InvenioIP - Technology Details

Institution: University of Maryland, Baltimore

Docket: LG-2006-021

Title: Analysis of a generalized four state kinetic scheme

Summary: The membranes of nerve, muscle and cardiac cells generate electrical signals and are central and critical components of the functioning of such cells. Experimental investigations of the nature of the molecular machinery that generates the electrical signals are characteristically conducted under voltage clamp conditions, utilizing either the two electrode voltage clamp or the patch clamp. A major avenue of investigation has been to compare the membrane currents recorded under voltage clamp conditions to the predictions of models of the underlying molecular machinery, in particular kinetic schemes of varying complexity. Kinetic schemes are readily described by a system of coupled differential equations, but such descriptions cannot be directly compared to the experimentally recorded membrane currents. The system of differential equations must first be combined into a single higher order differential equation and then solved (i.e. mathematically converted from a differential equation into an ordinary algebraic equation). The solution may then be directly compared to the experimental membrane currents. If an analytical solution for the kinetic scheme is not available, then iterative numerical methods must be used to define the predictions of the kinetic scheme, i.e. a numerical solution must be generated if an analytical solution is not available. A new iterative numerical solution must be generated each time the numerical value of any parameter of the kinetic scheme is changed; a tedious and time consuming process. Analytical solutions for two and three state kinetic schemes are available, but not generally for higher order schemes. The new technology summarized here consists of an analytical solution for a fully generalized four state kinetic scheme. Incorporating this analytical solution into data analysis software expands the range of theoretical analysis that can be accommodated by the software.

Applications: The sites in an electrically excitable cell membrane containing the molecular machinery responsible for generating electrical signals are called ion channels. The macroscopic membrane currents, recorded under voltage clamp, for many sodium selective and calcium selective ion channels characteristically display three distinct phases: a brief delay preceding the activation of the current, the activation phase and inactivation of the current. Four states are required for a kinetic scheme to display three processes. However, an analytical solution for a four state scheme of sufficient complexity to account for the known experimental behavior of sodium or calcium (and in some cases potassium) channels had not been available. The new technology summarized here consists of an analytical solution for a four state scheme that is fully generalized, i.e. every state can transit to every other state and any initial conditions are allowed. With a solution for a fully generalized scheme available, then the solutions for all special or reduced cases are also known, i.e. solutions for all possible arrangements of a four (or fewer) state scheme are obtained just by selecting the appropriate numerical values of the parameters.

Advantages:

- The fundamental, microscopic parameters of a kinetic scheme are the rate constants and the initial probabilities of the occupancy of each state. A rate constant is the probability of a transition from any given state to any other specified state per unit time. These microscopic parameters determine the macroscopic parameters that describe the time course of the experimentally recorded membrane currents, e.g. the time constants of and coefficients on the various exponential terms. The analytical treatment permits immediate direct calculation of the macroscopic parameters, just by specifying the array of microscopic parameters. Without the analytical treatment, a numerical interactive solution would have to be generated and the solution curve fit to define any macroscopic parameter.

State of Development:

- The analytical work is complete. Any arrangements of four, three and two state schemes can be specified just by the selection of values for the microscopic parameters.

R and D Required:

- Integration of the method into existing software applications.

Licensing Potential:

- UMB seeks to commercialize via an exclusive or non-exclusive license agreement with a company active in the area.

Patent Status:

- US Non-Provisional Application Number 11/687,635 Status Pending, filed March 17, 2007.

Related Publications:

- Goldman L. Quantitative analysis of a fully generalized four-state kinetic scheme. Biophys J. 2006 Jul 1;91(1):173-8

Files:

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