Projet de Recherche Doctoral Concours IPV 2021

Intitulé du Projet de Recherche Doctoral : An age-structured model for red blood cells and its application to pathologies and aging

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Equipe de Recherche *(au sein de l'unité)* **:**

Intitulé : **N/A**

Thématique de recherche :

Responsable d'équipe :

NOM : Prénom :

Ecole Doctorale de rattachement de l'équipe & d'inscription du doctorant : **ED 386**
Sciences mathématiques de Paris

Doctorants actuellement encadrés par le directeur de thèse (préciser le nombre de doctorants, leur année de 1ere inscription et la quotité d'encadrement) : 0

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Unité de Recherche :

Intitulé : Laboratoire de biologie intégrative des modèles marins

Code: UMR 8227

Equipe de Recherche *(au sein de l'unité)* **:**

Intitulé : **Physiologie et destin cellulaire**

Thématique de recherche : Canaux ioniques présents dans la membrane des globules rouges, leur régulation et leur rôle physiologique.

Responsable d'équipe :

NOM : **EGEE** Prénom : **Stéphane**

Ecole Doctorale de rattachement : **ED 515**
Complexité du Vivant
Ou si ED non SU :

Doctorants actuellement encadrés par le co-directeur de thèse (préciser le nombre de doctorants, leur année de 1ere inscription et la quotité d'encadrement) : 1, 2020, 100%

Cotutelle internationale : ☒ Non ☐ Oui, précisez Pays et Université :

Précisez ici les éventuels co-encadrants (non HDR)

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Unité de Recherche :

Intitulé : Laboratoire Jacques-Louis Lions

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Equipe de Recherche *(au sein de l'unité)* **:**

Intitulé : **N/A**

Thématique de recherche :

Responsable d'équipe :

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Ecole Doctorale de rattachement : **ED 386**
Sciences mathématiques de Paris
Ou si ED non SU :

Résumé (2000 caractères maximum) :

This project is concerned with erythrocytes (or red blood cells), it aims at writing a better model for simulations, applying it for parameter estimation in physiological, pathological as well as aging situations encountered by the red blood cell in its lifespan.

The finely tuned equilibrium of erythrocytes is broken in two main situations: pathologies such as sickle cell anemia, stomatocytosis or spherocytic anemia on the one hand, cell storage on the other. While improvements of the diagnosis and treatment of the formers would be of great help to the patients, a better understanding of the latter would lead to tremendous progress in the domain of transfusion. Common to these two situations are abnormal behaviours of several ion transport pathways in the membrane of the erythrocyte. This has been demonstrated by the team of Stéphane Égée in Roscoff, who has accumulated data from patients from all Europe over the past years. Concomitantly, the community of physiologists has progressively built a deterministic model for ion concentrations, the osmotic coefficient of hemoglobin, the membrane potential and the cell pH.

Biophysical modeling of the red blood cell in circulation has received a lot of attention over the last 30 years but still lacks a proper mathematical treatment. In a first part of the project, we will address several questions related to the validation and calibration of the model. Where needed, we will improve its numerical implementation to be able to cover pathological situations as well as experimental setups. We will confront our model to the electro-physiological data acquired by one of the team members. In a second part, we will turn to the more ambitious task of building an age-structured model for a population of red blood cells. Indeed, progressive senescence of the red blood cell is known to alter the properties of the cell during its 120 days long voyage through the circulation. Nonetheless a biophysical model incorporating this dimension still lacks to this day. We will implement it in the form of a McKendrick–von Foerster equation.

Joindre en annexe un descriptif du PRD avec références au format pdf (« NOM_2_IPV_2021 » / 3 pages maximum, taille police 11)

AVIS et VALIDATION de l'ECOLE DOCTORALE :

Avis favorable

à envoyer simultanément par e-mail à l'ED de rattachement et au programme : interfaces_pour_le_vivant@listes.upmc.fr avant le lundi 15 février minuit.

An age-structured model for red blood cells and its application to pathologies and aging

I. Current challenges in erythrocyte research

The homeostasis of erythrocytes is based on a finely tuned equilibrium relative to their deformability, allowing them to circulate for 120 days and for which the constancy of volume and ionic balance are essential keys. However, this equilibrium is broken in certain pathologies such as sickle cell anaemia, the most widespread genetic disease ($1/3.10^5$ births), hereditary stomatocytosis ($1/10^6$ births) or spherocytic anaemia ($1/10^6$ births). One of the common characteristics of these pathologies is an increased activity of the cationic transport pathways. Such leak leads ultimately to profound alteration of erythrocytes shape compromising their rheological properties within circulation and eventually their early withdrawal from the circulation. Clinical manifestations may be slight and include well-compensated hemolysis. In many pathologies the origin remains unexplained (20-30%)[1] but may be due to a defect in ionic transport as has just been demonstrated for erythrocytosis[2].

