Supplement 1:
Complete derivation for Step 1, finding $\boldsymbol{K}$ and $\boldsymbol{A}$

The dataset used as input to Step 1 of the algorithm is an ordered list of spike times $(t_1, ..., t_{N_s})$, where $t_1 < t_2 < ... < t_{N_s}$ and N_s is the number of spikes in the experimental record, together with the experimental response to this spike train, $R_{\mathrm{exp}}(t)$. We describe here an algorithm to minimize

$$I_0 = \int_{-\infty}^{+\infty} \left[R(t) - R_{\mathrm{exp}}(t)\right]^2 dt,$$

or, replacing $R(t)$ with the model assumed in Eq. 1 of the main text,

$$I_0 = \int_{-\infty}^{+\infty} \left[\sum_{i=1}^{N_s} K(t - t_i)A_i - R_{\mathrm{exp}}(t)\right]^2 dt,$$

with respect to the discrete variables A_i, $i = 1, ..., N_s$, and the continuous function $K(t)$. $K(t)$ is assumed to be causal, that is, to satisfy $K(t) = 0$ for $t \leq 0$, since the system cannot respond to a spike before the spike has occured, nor can it respond instantaneously.

In practice, we make two simplifications before tackling the problem. The first simplification is to discretize time into bins of duration Δt. Thus,

$$\begin{aligned} t &= n\Delta t \\ t_i &= n_i\Delta t \\ K_n &= K(n\Delta t) \\ R_n^{\mathrm{exp}} &= R_{\mathrm{exp}}(n\Delta t) \end{aligned}$$

where n and n_i are integers. Then I_0 is replaced by the Riemann sum I:

$$I = \sum_{n=-\infty}^{\infty} \left[\sum_{i=1}^{N_s} K_{n-n_i}A_i - R_n^{\mathrm{exp}}\right]^2 \Delta t.$$

The second simplification is to assume that the kernel K has finite memory, that is, that $K_n = 0$ for $n > N$ for some integer N. By the causality assumption, we also have $K_n = 0$

for $n \leq 0$. Thus, the nonzero values of K are at most $K_1, ..., K_N$.

Our task now is to minimize I with respect to the $N+N_s$ variables $K_1, ..., K_N$, $A_1, ..., A_{N_s}$. This is a calculus problem. To solve it, we differentiate I with respect to each of these variables and set the result equal to 0. In evaluating the derivatives, we make use of the relationships

$$\begin{aligned} \frac{\partial K_n}{\partial K_m} &= \delta_{nm} \\ \frac{\partial K_n}{\partial A_i} &= 0 \\ \frac{\partial A_i}{\partial K_n} &= 0 \\ \frac{\partial A_i}{\partial A_j} &= \delta_{ij} \end{aligned}$$

where $\delta_{ab} = 1$ if $a = b$, and $\delta_{ab} = 0$ otherwise.

Differentiating I with respect to K, we have

$$\begin{aligned} 0 = \frac{\partial I}{\partial K_m} = & \quad 2\Delta t \sum_{n=-\infty}^{\infty} \left[\sum_{i=1}^{N_s} K_{n-n_i} A_i - R_n^{\text{exp}} \right] \sum_{j=1}^{N_s} \delta_{n-n_j,m} A_j \\ = & \quad 2\Delta t \left[\sum_{i,j=1}^{N_s} K_{m+n_j-n_i} A_i A_j - \sum_{j=1}^{N_s} R_{m+n_j}^{\text{exp}} A_j \right]. \end{aligned}$$

In the last step, we have made use of the fact that the only value of n for which $\delta_{n-n_j,m}$ is nonzero is $n = m + n_j$. Let

$$P_n = \sum_{(i,j):n_i-n_j=n} A_i A_j$$

with the understanding that $P_n = 0$ if there are no pairs (i, j) such that $n_i - n_j = n$, and also let

$$Q_m = \sum_{j=1}^{N_s} R_{m+n_j}^{\text{exp}} A_j.$$

In this notation, the equation $0 = \partial I / \partial K_m$ becomes

$$\sum_{n=-\infty}^{\infty} K_{m-n} P_n = Q_m.$$

Recalling that the only nonzero values of K are $K_1, ..., K_N$, and changing indices, we obtain

