 months + 12 months (renewed once).

Context of the study:

Cell is the basic living unit of the human body. Its dynamic behaviors allow all biological processes to be occurred and regularized. The understanding of cell constituents and their property-function relationship plays a crucial role in the diagnosis, treatment and follow-up of diseases. Experimentation has been designed for studying cell behaviors. However, this approach is time-consuming and it is very hard to set up a long-term experiment. Thus, mathematical modeling of the cell has been considered as an alternative solution to reduce experiments and to test long-term hypotheses. Among the complex structures, cell membrane is the basic element to protect the cell from its surrounding environment as well as to allow the cell-environment interaction (e.g. substance exchange) [1-3]. This structure is commonly composed of a lipid bilayer and embedded proteins (Fig. 1a). However, accurate mathematical model of this complex structure remains a research challenge. Thus, the objective of this project is to develop such cell membrane model and to simulate its interactive behaviors with environmental factors leading to predict its behaviors under pathophysiological conditions.



(a)



(b)

Figure 1 Schematic representation of a human nervous cell and its constituents (a) and a 2D multi-agent model of the cell membrane (aligned lipid molecules in orange) with embedded water molecules (in blue) and proteins (in green) (b).

Post doc description:

Agent-based modeling and simulation (ABMS) has been considered as an attracting tool for multiscale modeling of the biological organs or systems of interest. In particular, this individual-based modeling approach allows to explore the molecule-cell structure/function and their interaction with upper scale behaviors (i.e. organ or system scales). This opens new dimensions to study the multi-scale interactions inside the human body [4]. Agent-based model consists of a collection of autonomous decision-making agents. Each agent has its proper state control driven by behavioral rules. ABMS has been recently used to simulate biological processes, multi-scale interactions, and emergent behaviors of complex biological systems. Agent-based models covered a large range of applications (e.g. cell lineage process, involvement of cancer stem cells (CSCs) in the evolution of metastatic cancer morphology, wound healing process, muscle fiber development process, bacterium-to-environment interaction, or natural “Killer” cell and “Tumor” cell interaction, or cancer modeling).

In a previous study, in the framework of a Master project in 2016, funded by Labex MS2T, a 2D multi-agent model of the cell membrane with embedded water molecules and proteins was developed (Fig. 2(b)). Amphiphilic molecule was modeled with a hydrophilic head and a long hydrophobic tail. The auto-assembly process was successfully simulated. This preliminary model showed the ability of the ABMS approach to deal with the complex cell membrane simulation. Thus, the objective of this present project is to extend this preliminary model into a complex 3D model. Moreover, more complex agent behaviors (e.g. action, evolution, interaction) will be modeled using knowledge-driven or experiment-driven rules expressing biological processes. To account for the high randomness of the exchanges at the membrane level, we intend to use the tools of queueing theory, aiming at a representation by spatial stochastic processes [5]. Specific channels will be modeled to manage the substance exchange in and out of cells. Then, the interaction of the membrane and membranotropic agents (e.g. negative-charged nanoparticles (TiO_2), ions or antimicrobial peptides/enzymes) will be simulated [2-3], relying on fluid and diffusion approximations of the random processes at stake (as in [6]) to represent the micro/macro change of scale. Finally, the application of the developed model for the prediction with positive-charged nanoparticle and membrane fusion will be performed. It is emphasized that outcomes of agent-based modeling and simulation will be validated against critical experimental observations

This project is breakdown into 4 following steps:

- Step 1: State-of-the-art of the agent-based simulation in single cell modeling and implementation environments (e.g. Netlogo[1], GAMA[2]).
- Step 2: Extend the current 2D model into a random 3D model with defined requirements.

[1] https://ccl.northwestern.edu/netlogo/

[2] https://github.com/gama-platform

- Step 3: Evaluate the outcomes of the developed model with critical experimental data.
- Step 4: Use the model for the prediction task (e.g. interaction with positive-charged nanoparticles).

Candidate's profile:

PhD in Computational Bioengineering, Computer Engineering.

Knowledge and practical expertise with ABMS

Knowledge and practical expertise with cell biology

Documents required to apply:

Send to karim.el-kirat-chatel@utc.fr, tien-tuan.dao@utc.fr and pascal.moyal@utc.fr

- Curriculum vitae
- Motivation letter
- At least two references and/or recommendation letters
- A statement of research experience and interests

Location:

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References:

[1] R Ranganathan. Signaling Across the Cell Membrane. Science 318(5854):1253-1254, 2007.
[2] El Kirat K, Morandat S, Dufrêne YF. Nanoscale analysis of supported lipid bilayers using atomic force microscopy. Biochim Biophys Acta 2010 ; 1798(4):750-65.
[3] Morandat S, Azouzi S, Beauvais E, Mastouri A, El Kirat K. Atomic force microscopy of model lipid membranes. Analytical and Bioanalytical Chemistry 2013 ; 405:1445-1461.
[4] TT Dao. Advanced Computational Workflow for the Multi-scale Modeling of the Bone Metabolic Processes. Medical & Biological Engineering & Computing, 55(6):923–933, 2017.
[5] L. Decreusefond and P. Moyal. Stochastic Modeling and Analysis of Telecom Networks. ISTE Wiley, 2012.
[6] Ph. Robert. Stochastic networks and queues. Springer-Verlag, 2003.