Reply to Balser, Roden, and Bennett

Dear Sir:

Drs. Balser, Roden, and Bennett do not address the question of how many roots exist with the global fitting procedure. An analytical approach is available (Goldman, Eq. 13). To define the rate constants at any one potential, six values are needed (not four as stated by Balser et al., 1990), while only five are provided by the current time course (not three as stated by Balser et al., 1990). Each additional step from the same initial conditions introduces the same number of new unknown terms as new experimental values, and so the data examined by Balser et al. (1990) can be equally well described by an infinite number of sets of k_{ij}'s. Invoking the presumed exponential dependencies between the k_{ij}'s and V provides only the general form of the relations between unknown terms. There are still fewer experimentally measured values than there are unknown terms. Nor is the number of independent unknown terms reduced by an exact relation between them. This approach does constrain the possible number of solutions, but there are still many roots. For example, for the simplest possible case of a linear dependency on V, ie.,

$$k_{ij} = A_{ij} + B_{ij}V,$$

there are in general nine roots. With steep exponential dependencies more terms in the expansion must be included.

There are, then, many possible solutions with the global fitting procedure. Hence, independently of noise in the data, the obtained result will depend on the initial guesses as Balser et al. (1990) found. The global fitting procedure does not seem to be a practicable method.

Balser et al. (1990) never used changing initial conditions to obtain a solution. This means analyzing currents at the same set of potentials, but with different pulse protocols. The point is to use the continuity of state occupancies to eliminate unknown terms. This is not possible with their protocols. They only attempted to solve for four ON steps from fixed initial conditions and again for four OFF steps with different fixed initial conditions. Moreover, the potential before and after the step must be the same for activation and tail currents analyzed together to provide a solution, while theirs were always different.

Our two approaches are conceptually different. I have shown, for at least one class of schemes with any number of states, how M experimental measurements can be provided for the M unknown terms. The global fitting procedure attempts to provide a unique solution with fewer than M measurements.

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