Why simulate?

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Electrophysiological experiments are tedious and time-consuming. A successful experimental day in manual patch clamping typically yields 7-9 data points, whereas determination of a simple dose-response relationship requires at least 15-20 samples. And if the interaction of multiple parameters are to be assessed then the number of experiments required to achieve certainty would quickly multiply.

Obtaining the raw data is just a first step. Once the biophysical properties of the ion channel block or stimulation are determined then the difficult task of analysis and interpretation of the results begins. Does the test compound have an influence on the properties of action potential? If so, are the changes significant? Are they sufficient to raise concern about an arrhythmogenicity? Are the effects contingent on specific ion concentrations? Calcium handling? Pacing rate? Or interaction of compound with multiple channels and pumps?

Computer simulations of action potentials allow you to quickly and systemically explore the effects of selected parameters on electrophysiological properties of heart cells. You can simulate individual ion channel block or stimulation, changes in the pacing rate and intracellular ionic concentrations, properties of Ca2+ buffers, and more. You can easily re-create voltage- and current-clamp protocols. In fact, you can precisely control almost any physiological cellular parameter. You can also compare results from simulations performed in various cell models (cardiac atrial and ventricular, neuronal, skeletal muscle) and various species (guinea pig, canine, rabbit, or human) and records obtained from patch clamp or microelectrode experiments.

The insight obtained in simulations can help you with integrative interpretation of experimental data. Simulations allow you to explore multiple "what if" scenarios in a fraction of the time required for patching of a single cell. They also allow you to plan for follow up experiments and to optimize candidate conditions without wasting of precious resources.

1. How do you do it?

1. Install the CESE platform that best fits your research goals.
2. Select the model that best represents the cell type and conditions that you wish to examine.
3. Install the model in the models directory of the CESE platform.
4. Determine the variables that you wish to modify, determine the number of iterations that you wish to simulate, and set base parameters.
5. Select the output that you would like to see displayed (this can be changed at any point).
6. Select "Start simulation".
7. Compare the outputs to other simulated traces, different models, or real-life data that has been imported into the CESE environment.

2. How your research can benefit from simulations?

Time: The average material preparation time for a single cardiac electrophysiology experiment is 2-3 hours - with no guarantee that the results will be reproducible and consistent between experiments. In that time you could have performed hundreds of computer simulations evaluating tens of variables. This allows you to have an in depth understanding of the potential effects of a given parameter or combination of parameters on ion channels and action potentials before beginning the process of electrophysiological recordings.

Money: A single CESE system with 3 models installed will cost approximately the price of 5-7 days of experimentation in terms of disposables, and technical support time. Subsequent integration of CESE into your pre-experimentation optimization, and post-result interpretation will save you money in terms of manhours, disposables, expensive drugs, and animal care.

Uncertainty: Intrinsic to cutting edge research is the concept of uncertainty and whether the excitement around an observation that one has just made is an artifact of experimental set-up, or the subject of misinterpretation. Simulation allows one to test the observation, and the factors relating to it, under controlled conditions before making the big announcement. It allows you to informatively speculate and develop the next step in evaluating a hypothesis without committing vast resources to a range of redundant experiments. Simulation gives you the capacity to make the most out of every dollar that will be spent on "wet" experiments.

Contact Simulogic to discuss how simulations and the CESE platform can complement your research goals.