

CONTROLLABILITY OF EXCITABLE SYSTEMS *

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Abstract. Mathematical models of cell electrical activity typically consist of a current balance equation, channel activation (or inactivation) variables and concentrations of regulatory agents. These models can be thought of as nonlinear filters whose input is some applied current I (possibly zero) and output is a membrane potential V . A natural question to ask is if the applied current I can be deduced from the potential V . For a surprisingly large class of models the answer to this question is yes. To show this, we first demonstrate how many models can be imbedded into higher dimensional quasilinear systems. For quasilinear models, a procedure for determining the inverse of the nonlinear filter is then described and demonstrated on two models: 1) the FitzHugh-Nagumo model and 2) the Sherman-Rinzel-Keizer (SRK) model of bursting electrical activity in pancreatic beta-cells. For the latter example, the inverse problem is then used to deduce model parameter values for which the model and experimental data agree in some measure. An advantage of the correlation technique is that experimental values for activation (and/or regulatory) variables need not be known to make the estimates for these parameter values.

Key words. excitable systems, control, parameter identification, bursting

1. Introduction. Mathematical models of electrical activity in single cells comprise of a set of differential equations, one of which represents a balance of transmembrane ionic currents. An external electrical stimuli is modelled by including an applied current in the current balance equation. Chemical stimuli are often modelled either by varying concentrations of relevant agents or by varying parameters which are believed to be correlated to the stimulating chemical.

If the transmembrane potential of a cell at time t is $V(t)$, the model equations have the form:

$$(1.1) \quad C_m \frac{dV}{dt} = - \sum_X I_X(V, \vec{w}) - I(t),$$

$$(1.2) \quad \frac{d\vec{w}}{dt} = W(V, \vec{w}), \quad \vec{w} \in \mathbb{R}^m.$$

The first of these equations represents a balance of capacitive currents (left side), currents through ionic channels (right side) and the applied current I . The parameter C_m is the total capacitance, I_X are the transmembrane currents through ionic channels (e.g. voltage-gated sodium, calcium inactivated potassium), and \vec{w} are variables which describe gating and other regulatory effects for each ionic channel of type X . Often, many of these variables evolve slowly.

A common experiment in electrophysiology is to isolate a cell, inject a known current $I(t)$ into the cell and then measure the resulting membrane potential $V(t)$. The aim in such experiments is to deduce what ionic currents are relevant for the given cell and hopefully deduce quantitatively accurate functional forms for I_X .

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In this regard the cell may be regarded a nonlinear filter in which the input $I(t)$ illicit a response $V(t)$. In this study we address the inverse problem, namely, if $V(t)$ is known is there a way to deduce what the stimulus $I(t)$ must have been? Surprisingly, the answer to this question is yes for a great many models.

The approach we take is direct. Given a model we outline a procedure for explicitly deducing the inverse problem. This procedure requires that \vec{w} occur linearly in the given model (1.1)-(1.2). To be specific, the model equations must be of the form

$$(1.3) \quad \frac{dv}{dt} = f(v) - \vec{F}(v) \cdot \vec{w} + I(t),$$

$$(1.4) \quad \frac{d\vec{w}}{dt} = \vec{b}(v) - A(v)\vec{w}$$

for some scalar function f , vector valued functions $\vec{F}, \vec{b} \in \mathbb{R}^m$ and matrix $A \in \mathbb{R}^{m \times m}$. Since \vec{w} occurs linearly in these equations but the potential v does not, we shall refer to (1.3)-(1.4) as quasilinear.

In many excitable cell models, (1.4) is an appropriate form since the variables $\vec{w} = (w_1, w_2, \dots, w_m)^T$ often obey relaxation equations:

$$(1.5) \quad \frac{dw_i}{dt} = \frac{W_i(v) - w_i}{\tau_i(v)}, \quad i = 1, 2, \dots, m.$$

In vector form, this can be written as (1.4). Such relaxation variables, however, do not always occur linearly in (1.3).

In section 2, we show that despite the fact that many models (1.1)-(1.2) are not quasilinear, they can be embedded in a higher dimensional system which is quasilinear. This embedding is explicit and we demonstrate it on the Hodgkin-Huxley model for electrical activity in the squid giant axon.

