Notes on changes made to HJCFIT (February and October 2006)

During the course of comparing the DOS and Windows version of HJCFIT, it came to light that there are sometimes numerical problems in computing the areas of the components in the asymptotic HJC distributions. These problems have now been fixed in both versions. Fortunately they make little difference to the results that are obtained, even in difficult cases like the glycine receptor flip model, though they cause a different route to be taken on the approach to the maximum in the likelihood surface, so the results will not be identical.

The problem

The calculation of the amplitudes of the components of the asymptotic distribution involves solving for $\boldsymbol{r}$ of equations of the form

$$\boldsymbol{r}\,\boldsymbol{W}(s_m) = \boldsymbol{0} \quad , \tag{1}$$

where $\boldsymbol{r}$ is a row vector, and $\boldsymbol{W}$ is a matrix, as defined at the bottom of left column on p. 394 of Hawkes, Jalali & Colquhoun (1992) (HJC92). The elements of $\boldsymbol{r}$ add to one $\boldsymbol{ru}$ = 1, where $\boldsymbol{u}$ is a column vector of ones.
These equations have a non-trivial solution only if $\boldsymbol{W}$ is singular. This is the case because s_m are defined by the roots, the solutions of

$$\det[\boldsymbol{W}(s)] = 0 \quad . \tag{2}$$

The values of s for which this is true give the time constants of the asymptotic HJC distributions of apparent open and shut time, thus

$$\tau_m = -\frac{1}{s_m} \quad . \tag{3}$$

Equation 1 has the same form as the equation for equilibrium occupancies, and so can be solved by the methods in the ***Q** matrix cook book* (Colquhoun & Hawkes, 1995) (CH95).

Because $\boldsymbol{W}(s) = s\boldsymbol{I} - \boldsymbol{H}(s)$, this is not s standard eigenvalue problem (for which $\boldsymbol{H}$ would be constant, not a function of s) (HJC92, p. 393). The roots, defined in (2) are found by a bisection method. Problems can arise because $\det[\boldsymbol{W}(s)]$ can be an *enormously* steep function of s. This means that the root can be located with good accuracy, yet $\det[\boldsymbol{W}(s)]$ may still be far from zero, contrary to the assumption needed to solve eq. (1).

The changes

Once the roots have been located, eq (1) was originally solved by appending a column of ones to $\boldsymbol{W}$, as in CH95, p. 597. This is fine for working out the equilibrium occupancies, but for the present problem it can give rise to very ill-conditioned matrices that are hard to invert precisely (in eq. 17, p. 597, CH95).

Two measures seem to have cured these problems in the cases that have been tested so far. Firstly, the bisection routine has been improved, so that the accuracy of s is no

longer used as the sole criterion for the number of bisection steps that are done. If necessary, bisection is continued until the result is lost in rounding error. And the best (nearest to zero) value is output (not necessarily the last one). In most cases this results in det[$\boldsymbol{W}(s)$] being small enough to allow solution of (1).
Secondly, the solution of (1) is now done by the 'reduced Q matrix method' (CH95, p. 596). This method is less likely to produce ill-condition matrix inversion.

Checks

(1) During iterations, a message will be printed on the screen if the matrix inversion required by the 'reduced Q matrix method' is bad
'Matrix inversion bad in solving $\boldsymbol{rW} = \mathbf{0}$, $k = 7$'
In this case 'bad' means that when the matrix is multiplied by its inverse, the resulting unit matrix has errors greater then 0.01 (k is the number of open or shut states, depending on whether the error occurs during calculation of the apparent open or shut time distribution). When such a large error occurs the calculation is abandoned, and the parameter vector replaced.

(2) When the fit has converged, the solution of (1) is checked by calculation of $\boldsymbol{rW}$, from the final estimates of the rate constants. The result should be a vector of zeros. If any of the elements are bigger (in absolute value) than 0.01, a warning is printed on the screen and print file, as follows

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WARNING: error in solving $\boldsymbol{rW} = 0$. If result not close to
zero there may be errors in amplitudes of components
of the asymptotic HJC distribution,

followed by the value of the current root and the result found for $\boldsymbol{rW}$

This message is printed only if any of the elements (which should be zero) are greater than 0.01.

These revised methods have been incorporated in the Windows version of HJCFIT.

References

Hawkes, A. G., Jalali, A. & Colquhoun, D. (1992). Asymptotic distributions of apparent open times and shut times in a single channel record allowing for the omission of brief events. *Philosophical Transactions of the Royal Society London* **B337**, 383-404.

Colquhoun, D. & Hawkes, A. G. (1995). A Q-matrix Cookbook. In *Single channel recording*, Sakmann, B. & Neher, E., pp. 589-633, Plenum Press, New York.

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Addendum October 2006
The reduced $\boldsymbol{Q}$ matrix method does not work when there is only one open state (or one shut state). In this case the reduced $\boldsymbol{Q}$ matrix is 0×0. The equation $\boldsymbol{rW} = \mathbf{0}$, becomes all scalar, with $W = 0$, so r can have any value, but since its elements add to 1 we have $r = 1$. This has now been incorporated so HJCFIT now works again when there is only one open (or shut) state.