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NEUROCOMPUTING

Neurocomputing 38–40 (2001) 1651–1656

www.elsevier.com/locate/neucom

Model fitting as an aid to bridge balancing in neuronal recording

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Abstract

When recording intracellularly, the resistance across the cell membrane must be monitored. However the resistance seen by the recording amplifier consists of the access resistance (between the electrode and the cell) in series with the cell resistance. When the stray capacitance is low, the time constant of the cell and that associated with the recording setup are different and the two resistance values can be easily determined visually. We describe a model-fitting method which can automatically infer the electrode and cell capacitances and resistances in more difficult cases. © 2001 Published by Elsevier Science B.V.

Keywords: Bridge balancing; Intracellular; Model fitting; Patch clamp

1. The problem

In current clamp (or Bridge) mode of intracellular or patch clamp recording, the electrode ruptures a neuron's cell membrane with the goal of recording the potential across this membrane. This is measured with electronic circuitry connected between the contents of the electrode and the extracellular bath [2,1]. A simplified version of the circuit is shown in Fig. 1 where R_m and C_m are the resistance and capacitance of the cell membrane, R_e is the resistance at the electrode-cell interface, C_i is the capacitance at the amplifier input and is due to the capacitance between the electrode

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0925-2312/01/$ - see front matter © 2001 Published by Elsevier Science B.V.
PII: S0925-2312(01)00525-2

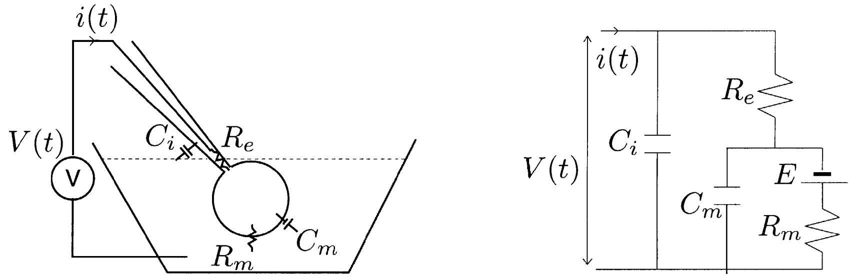


Fig. 1. Assumed circuit.

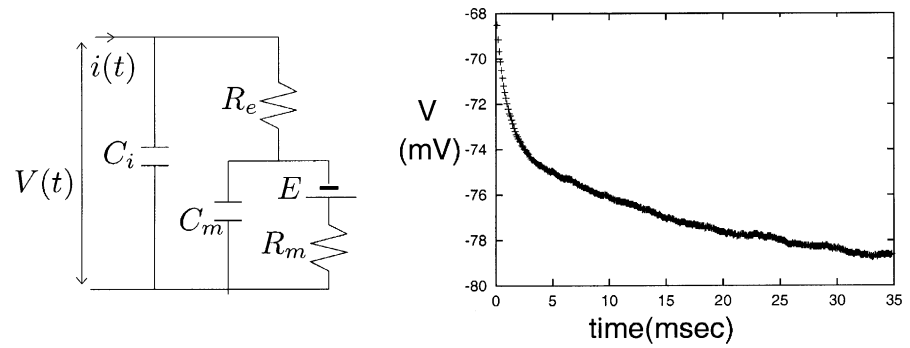


Fig. 2. Example data $V(t)$.

and ground as well as the capacitance to ground at the input of the amplifier circuit. E is the membrane potential of the cell.