Then, in section 3, we outline the procedure to invert quasilinear models by deriving a single differential equation for I which depends only on v . This procedure is demonstrated on the FitzHugh-Nagumo model ([2, 5]) where the associated differential equation for $I(t)$ is solved to derive an explicit expression for the current I which illicit a given arbitrary (smooth) response $v(t)$.

Lastly, in section 4, we demonstrate how the inversion procedure can be used to estimate model parameters from experimental data. As with most parameter identification problems, the problem associated with the parameter estimation is ill-posed. This is discussed, a regularization scheme is introduced and then demonstrated on a model of electrical activity in the pancreatic β cell.

2. Transformation to Quasilinear Form. Here we discuss how some common nonlinearities occurring in excitable cell models (1.1)-(1.2) can be eliminated by introducing new variables and embedding solutions of (1.1)-(1.2) in a quasilinear system (1.3)-(1.4) with degree $n > m$.

Arguably the most common nonlinearity which occurs in excitable cell models are those which arise from modelling voltage activation (and/or inactiva-

tion) in ionic channels. Two such examples occur in the Hodgkin-Huxley model:

$$(2.1) \quad C_m \frac{dV}{dt} = -I_{Na}(V, m, h) - I_K(V, n) - I_L(V)$$

$$(2.2) \quad \frac{d\phi}{dt} = \frac{\phi_\infty(V) - \phi}{\tau_\phi(V)} = \alpha_\phi(V) - \beta_\phi(V)\phi \quad , \quad \phi = m, h, n$$

where I_{Na} , I_K and I_L are voltage-gated sodium, voltage-gated potassium and leakage currents, respectively. The voltage-gated currents have the form

$$(2.3) \quad I_{Na} = g_{Na} m^3 h (V - V_{Na}) \quad ,$$

$$(2.4) \quad I_K = g_K n^4 (V - V_K) \quad ,$$

where g_{Na} , g_K are (constant) maximal conductances and V_{Na} , V_K are sodium and potassium Nernst potentials, respectively.

Defining $\vec{w} = (w_1, w_2, w_3) = (m, h, n)$ this model fails to be quasilinear since w_i occur in a nonlinear fashion in (2.1). However, if we defined new variables $W_1 = m^3 h$ and $W_2 = n^4$, (2.1) would be linear in $\vec{W} = (W_1, W_2)$. But then, (2.2) would not be linear in \vec{W} . To circumvent this difficulty we introduce several new variables. First we consider the nonlinearities of the type in (2.4).

Assume I_X has the form

$$(2.5) \quad I_X = g(V)\phi^n \quad ,$$

where g is some function, n is an integer and the activation variable $\phi(t)$ satisfies the relaxation equation (2.2). Define the variables

$$(2.6) \quad z_i = \phi^i \quad , \quad i = 1, 2, \dots, n.$$

Differentiating z_i in t and using (2.2) we find

$$(2.7) \quad \frac{dz_i}{dt} = i\phi^{i-1} \frac{d\phi}{dt} = i\alpha_\phi z_{i-1} - i\beta_\phi z_i$$

for $i = 2, 3, \dots, n$. The equation for z_1 is (2.2). Defining $\vec{z} = (z_1, z_2, \dots, z_n)$ these equations can be written

$$(2.8) \quad \frac{d\vec{z}}{dt} = \vec{b}(V) - A(V)\vec{z}$$

where $\vec{b}(V) = (\alpha_\phi(V), 0, \dots, 0)^T$ and

$$(2.9) \quad A(V) = \begin{bmatrix} \beta_\phi & 0 & \dots & \dots & \dots & 0 \\ -2\alpha_\phi & 2\beta_\phi & 0 & \dots & \dots & 0 \\ 0 & -3\alpha_\phi & 3\beta_\phi & 0 & \dots & 0 \\ \vdots & 0 & \ddots & \ddots & \ddots & 0 \\ 0 & \dots & \dots & 0 & -n\alpha_\phi & n\beta_\phi \end{bmatrix} .$$

Thus, $I_X = g(V)z_n$ is linear in z_n and (2.8) has the form (1.4). It is important to note that although the resulting system has $n - 1$ new variables, the initial conditions on the z_i are dependent. In particular, $z_i(0) = z_1(0)^i$. For the Hodgkin-Huxley model, $\phi(t) = n(t)$ is the potassium activation variable.

