DYNAMIC DISCRIMINATION OF IONIC TRANS-MEMBRANE CONDUCTANCES

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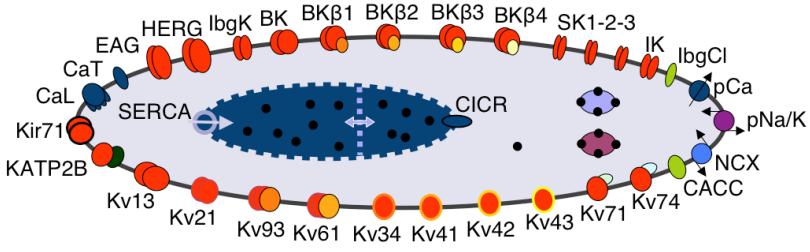
Fast signal conduction within excitable tissues is based on rapid transient inversion of the electrical potential difference that is maintained across the cell membrane by all animal cells. The uterine smooth muscle (myometrium) is an example of such tissues. The repertoire of ionic conductances found in a myometrial smooth muscle cell, represented diagrammatically in the diagram below, has an intriguing make-up: there are only two ion channels that carry the depolarizing current (mediated by Ca^{2+} ions) and over thirty different species of ion channel (depicted as red in the diagram to the left) that carry K^+ currents which act to repolarize and stabilise the resting membrane potential.



At first glance, it might seem surprising that an "excitable" tissue devotes the greater part of its proteome to the suppression of electrical activity. To account for this, it is generally held that each of these "suppressing" conductances modulates and shapes the electrical activity of the cell in a subtly different way. This explanation is eminently reasonable, inasmuch as each channel changes its conductance as a function of trans-membrane voltage difference, and the speed at which these changes happen is also dependent on this potential difference. These dependencies, which are referred to collectively as *gating kinetics*, are different for the various K^+-channel species. The purpose of this project is to explore this hypothesis in a systematic way, and as a result develop protocols that would allow the experimenter to discriminate between the various species of channels and hence be able to infer the "conductome" of the cell from its dynamic properties.

The starting point of this project is the gating kinetics for each species, which has already been defined as a system of ordinary differential equations. The basic idea is to impose on the cell a time-dependent trans-membrane voltage waveform (i.e. a forcing function $V(t)$) that will accentuate, in a suitably defined sense, the differences between the various species. This theoretical approach closely parallels a protocol that is routinely carried out in the lab: the waveform is "played into" the cell using an electrode inserted into the cell, and the currents carried by the membrane are measured simultaneously. Thus the results of the project can be directly transferred to the lab, and this can certainly form the basis for an interesting PhD project.

Programme of Work Initially perform an exploratory analysis using a fairly generic range of waveforms (e.g. sinusoids) by means of computer simulations using a package of the student's own choice (but *Mathematica* highly recommended). Then develop a more systematic theory of wave-shape tailored to the purpose at hand. Formulate experimental protocols that will allow the experimenter to maximise the amount of information gained from the "playback" protocol described above.

The student will interpret and modify systems of ordinary differential equations in a biological setting; perform simulations and, dependent on the initial skill level of the student and the pace at which progress is made; and develop code that optimises the input wave form for a given set of ionic conductance species.

Initial reading

Keener, J. and J. Sneyd (1998) *Mathematical Physiology*. Springer
Weiss, T. F. (1996) *Cellular Biophysics: Electrical Properties*. MIT Press