$$\sum_{n=1}^{N} P_{m-n} K_n = Q_m, \tag{S1}$$

which holds for $m = 1, ..., N$ and therefore has the form of a linear system of N equations in the N unknowns $K_1, ..., K_N$. It is clear from the definition of P that the matrix $\mathcal{P}$ with the elements $\mathcal{P}_{mn} = P_{m-n}$ is a symmetric Toeplitz matrix, and it can be shown that this matrix is positive definite (except in the trivial case that all of the A_i's are equal to zero). These properties of its matrix guarantee that the above linear system has a solution $K_1, ..., K_N$, and moreover that the solution is unique. Note, however, that the solution depends upon the A_i's, which are also unknown.

Differentiating I with respect to the A_i's, we have

$$\begin{aligned} 0 = \frac{\partial I}{\partial A_k} = & \quad 2\Delta t \sum_{n=-\infty}^{\infty} \left[\sum_{i=1}^{N_s} K_{n-n_i} A_i - R_n^{\exp} \right] \sum_{j=1}^{N_s} K_{n-n_j} \delta_{jk} \\ = & \quad 2\Delta t \sum_{n=-\infty}^{\infty} \left[\sum_{i=1}^{N_s} K_{n-n_i} A_i - R_n^{\exp} \right] K_{n-n_k}. \end{aligned}$$

Let

$$\begin{aligned} X_{ki} = & \quad \sum_{n=-\infty}^{\infty} K_{n-n_k} K_{n-n_i} \\ Y_k = & \quad \sum_{n=-\infty}^{\infty} R_n^{\exp} K_{n-n_k}. \end{aligned}$$

The sums over n that appear in these definitions of X_{ki} and Y_k each involve only a finite number of nonzero terms, since $K_n = 0$ for $n \leq 0$ and also for $n > N$. Expressed in terms of X and Y, the equations for the A_i's take the form of a linear system:

$$\sum_{i=1}^{N_s} X_{ki} A_i = Y_k \tag{S2}$$

for $k = 1, ..., N_s$. It is clear that the matrix X of this linear system is a symmetric, banded matrix, and it can be shown that X is positive definite. It follows that a solution $A_1, ..., A_{N_s}$ of this linear system exists and moreover is unique. Note, however, that this solution depends on $K_1, ..., K_N$, which appears in the definitions of X and Y.

In the foregoing, we have found a linear system that determines K given A, Eq. S1, and a linear system that determines A given K, Eq. S2. To solve for the values of K and A that simultaneously minimize I, we use the following iterative scheme:

$$\begin{aligned} \hat{K}^{(l+1)} &= (\mathcal{P}^{-1}Q)^{(l)} \\ \hat{A}^{(l+1)} &= (X^{-1}Y)^{(l+1)} \end{aligned}$$

for $l = 0, 1, ...$ Recall that $\mathcal{P}$ and Q depend on A. Thus $(\mathcal{P}^{-1}Q)^{(l)}$ is shorthand for the value of $\mathcal{P}^{-1}Q$ when $A = \hat{A}^{(l)}$. Similarly, $(X^{-1}Y)^{(l)}$ is shorthand for the value of $X^{-1}Y$ when $K = \hat{K}^{(l)}$. To start the iterations, we arbitrarily set $\hat{A}_i^{(0)} = 1$ for $i = 1, ..., N_s$.

For $l \geq 1$, the iterative scheme defined above generates an estimate $\hat{K}^{(l)}$ of K and an estimate $\hat{A}^{(l)}$ of A. We can use these to construct an estimate $\hat{R}^{(l)}$ of R according to

$$\hat{R}_n^{(l)} = \sum_{i=1}^{N_s} \hat{K}_{n-n_i}^{(l)} \hat{A}_i^{(l)}.$$

Then we can follow the progress of the algorithm by monitoring

$$I^{(l)} = \sum_{n=-\infty}^{\infty} \left[\hat{R}_n^{(l)} - R_n^{\text{exp}} \right]^2 \Delta t.$$

Since each step of our iterative scheme finds the optimal value of K or A, given the current estimate of A or K, respectively, it is guaranteed that

$$I^{(l+1)} \leq I^{(l)}.$$

Moreover, since $I^{(l)}$ is bounded from below by 0, it is also guaranteed that $I^{(l)}$ converges as $l \to \infty$. This does not by itself guarantee that $\hat{K}^{(l)}$ and $\hat{A}^{(l)}$ converge, but that is what we usually observe in practice (see main text).

