A proposal for handling the matrix square root problem in the numerical simulation of channel noise described by the fluctuating Hodgkin-Huxley equations.

by

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Nearly a quarter of a century ago, Yan-nan Lu and I proposed a method for making the Hodgkin-Huxley equations stochastic [1]. We were prompted to do so by work reported in a seminar at Georgia Tech by Louis DeFelice. He and his colleagues described an empirically tested automaton model that treated each and every ion channel element directly. They did this using Monte Carlo (MC) methods. Having written several papers about chaos and fluctuations (some with Joel Keizer [2]) based on the methods of Thomas Kurtz we were familiar with the idea of contracting the description that could take one from an MC model to a master equation model and then to a Fokker-Planck model and finally to a Langevin model. This vision followed ideas put forth many years earlier by George Uhlenbeck and several coworkers.

The contraction, while tedious, was doable and resulted in the paper referred to above [1, 3]. The diffusive behavior brought in by the fluctuations required matrix couplings of vector components of noise terms. For the potassium channels this meant 4 by 4 matrices and for sodium channels it meant 7 by 7 matrices [3]. To get the Langevin picture used in numerical simulations, the square root of the diffusion matrix in the Fokker-Planck equation had to be extracted at each time step. Extracting a square root matrix at each step is computationally time consuming. For a 4 by 4 symmetric, positive definite matrix the square root is well defined, unique, and actually rendered in closed form based on its eigenvectors and eigenvalues determined in closed form from its characteristic equation, a fourth order polynomial. However, using a call-up routine at each time step is also slow and for the 7 by 7 case of sodium not even possible in closed form. For these reasons Lu and I proposed a phenomenological simplification placing the noise directly on the channel subunit terms. This

was indeed fast even if over the ensuing decades numerous papers appeared citing deviations from empirical observations or from the implementation of the Monte Carlo approach. Eventually Eric Shea-Brown and colleagues [4], as well as others, rediscovered in our work the more detailed matrix dependent approach. It was shown by them to agree remarkably well with the Monte Carlo standard. For many channels it was even faster than the MC method since it is independent of actual numbers of channels, only on their density, when the numbers are large, while the MC method grows in size with the number of channels.

Recently I studied the 7 by 7 matrices to see if there were any special properties that might make them tractable. The characteristic equation determined from a 7 by 7 determinant contains 5040 individual terms. However, nearly half of the matrix elements are zero. It turns out that only 41 non-zero terms of the possible 5040 occur. Still I could not find any simplification to the characteristic equation.

Another approach to getting the square roots is to use iterated maps such as the Denman-Beavers iteration. If one simply takes the diffusion matrix at some time step and repeatedly applies the iteration, then when a desired accuracy is achieved after, say, k iterations, one can use the approximate square root produced. This can take time and there are serious stability problems with the Denman-Beavers iteration. Moreover the diffusion matrix is evolving in time. This realization suggests the proposal below that mixes together the iterative time evolution with the root finding. For each iterative step that advances all H-H quantities one time step we will try to arrange matters so that a *single* iteration also advances the square root matrix.

Proposed method:

1) Initialize all quantities for time $t = 0$. This will include the potassium and sodium diffusion matrices given by explicit formulae (see e.g. [3, 4]).
2) For the initial time only, use your method of choice to obtain the square root matrices. Label the diffusion and square root matrices respectively as D_0 and S_0. There will be one of each for potassium and
for sodium.

3) Iteration for the $n + 1$ time step will update all quantities including the diffusion matrices but not yet their square roots. This will generate diffusion matrix D_{n+1}. Now recognize that in the previous iteration we have just determined the square root matrix for a D_n that is only slightly different from D_{n+1}. Thus S_{n+1} is only slightly different from the previously determined S_n. So don't use a multi-step iteration algorithm but instead do a *one step* iteration:

4) $S_{n+1} = S_n + \frac{1}{2} S_n^{-1}(D_{n+1} - D_n)$.

5) Note that *D* is of order Δt so that *S* is order $\Delta t^{1/2}$. Thus the right hand side of 4) is of order $\Delta t^{1/2}$. For small Δt, $\Delta t^{1/2}$ is larger, in dimensionless units. In this work the α/β rates are in $msec^{-1}$. The choice of step size, Δt, is $5\ \mu sec$. Thus the dimensionless time step is much less than one.

6) Squaring both sides of 4) implies that we do indeed have the square root to order Δt. The eigenvalue/eigenvector structure of D_n and S_n also implies that they, and S_n^{-1}, commute. However, S_n and D_{n+1} may not but their commutator is order $\Delta t^{3/2}$, so we need not worry about the matrix order in the products generated by squaring both sides of 4), at least to order Δt. Finally note that the square of $S_n^{-1}(D_{n+1} - D_n)$ is small compared to the cross term $(D_{n+1} - D_n)$. The square and the cross term are both the same order in Δt, but $(D_{n+1} - D_n)^2$ is small because it is the difference of two nearly equal quantities, depending on the step size. Put another way, in dimensionless time, $(D_{n+1} - D_n)^2$ is much smaller than $(D_{n+1} - D_n)$ for small enough step size. (The membrane potential has an excursion within the range $-80\ mV$ to $60\ mV$. Over this range each of the α/β rates is less than $10\ msec^{-1}$, and mostly less or much less than $1\ msec^{-1}$. In a time step the membrane voltage, V, changes a small amount and this induces a small change in the α/β rates. By choosing the step size small enough we can guarantee the requirement that the squared term is negligible compared to the cross term.)

This is the proposal I offer to any of you geared up to execute a computation of this scale, which I no longer am. I am open to criticism of the proposal or to proposed improvements. If I am flat out wrong, please say so! Thanks for your interest.

[1] "Emergent Collective Behavior in Large Numbers of Globally Coupled Independently Stochastic Ion Channels", by R. F. Fox and Yan-nan Lu, *Physical Review E* **49**, 34213431 (1994).

[2] "Amplification of Intrinsic Fluctuations by Chaotic Dynamics", R. F. Fox and J. Keizer, *Physical Review A* **43**, 17091720 (1991)

[3] "Stochastic Versions of the Hodgkin-Huxley Equations", R. F. Fox, *Biophysical Journal* **72**, 20682074 (1997)

[4] "Stochastic differential equation models for ion channel noise in Hodgkin-Huxley neurons," by Joshua H. Goldwyn, Nikita S. Imennov, Michael Famulare, and Eric Shea-Brown, *Physical Review E* **83**. 041908 (published error corrected 14 April 2011)