Now we turn to currents I_X of the form

$$(2.10) \quad I_X = g(V)\phi^n\psi^m$$

where g is some function, n, m are integers and the activation variables $\phi(t)$ and $\psi(t)$ satisfy relaxation equations of the form (2.2). Define the new variables

$$(2.11) \quad Z_{i,j} = \phi^i\psi^j, \quad i = 0, 1, \dots, n, \quad j = 0, 1, \dots, m, \quad i + j \neq 0.$$

Again, we differentiate $Z_{i,j}$ in t and use the relaxation equations (2.2) for ϕ and ψ to find

$$(2.12) \quad \frac{dZ_{i,j}}{dt} = i\alpha_\phi Z_{i-1,j} - (i\beta_\phi + j\beta_\psi)Z_{i,j} + j\alpha_\psi Z_{i,j-1}.$$

From (2.12) it is apparent that the derivative of $Z_{i,j}$ depends linearly on two other $Z_{k,l}$ variables. This dependence is illustrated in Figure 1 where each $Z_{i,j}$ variable is indicated by circle. The derivative of $Z_{i-1,j}$ will in turn depend on $Z_{i-2,j}$, $Z_{i-1,j}$ and $Z_{i-1,j-1}$. It is evident that by introducing $(n+1)(m+1) - 1$ variables, I_X will be linear in $Z_{n,m}$ and the resulting system for $Z_{i,j}$ will be of the form (1.4).

For the Hodgkin-Huxley sodium current, ϕ and ψ are current activation and inactivation variables, respectively, with $n = 3$ and $m = 1$ so that the current equation is linear in $\phi^3\psi$. The inflated quasilinear system corresponding to this current requires the addition of 6 new variables. Defining

$$(2.13) \quad \vec{Z} = (Z_{1,0}, Z_{0,1}, Z_{1,1}, Z_{2,0}, Z_{2,1}, Z_{3,0}, Z_{3,1})^T$$

the system for \vec{Z} has the form

$$(2.14) \quad \frac{d\vec{Z}}{dt} = \vec{b}(V) - A(V)\vec{Z}$$

where

$$A(V) = \begin{bmatrix} \beta_\phi & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \beta_\psi & 0 & 0 & 0 & 0 & 0 \\ -\alpha_\psi & -\alpha_\phi & \beta_\phi + \beta_\psi & 0 & 0 & 0 & 0 \\ -2\alpha_\phi & 0 & 0 & 2\beta_\phi & 0 & 0 & 0 \\ 0 & 0 & -2\alpha_\phi & 2\beta_\phi + \beta_\psi & \alpha_\psi & 0 & 0 \\ 0 & 0 & 0 & -3\alpha_\phi & 0 & 3\beta_\phi & 0 \\ 0 & 0 & 0 & 0 & -3\alpha_\phi & 3\beta_\phi + \beta_\psi & \alpha_\psi \end{bmatrix}$$

and $\vec{b} = (\alpha_\phi, \alpha_\psi, 0, 0, 0, 0, 0)^T$. Again we note the initial conditions are dependent on one another via the definition of $Z_{i,j}$.