Supplement 2:
Complete derivation for finding *H* in Step 2

As explained in the main text, a key feature of our algorithm in Step 2 is the simplification of Eq. 2 to the equation

$$S(t) = \sum_{j:t_j<t} H(t - t_j).$$

This equation can then be used to find $H(t)$ by an algorithm analogous to that in Step 1. The input to this algorithm is an ordered list of spike times (usually the same spike times as in Step 1) $(t_1, ..., t_{N_s})$, where $t_1 < t_2 < ... < t_{N_s}$, together with the corresponding $S_{\exp}(t)$ constructed as explained in the main text. We wish to minimize

$$\begin{aligned} I_0 = & \int_{-\infty}^{+\infty} \left[S(t) - S_{\exp}(t)\right]^2 dt \\ = & \int_{-\infty}^{+\infty} \left[\sum_{j=1}^{N_s} H(t - t_j) - S_{\exp}(t)\right]^2 dt \end{aligned}$$

with respect to the continuous function $H(t)$. We proceed with a similar discretization of time as in Step 1:

$$\begin{aligned} t = & \quad n\Delta t \\ t_j = & \quad n_j \Delta t \\ H_n = & \quad H(n\Delta t) \\ S_n^{\exp} = & \quad S_{\exp}(n\Delta t) \end{aligned}$$

where n and n_i are integers. Then I_0 is replaced by the Riemann sum I:

$$I = \sum_{n=-\infty}^{\infty} \left[\sum_{j=1}^{N_s} H_{n-n_j} - S_n^{\exp}\right]^2 \Delta t.$$

As in Step 1, we assume that the kernel H is causal and has finite memory, so that $H_n = 0$ for $n \leq 0$ and also for $n > N$ for some integer N. Thus, the nonzero values of H are at most $H_1, ..., H_N$.

To minimize I with respect to the variables $H_1, ..., H_N$, we differentiate I with respect to each of these variables and set the result equal to 0. We make use of the relationship

$$\frac{\partial H_n}{\partial H_m} = \delta_{nm}$$

where $\delta_{nm} = 1$ if $n = m$, and $\delta_{nm} = 0$ otherwise.

Thus,

$$\begin{aligned} 0 = \frac{\partial I}{\partial H_m} = & \quad 2\Delta t \sum_{n=-\infty}^{\infty} \left[\sum_{j=1}^{N_s} H_{n-n_j} - S_n^{\text{exp}} \right] \sum_{i=1}^{N_s} \delta_{n-n_i,m} \\ = & \quad 2\Delta t \left[\sum_{i,j=1}^{N_s} H_{m+n_i-n_j} - \sum_{i=1}^{N_s} S_{m+n_i}^{\text{exp}} \right]. \end{aligned}$$

In the last step, we have made use of the fact that the only value of n for which $\delta_{n-n_i,m}$ is nonzero is $n = m + n_i$. Let

$$W_n = \sum_{(i,j):n_j-n_i=n} 1$$

with the understanding that $W_n = 0$ if there are no pairs (i, j) such that $n_j - n_i = n$, and also let

$$Z_m = \sum_{i=1}^{N_s} S_{m+n_i}^{\text{exp}}.$$

The equation $0 = \partial I/\partial H_m$ then becomes

$$\sum_{n=-\infty}^{\infty} H_{m-n} W_n = Z_m.$$

Recalling that the only nonzero values of H are $H_1, ..., H_N$, and changing indices, we obtain

$$\sum_{n=1}^{N} W_{m-n} H_n = Z_m.$$

This holds for $m = 1, ..., N$, and therefore has the form of a linear system of N equations in the N unknowns $H_1, ..., H_N$. It is clear from the definition of W that the matrix $\mathcal{W}$ with the elements $\mathcal{W}_{mn} = W_{m-n}$ is a symmetric Toeplitz matrix, and it can be shown that this matrix is positive definite. These properties of its matrix guarantee that the above linear system has a solution $H_1, ..., H_N$, and moreover that the solution is unique.