This ionic balance is also compromised in the case of cells stored in cold storage as they are for blood transfusion. Indeed, among the so-called storage lesions, alterations in shape, volume and ionic balance are among those that compromise transfusion efficiency. Currently, there is a lot of evidence pointing to cation channels as major players in this threat, particularly during reinfusion in patients compromising the post-transfusion life of red blood cells. The question we want to address in this doctoral research project can be formulated as such: **what are the consequences of the pathologies afore mentioned and of the aging process on the homeostatic and rheological properties of the red blood cell?**

II. Data and existing model

For the pathologies discussed in I, the team of Stéphane Égée in Roscoff investigates patients' blood from all Europe. The data produced in the team pertains to three categories: biochemical measures (volume, K+ and Na+ concentrations), electrochemical measures (potential) and morphologic ones (projected surface, circularity or surface/perimeter ratio, aspect ratio).

A model has emerged in the 1980s in the form of a differential-algebraic system of equations: it mostly takes into account the biochemistry and the electrochemistry of the cell, not the morphology. An early version of the model[3] has been implemented in Python by Marie Postel and Benoît Sarels. In this dimension 11- version H^+, Na^+, K^+ and Cl^- fluxes are modeled and the kinetics of the different solutes concentrations can be computed, along with the variations of the osmotic coefficient of hemoglobin, the membrane potential and the cell pH. It faithfully reproduces observed behaviors in most situations. However new experimental setups have shown that a cationic conductance path participates to electrolytes exchanges (Na^+ ,K^+, Ca^{2+}) as soon as the membrane equilibrium is unset[4]. This is taken into account in a more recent version of the model[5].

III. The doctoral research project

It is known that some of the pathologies afore mentioned alter the behavior of ionic transporters[6,7]. The same is true for *in vitro* aging. It is believed that many pathologies are associated to exacerbated activities of ion channels, but to what extent is largely unknown. Indeed, quantitative measures are hardly possible to begin with. We believe that a cautious and meticulous use of a mathematical model could shed some light on these matters. The goal of the research project can be described as such: **extend the existing single-cell model in the light of new recent knowledge, build a new model at the level of a population of cells, and use this model to infer what channels are altered in each situation of pathology or aging.**

A **first part of the project** will be devoted to extend the single-cell model alluded to above and submit it to a proper mathematical treatment. This includes the following:

- **Morphology**. The morphology of the red blood cell is absent from the current model, where only the volume is a variable. We will integrate the morphology of the cell in the model to be able to precisely reproduce the behavior of channels sensitive to either surface tension or curvature of the membrane.
- **Sensitivity analysis**. A sensitivity analysis will be carried out, relying on state of the art methodology[8]. No special attention has been given to this matter, although even in its simplest initial version[3], the model depends on about 30 numerical parameter values. Some of these values can be inferred from the experimental setup but a too large number of them has to be fitted by comparing the outputs of the model with the data measurements. Another path to follow is to quantify the propagation of uncertainties on the parameters.
- **Numerical scheme**. In some contexts, the parameters of the ionic transport may vary over time. This as well will be investigated. A first improvement will consist in allowing discontinuities in the coefficients of permeability. That would lead to improving the numerical scheme so that it is able to calculate the boundary layer resulting from these discontinuities.

In a **second part of the project**, we will turn to the more ambitious task of building an age-structured model for a red blood cells population. We will follow the dynamics of alterations in cell homeostasis during circulation. Indeed, if the circulating population of red blood cells is made up of cells of different ages, some are in better shape than others and this heterogeneity is mostly linked to the age of the cell[9,10]. The simple fact of having 5% of this population close to the conditions of elimination can have important consequences in medical terms for a patient[11]. This second part will consist of:

- **Model construction.** We will build a model at the level of the population of red blood cells in the circulation. The one property that helps to segregate this population is the age of the cell. Consequently, all variables and possibly all parameters in the system will be time- and age-dependent. Different hypotheses will be tested: weak, mild or strong dependency of the parameters on the time and the age variables.
- **Simulations.** This model will require numerical simulations for transport equations and integro-differential equations. The numerical work can be carried out using a language in which the student is proficient or building upon the proto-model in Python.
- **Parameter estimation.** When the model is carefully calibrated, we will use it to compare its outputs to the data already produced by Stéphane Égée's team in Roscoff. This work of parameter estimation will be automated by the use of probabilistic programming, for instance through the use of a dedicated Python numerical library PyMC3.

IV. Implementation

We seek a student with a mathematical background, ideally coming from the Master of Mathematics, specialty "Mathématiques de la modélisation", major "Mathématiques appliquées aux sciences biologiques et médicales". A knowledge of partial differential equations for structured models is required. Previous experience with and appetency for scientific programming will be appreciated.

The PhD student will be based mainly in Paris and benefit from yearly rotations at the Roscoff Marine Station on a 9 months / 3 months basis. The funding for travel to and hosting in Roscoff is already secured. The student will be able to rely on the team expertise in multiscale and age-structured models[12,13,14,15]. In Roscoff, he/she will benefit from a strong interdisciplinary environment and ongoing collaborations with partners in Europe for the applications to the medical sciences.

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