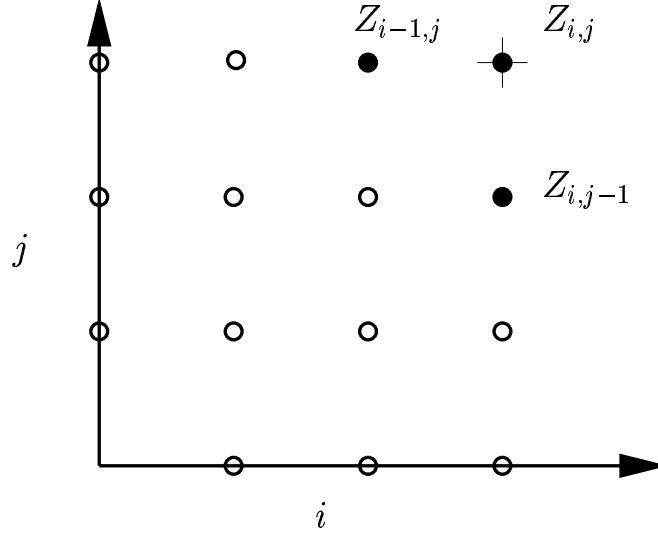


FIG. 1. Figure showing the dependence of the derivative of $Z_{i,j}(t) = \phi^i \psi^j$ (located at cross) on other $Z_{i,j}$ variables. The derivative of $Z_{i,j}$ depends linearly on $Z_{i,k}$ variables indicated by solid circles.

In summary, the methods outlined in this section can be used to embed the Hodgkin-Huxley model in an 11-th order quasilinear system. Given the dependence of the initial conditions on one another, we see that solutions of the 4-rth order Hodgkin-Huxley model are in fact projections of trajectories on a differentiable manifold embedded in the 11-th order solution space of the corresponding quasilinear system.

3. Controllability. In this section we outline a procedure for inverting initial value problems of the form (1.3)-(1.4). We define the initial condition $\vec{v}_0 = (v(0), \vec{w}(0))^T \in \mathbb{R}^{m+1}$ and assume that for the applied current $I(t)$

$$(3.1) \quad \vec{I}(t) = \left(I, \frac{dI}{dt}, \dots, \frac{d^{m-1}I}{dt^{m-1}} \right)^T$$

is continuous. Lastly, we let $\vec{I}_0 = \vec{I}(0)$.

With these definitions and assumptions, we can view (1.3)-(1.4) as a nonlinear filter whose input is (I, \vec{v}_0) and output is $(v(t), \vec{I}_0)$, i.e., there is some operator

$N : (I, \vec{v}_0) \rightarrow (v, \vec{I}_0)$. In words, if the input current and initial cell state are known, the model yields an output voltage v . And since $I(t)$ is known, \vec{I}_0 can be found.

A natural question to ask is whether N has an inverse. That is to say, if the output $v(t)$ is known, can $I(t)$ be predicted given \vec{I}_0 ? Surprisingly, the answer to this question is yes in a great many instances. To demonstrate this fact, we explicitly compute the inverse operator. Owing largely to the linearity of (1.3)-(1.4) in \vec{w} , repeated differentiations of (1.3) and substitutions using (1.4) results in a procedure whereby \vec{w} can be eliminated resulting in a linear differential equation for $I(t)$ involving $v(t)$ and its derivatives.

Solving (1.3) for I we have

$$(3.2) \quad I = H_0 \left(v, \frac{dv}{dt} \right) + \vec{K}_0(v) \cdot \vec{w} = \frac{dv}{dt} - f(v) + \vec{F}(v) \cdot \vec{w}.$$

Differentiating (3.2) in t results in the calculations

$$(3.3) \quad \begin{aligned} \frac{dI}{dt} &= \frac{dH_0}{dt} + \vec{w}^T \frac{d\vec{K}_0}{dt} + \vec{K}_0^T \frac{d\vec{w}}{dt} \\ &= \frac{dH_0}{dt} + \vec{w}^T \frac{d\vec{K}_0}{dt} + \vec{K}_0^T (\vec{b} - A\vec{w}) \\ &= \frac{dH_0}{dt} + \vec{K}_0^T \vec{b} + \vec{w}^T \frac{d\vec{K}_0}{dt} - \vec{K}_0^T A\vec{w} \\ &= \left(\frac{dH_0}{dt} + \vec{K}_0^T \vec{b} \right) + \vec{w}^T \left(\frac{d\vec{K}_0}{dt} - A^T \vec{K}_0 \right) \end{aligned}$$

which can be written in the form

$$(3.4) \quad \frac{dI}{dt} = H_1 \left(v, \frac{dv}{dt}, \frac{d^2v}{dt^2} \right) + \vec{K}_1 \left(v, \frac{dv}{dt} \right) \cdot \vec{w}$$