In order to correctly interpret total resistance drifts and to compensate appropriately for any injected current, it is crucial to distinguish the resistance of the cell from that of the electrode. The user usually determines the electrode resistance by injecting a current step of height i into the electrode and observing the resulting voltage $V(t)$ (see Fig. 2 for an example). If we assume that the unknowns R_m, C_m, R_e, C_i and E are constant during this step then the resulting voltage $V(t)$ is a sum of a step response and two decaying exponentials. The height of the voltage step is

$$\Delta V = i(R_m + R_e).$$

For configurations that afford low stray capacitance, C_i, and access resistance R_e, the time constants of the two exponential decays are vastly different (the slower time constant can be associated with the voltage drop across the cell and the faster one with the drop across the electrode) allowing for clear determination of the electrode resistance (obtained by dialing the “Bridge Balance” knob until the steep part of the curve just disappears). With the "visualized patch" technique, shallower electrode entry angles are required which greatly increases the capacitance across the electrode. Also more myelinated tissue can partially clog electrode tips resulting in higher access resistances. Together, these effects can lead to curves where the separation between voltage drop across the electrode and that across the cell are not so obvious.

2. The method

We describe a procedure to automatically determine the values of the resistances and capacitances with error estimates assuming that the system fits the model shown in Fig. 1. The fit can be visually assessed as a measure of confidence in the model.

Advantages of this approach include:

(1) It removes the qualitative nature of bridge balancing allowing more accurate determination of R_e in difficult cases.

(2) It uses all the data from the curve not just points near the "knee", allowing determination of the parameters under higher noise conditions (with correspondingly larger error estimates).

(3) It does not require capacitance compensation (which may cause instability if conditions drift).

(4) It gives the values of C_i and C_m as well as the resistances.

A physical model corresponding to the circuit in Fig. 1 is fitted by maximum likelihood [3] to the entire voltage trace $V(t)$. The equation for the voltage is

$$V(t) = i[a\mathrm{e}^{-\mu_1(t-t_0)} + b\mathrm{e}^{-\mu_2(t-t_0)} + c] + V(t_0),$$

where

$$\mu_1 = \frac{(C_i R_e + C_i R_m + C_m R_m)}{2 C_i R_e C_m R_m} + s/2,$$

$$\mu_2 = \frac{(C_i R_e + C_i R_m + C_m R_m)}{2 C_i R_e C_m R_m} - s/2,$$

$$s = \frac{\sqrt{C_i^2 R_e^2 + 2C_i^2 R_e R_m - 2 C_i R_e C_m R_m + C_i^2 R_m^2 + 2 C_i R_m^2 C_m + C_m^2 R_m^2}}{C_i R_e C_m R_m},$$

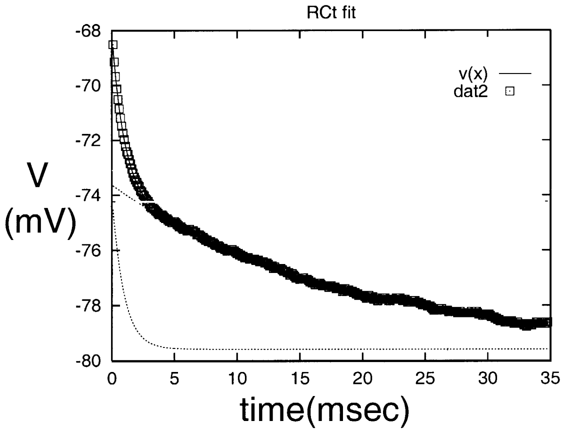
$$a = (\mu_2 c - 1.0/C_i)/s,$$

$$b = (-\mu_1 c + 1.0/C_i)/s.$$

$$c = R_e + R_m.$$

Note that when $R_m \gg R_e$ and $C_m \gg C_i$ the time constants tend towards $1/(R_e C_i)$ and $1/(R_m C_m)$, but in general both time constants involve all terms.

The inputs to the model-fitting method are the initial voltage $V(t_0)$, the size of the current step i, and the trace $V(t)$ for $t > t_0$. The software infers the values of



Inferred parameters		
$R_m=$	106.9 ± 0.5	MΩ
$R_e=$	128.2 ± 0.5	MΩ
$C_i=$	7.8 ± 0.1	pF
$C_m=$	163 ± 2	pF
$t_0=$	-0.030 ± 0.008	msec

Fig. 3. Example fit. Current pulse size was -0.05 nA. The two dotted curves show the two exponential decays.

