INTERNSHIP IN CELLULAR ELECTROPHYSIOLOGY

About the company:

$\mathcal{C}ompL\mathcal{e}X$ $\mathcal{B}iosystem\mathcal{S}$ $\mathcal{I}$nc. is a new company with expertise in modeling & simulation of biological systems, and microelectronic for medical devices. In terms of products, its current portfolio is composed of a scientific data viewer, cell electrophysiology software, and a simulation system for traveling electrochemical waves in excitable tissue. Services are related to these products. They include: cell line characterization, modeling & simulations for medical device prototyping, drug discovery, and the set up of computational platforms for Life Science & Engineering applications.

Anticipating the need of highly qualified personnel to support our products and services on cell line characterization, we are offering an internship in Cellular Electrophysiology for the summer period of 2019.

Context:

The product and service line in question supports our effort to prototype medical devices and predict drug efficacy or adverse side effects.

Modeling & simulations for device prototyping and drug action consists to quantify the motion of ions across cell and organelle membranes which dictate the spatial extent of transmembrane voltageand consequentkly govern the dynamics of traveling electrochemical wave in tissue. In turn traveling electrochemical waves alter intracellular chemistry and control an organ function. For example in the heart it coordinates mechanical contraction, in the gut it governs motility, in nerves it potentiates or depletes conduction at synaptic junctions. At a microscopic level, the motion of ions across the cell and organelle membrane is controlled by gated membrane channels, and receptors. We should mentions that Intracellular buffers sequester and release ions with specific conditions and are also an important elements of traveling wave dynamics, but are not further discussed further here. When we prototype medical devices or attempt to predict the therapeutic benefits or adverse side effects of a drug we determine how external electrical stimulation or drug alter the course of traveling waves. Clearly, to do so it is imperative to have in hands a precise mathematical description of the kinetics of all channels, and receptors participating to traveling electrochemical waves.

Membrane channels and receptors kinetics are estimated in isolated cells. In electrophysiology the gating of channels and receptors is represented with well established Mathematical formulations. Each consists of differential equations comprising parameters and functions of one variable (voltage or ion concentration) that are estimated from an experimental data. The data set in question is generated subjecting a cell to a sequence of voltage clamp stimulations, wich are repeated in the presence and absence of a chemical blocking agent such that channel or receptor response can be isolated.

So far estimation procedures have been all based on the minimization of an objective function. Basically, the model response to voltage clamp stimulation is compared to experimental measurements and parameters as well as function of the mathematical formulation are iteratively

adjusted until model prediction and experimental data match. We documented several problems with such approach and introduced a new procedure to overcome them. Our procedure treat the estimation problem as an inverse problem. In that perspective we find model parameters, functions of one variable and initial conditions, inverting the underlying differential equation. This way we can determine, a-priori, whether the data sufficiently constrain the estimation problem, and if it does we can unambiguously estimate all unknown. In addition our procedure can cope with the ill-posed nature of that problem. Based on this analysis we have come to realize that conventional stimulation protocols cannot sufficiently constrain the estimation problem. This led us to document new voltage clamp stimulation protocols for the purpose of the characterization of channel and receptor kinetics. Overall the new stimulation protocols, data pre-processing for the application of our method, processing to determine whether the conditions of application of the theorems are respected, and the processing for the inverse solution itself are integrated in one cell electrophysiology method that is materialized in our cell line characterization software.

At this stage, with anticipated NIH support, we are initiating the characterization of murine ventricular cells. Such characterization will seed an electrophysiology data base (eDB) containing acquisition records as well as analytical results. The eDB include query system to incorporate eDB component in a cell model. The later will be at the basis of traveling wave simulqtion in excitable tissue. Longer term we plan to orchestrate a scientific community effort to populate the eDB with recordings & analysis of multiple cell types in various conditions (e.g. epoxic, ischemic). In addition to the cell electrophysiology software we plan to provide to the scientific community the tools necessary to incorporate eDB components in a cell electrophysiology model. This each participant will be able to assess the implications of his/her recordings in cell electrophysiology.

In that perspective, the applicant is expected to become familiar with our proprietary method, be able to apply it (experiment and Mathematical analysis), teach it, and support our customers with their application of this one.

Qualifications:

- ◇ Bachelor's degree in Bioengineering, Electrical Engineering, or related fields that combines quantitative methods in Science & Engineering with Biology.
- ◇ Good knowledge of Biology. Understanding of organ systems: heart, lung, kidney, gastrointestinal. Knowledge of important cellular processes: metabolism, excitability, secretion, genetics.
- ◇ Quantitative methods in cellular electrophysiology. Representation of a cell membrane with voltage gated channels with equivalent electric circuit. How to use such circuit to predict how cells respond to electrical stimulation and drugs.
- ◇ Modeling & simulations being a central theme of the company, a solid background in applied Mathematics, specifically: vector calculus, numerical methods to solve ordinary and partial differential equations, and linear algebra, is essential

- ◇ Well versed with the programming of scientific applications with the procedural languages (e.g. C/C++).
- ◇ Desirable: Knowledge of instrumentation to gather the electrical activity of isolated cells, e.g., microelectrodes recording, electrodes recording in the cell attached configuration.
- ◇ Impeccable written and verbal communications skills.

Duties:

- ◇ Understand our proprietary method to generate and analyze cell electrophysiology data with the objective to formulate kinetic models of gated channels, and receptors.
- ◇ Be familiar with cell electrophysiology recordings as stipulated by our proprietary method. Contribute to populate our cell electrophysiology data base with recordings from murine cells.
- ◇ Teach our customers how to perform quality cell electrophysiology recordings with the purpose of characterizing the kinetics of membrane channels and receptors. The recordings in question follow protocols documented in our proprietary method.
- ◇ Use our proprietary analytical methods to deduce the kinetics of membrane channels and receptors from cell electrophysiology recordings. Based on such analysis contribute to populate our eDB with kinetic models of channels and receptors.
- ◇ Teach our customers how to analyze cell electrophysiology data with our proprietary analytical method.
- ◇ Contribute to develop lecture material.

To apply:

Follow the Openings tab. Register, then apply to the desired position. You will get instructions to upload cover letter and resume. Make sure your resume or cover letter includes at least 2 references. Address your application to Dr. Jacques Beaumont and clearly indicate the position you apply to.

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