for some functions H_1 and \vec{K}_1 . Proceeding inductively, repeated differentiations of this equation in t and using the same substitutions it is easily seen that one can obtain a set of equations of the form:

$$(3.5) \quad \frac{d^n I}{dt^n} = H_n \left(v, \frac{dv}{dt}, \dots, \frac{d^{n+1}v}{dt^{n+1}} \right) + \vec{K}_n \left(v, \frac{dv}{dt}, \dots, \frac{d^n v}{dt^n} \right) \cdot \vec{w}$$

where $n = 1, \dots, m-1$. In matrix notation (3.2),(3.5) can be written

$$(3.6) \quad \vec{I} = \vec{H} + K\vec{w}$$

where $\vec{H} = (H_0, H_1, \dots, H_{m-1})^T$ and the matrix $K \in \mathbb{R}^{m \times m}$ has $\vec{K}_n, n = 0, 1, \dots, m-1$, as rows. So long as K is nonsingular,

$$(3.7) \quad \vec{w} = K^{-1}(\vec{I} - \vec{H})$$

which when substituted into (1.3) yields

$$(3.8) \quad \frac{dv}{dt} = f(v) - \vec{F}(v) \cdot K^{-1}(\vec{I} - \vec{H}) + I.$$

This is a linear differential equation for $I(t)$ of degree $m - 1$. Given the initial condition \vec{I}_0 and $v(t)$ the solution $I(t)$ defines the inverse operator $N^{-1} : (v, \vec{I}_0) \rightarrow (I, \vec{v}_0)$.

Before explaining the significance of this result we first illustrate the procedure on a simple model. For this we choose the FitzHugh-Nagumo model ([2, 5])

$$(3.9) \quad \dot{v} = \frac{dv}{dt} = f(v) - w + I(t),$$

$$(3.10) \quad \dot{w} = \frac{dw}{dt} = \varepsilon(v - \gamma w),$$

where $f(v) = v(1 - v)(v - a)$ and (a, γ, ε) are parameters. Differentiating (3.9) in t we find

$$(3.11) \quad \begin{aligned} \ddot{v} &= f'(v)\dot{v} - \dot{w} + \dot{I} \\ &= f'(v)\dot{v} - \varepsilon(v - \gamma w) + \dot{I} \end{aligned}$$

Solving for w we find

$$(3.12) \quad w = \frac{1}{\varepsilon\gamma} \left(\ddot{v} - f'(v)\dot{v} + \varepsilon v - \dot{I} \right).$$

Substituting this into (3.9) we obtain

$$(3.13) \quad \dot{I} + \varepsilon\gamma I = B(v, \dot{v}, \ddot{v})(t) = \ddot{v} - f'(v)\dot{v} + \varepsilon v + \varepsilon\gamma(\dot{v} - f(v)).$$

Given an initial condition $I(0) = I_0$ the solution of this first-order differential equation is:

$$(3.14) \quad I(t) = N^{-1}(v, I_0) = e^{-\varepsilon\gamma t} \left(I_0 + \int_0^t e^{\varepsilon\gamma s} B(v, \dot{v}, \ddot{v})(s) ds \right),$$

demonstrating explicitly a formula for the inverse of N . For example, (3.14) can be used to compute the stimulus $I(t)$, $I_0 = 0$ which yields an output $v(t) = \sin^2 t$. Performing this calculation explicitly¹ we plot the corresponding $I(t)$ in Figure 2 for a fixed set of parameter values. In this example, the cell is initially at rest since for $v(t) = \sin^2 t$, $(v(0), v'(0)) = (0, 0)$.