$R_{\rm m}$, $R_{\rm e}$, $C_{\rm i}$ and $C_{\rm m}$, along with value of the step onset time t_0. These five variables are reported with error bars. More information about the code can be found in Appendix A.

If some parts of the voltage trace $V(t)$ are missing or corrupted, the fitting method can be applied to whatever data are available and will still give reliable results, but with appropriately larger error bars on the inferred parameters.

Fig. 3 shows the fit found for the dataset of Fig. 2. Also shown are the two exponential decays.

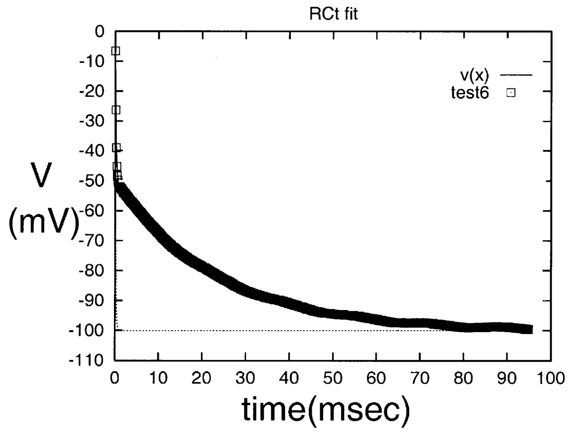
3. Current limitations

The model currently assumes that the data are corrupted by additive Gaussian independent noise. This assumption is clearly not true (since correlations in the noise are visible to the eye) and leads to smaller error bars than appropriate. This problem can be addressed with more accurate noise models (perhaps specifically including a 60 Hz component).

Fig. 4 shows the results when the method is applied to data from an artificial cell with known parameters. The inferred parameters are close to the true values but, as anticipated, the error bars are overly confident because the noise is correlated.

Acknowledgements

This work was supported by a grant from the Alfred P. Sloan foundation. We thank Henry Markram, Greg Hjelmstad and especially Cooper Roddey for helpful comments.



Inferred parameters		
$R_m =$	49.67 ± 0.04	MΩ
$R_e =$	49.58 ± 0.04	MΩ
$C_i =$	3.01 ± 0.03	pF
$C_m =$	459 ± 1	pF
$t_0 =$	0.0834 ± 0.0009	msec

Fig. 4. Example fit 2. Current pulse size was -1 nA. This trace was obtained from a model cell with specified parameters $R_m = 50$ MΩ, $R_e = 50$ MΩ, and $C_m = 470$ pF.

Appendix. A

Software and further information can be obtained from http://www.keck.ucsf.edu/~desa/RCfit.html

doit.p is a perl program that invokes gnuplot's gnufit utility. It requires GNUPLOT 3.5 or better and has been tested with

```
GNUPLOT
    Unix version 3.5 (pre 3.6)
    patchlevel beta 340
    last modified Tue Nov 25 22:57:44 GMT 1997
```

and

```
GNUPLOT
    unix version 3.5
    patchlevel 3.50.1.17, 27 Aug 93
    last modified Fri Aug 27 05:21:33 GMT 1993
```

report.p is called by doit.p to present the results.

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[1] A. Finkel, Axoclamp-2A Microelectrode Clamp Theory and Operation, Axon Instruments, Inc., Foster City, CA, 1989.

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Virginia R. de Sa received her B.Sc. Engineering in Mathematics and Engineering from Queen's University in 1988 and her Ph.D. in Computer Science from the University of Rochester in 1994. She is currently a Sloan postdoctoral fellow in the Keck Center for Integrative Neuroscience at the University of California, San Francisco. Her research interests include neural coding, cortical plasticity and unsupervised neural network learning algorithms.

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