Now we explain the significance of these results. It is clear that given the solution (v, \vec{w}) of (1.3)-(1.4) one can easily find $I(t)$ by simply solving (1.3). Therefore, the elimination of \vec{w} from the model equations seems irrelevant to defining the inverse of N . However, in most experimental situations it is often difficult or impossible to measure v and \vec{w} simultaneously. Voltage measurements, on the other hand are always made. And, if the sampling rate for this measurement is sufficiently fast, estimates of v and its derivatives are easily obtained. In this regard, the elimination of \vec{w} is paramount to developing a technique for estimating

¹Done symbolically with MapleTM

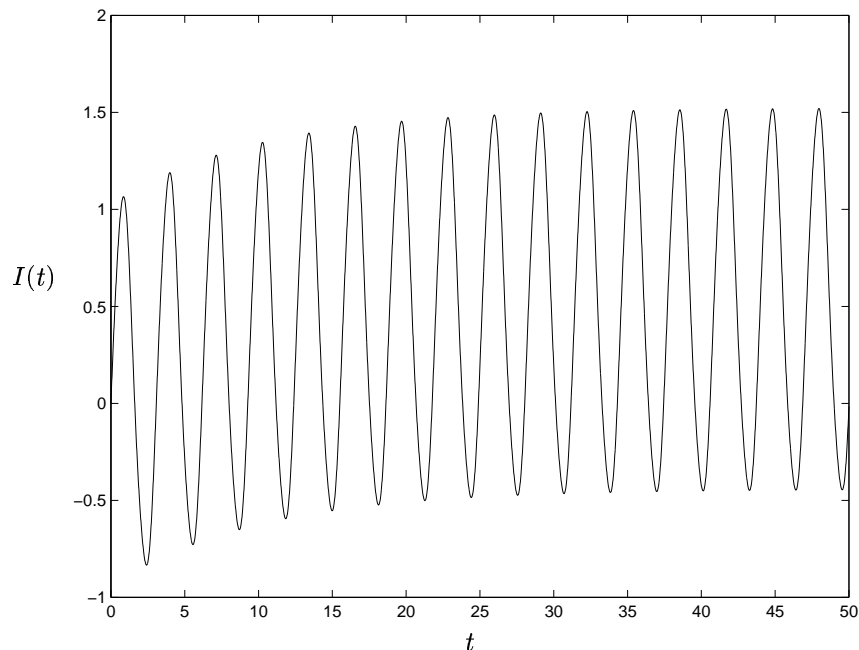


FIG. 2. The input $I(t)$ for the FitzHugh-Nagumo which yields an output $v(t) = \sin^2 t$ for $(a, \gamma, \varepsilon) = (1/3, 1, 1/10)$

model parameters and unknown input currents when only $v(t)$ and its derivatives can be measured. These techniques we describe in the next section.

Before we conclude this section, however, we cast the inverse problem as a control theory problem. In [1], Casti defines a variety of different control problems. One which most closely mimics our system is the “realization-identification” problem. For example, consider the system

$$(3.15) \quad \dot{x} = f(x(t), t) + u(t)g(x(t), t),$$

$$(3.16) \quad y(t) = h(x(t)),$$

where $u(t)$ is an input, $x(t)$ is a state and $y(t)$ is the output. For the “realization-identification” problem associated with this system one tries to find f , g and h so that $y(t)$ is known in terms of $u(t)$. The control problem associated with (1.3)-(1.4) is a minor modification of the realization-identification problem. If we define $g = 1$, $u(t) = (I(t), \vec{0})^T$, $x(t) = (x_1(t), \dots, x_{M+1}(t))^T = (V(t), \vec{w}(t))^T$ and $h(x) = x_1(t)$ our problem is one of finding f given the input and output.

4. Parameter Identification. We now use the formulation of the inverse problem to describe a method for estimating unknown model parameters given that the output potential $v(t)$ and input current $I(t)$ are known. We define two classes of problems:

P A model (1.3)-(1.4) for a given electrophysiological experiment is suspect but that estimates for all but n parameters $\lambda = (\lambda_1, \dots, \lambda_n)$ are known. In the experiment, an input current $I_e(t)$ and measured potential $V_e(t)$ are found for a discrete set of times t_1, t_2, \dots, t_N . The problem is then finding λ so that the model most closely agrees with the measured output V_e .

P* A model (1.3)-(1.4) for a given experiment is suspect but since the stimulus is chemical, $I(t) = 0$. In this case one may still be interested in estimating unknown parameters λ defining the model.

Though these problems may seem different to experimentalists, the correlation technique illustrated here is the same.

From (3.8), we define

$$(4.1) \quad \Lambda^* = \Lambda^*(\lambda, v, I) = \left\| \frac{dv}{dt} - f(v) + \vec{F}(v) \cdot K^{-1}(\vec{I} - \vec{H}) - I \right\|$$

where $\| \cdot \|$ is some norm (perhaps simply absolute value). Then for problem P one might attempt to minimize ²

$$(4.2) \quad \Lambda(V_e, I_e, \lambda) = \sum_{i=0}^N \Lambda^*(\lambda, V_e(t_i), I_e(t_i))$$

in λ . If the agreement were exact, one would have $\Lambda = 0$. For a given model, Λ^* is known but since $V_e(t)$ is only known at discrete times and noise is often present, estimation of the derivatives evaluated at $t = t_k$ is an issue in itself.

Before addressing the issues of derivative estimation and data smoothing, there is a more fundamental theoretical issue of well posedness. In general, Λ will not have a unique minimum. To illustrate this, consider problem P* for which

$$(4.3) \quad \Lambda^*(\lambda, v, I) = \left\| \frac{dv}{dt} - f(v) - \vec{F}(v) \cdot K^{-1} \vec{H} \right\|$$

If $v(t)$ is any solution of the differential equation (3.8), Λ^* will be identically zero. It is often the case that the model equations possess a rich bifurcation structure in parameter space. For some λ , (3.8) may possess stable fixed points while for other λ the model may have stable periodic solutions or other attractors. Thus, a minimization of Λ in λ may limit on a value of λ corresponding to a fixed point where the output $v(t)$ is clearly periodic (and vice-versa). To illustrate this, we note that for the FitzHugh-Nagumo model with $I = 0$ in (3.13),

$$(4.4) \quad \Lambda^* = \left\| \ddot{v} - f'(v)\dot{v} + \varepsilon v + \varepsilon\gamma(\dot{v} - f(v)) \right\| .$$

²For problem P*, the only difference is that $I_e = 0$.

To correlate periodic solutions of this model to data one might introduce phase and scaling variables for time and the potential:

$$(4.5) \quad \tau = \delta_t(t - \phi_t),$$

$$(4.6) \quad u = \delta_v(v - \phi_v),$$

$$(4.7) \quad \lambda = (\delta_t, \delta_v, \phi_t, \phi_v) \in \mathbb{R}^4.$$

Then, with $v = \phi_v + u/\delta_v$, as $\delta_t \rightarrow 0$ and $\delta_v \rightarrow \infty$,

$$(4.8) \quad \begin{aligned} \Lambda^* &= \left\| \frac{\delta_t}{\delta_v} \left(\delta_t \frac{d^2 u}{d\tau^2} + (\varepsilon\gamma - f'(v)) \frac{du}{d\tau} \right) + \varepsilon v - \varepsilon\gamma f(v) \right\| \\ &\rightarrow \varepsilon\gamma \left\| f(\phi_v) - \gamma^{-1}\phi_v \right\| \\ &= 0 \end{aligned}$$

if $v = \phi_v$ is a steady state of the model. In other words, if ϕ_v is a steady state, the parameter search $\lambda \rightarrow (0, \infty, 0, \phi_v)$ will drive Λ to a minimum regardless of what the data is. For this reason, a penalty function \mathcal{P} should be introduced to avoid parameter searches which yield undesirable solutions such as steady states. In general, if $V_\lambda(t)$ is a solution of the model equations for a given parameter value λ , a penalty function $\mathcal{P} = \mathcal{P}(V_e, V_\lambda, \lambda)$ should be introduced and then the functional

$$(4.9) \quad M = M(V_e, I_e, V_\lambda, \lambda) = \Lambda(V_e, I_e, \lambda) + \mathcal{P}(V_e, V_\lambda, \lambda)$$

should be minimized in λ . The penalty function should be chosen so that it is numerically larger at λ for which V_λ is an undesirable solution (such as a steady state) while smaller at other solutions (such as periodic solutions). In the next section we illustrate this procedure using the penalty function which is an approximation of the L^2 norm $\|V_\lambda(t) - V_e(t)\|$ on the time interval $[0, T]$ over which the sampling of the data $V_e(t)$ was measured.

4.1. An Example: Parameter estimation in the SRK model. In this section we demonstrate how to use experimentally measured potential time series to estimate parameters in Sherman-Rinzel-Keizer (SRK) model of β -cell electrical activity (Sherman et al. 1988). The model equations are:

$$(4.10) \quad C_m \frac{dv}{dt} = -I_{Ca-v}(v) - I_K(v, n) - I_{K-Ca}(v, c),$$

$$(4.11) \quad \frac{dn}{dt} = \frac{n_\infty(v) - n}{\tau_n(v)},$$

$$(4.12) \quad \frac{dc}{dt} = f(-\alpha I_{Ca-v}(v) - k_{Ca}c).$$

The dependent variables v , n , and c are the transmembrane potential, the activation variable for the voltage-gated potassium channel, and the intracellular (free) calcium concentration, respectively. Equation (4.10) is a current balance equation

where the terms on the right side represent the transmembrane currents due to voltage-gated calcium channels (I_{Ca-v}), voltage-gated potassium channels (I_K), and calcium-activated potassium channels (I_{K-Ca}). Formulae for these currents and standard parameter values used in [8] are tabulated in Appendix I. The nondimensionalization of this model reveals [7] that the calcium-activated potassium current can be approximated by

$$(4.13) \quad I_{K-Ca} = g_{K-Ca}c = \frac{\bar{g}_{K-Ca}}{K_d}c.$$

We adopt this approximation here and then note that (4.10)-(4.12) is linear in $\vec{w} = (n, c)$ and has the form (1.3)-(1.4). Therefore, by the procedure outlined in section 2, n and c can be eliminated from the equations. The resulting (equivalent) third-order equation for $v(t)$ is derived in Appendix II:

$$(4.14) \quad \Lambda \equiv H_2 \left(v, \frac{dv}{dt}, \frac{d^2v}{dt^2}, \frac{d^3v}{dt^3} \right) + \vec{K}_2 \left(v, \frac{dv}{dt}, \frac{d^2v}{dt^2} \right) \cdot (n^*, c^*)^T = 0.$$

A sample of experimentally measured values for the membrane potential were obtained from David Mears (National Institutes for Health). This data is shown in Figure 3 (top trace). The potential $V_e(t)$ was obtained from a single mouse pancreatic β -cell in an intact islet of Langerhans bathed in a 10mM glucose concentration. The sampling rate for the data was 150Hz which translates to a measured V_e value every $\Delta t = 6.7$ msec. The membrane potential for this experiment (type P^*) is seen to lie roughly in the range of 20-30mV. Superimposed on this figure (bottom trace) is a numerical integration of the SRK model using the “standard” parameter values given in [8]³.

Though the experimental data and theoretical prediction depict bursting oscillations, both are badly out of phase, have different periods and voltage ranges. Since these are the dominant differences we introduce into the model equations scaling and phase parameters λ as defined in (4.5)-(4.6). All other parameters in the model equations were fixed at their original values. To define the measure M in (4.9) we use Λ computed in (4.14) and a penalty function \mathcal{P} equal to the square of the L^2 norm

$$(4.15) \quad \mathcal{P} = \| V_e(t) - V_\lambda(t) \|_{L^2[0,T]}^2 = \int_0^T (V_e(t) - V_\lambda(t))^2 dt,$$

where T was chosen as 30 seconds (4 burst durations in the experimental data). To evaluate Λ using experimental data, we approximated derivatives using a series of smoothing and discrete differentiation procedures.

First, data was smoothed using a sliding window average. Given the sampling times are $t_k, k = 1, 2, \dots, N$ with $\Delta t = t_{k+1} - t_k$ for all k , a smoothed time series $S(V_e) = \{S_k(V_e)\}_{k=1}^{N-p}$ of the data $V_e(t)$ was computed using

$$(4.16) \quad S_k(V_e) = \frac{1}{p} \sum_{i=k}^{i=k+p} V_e(t_i) \simeq \frac{1}{p\Delta t} \int_{k\Delta t}^{(k+p)\Delta t} V_e(t) dt$$

³tabulated in Appendix I

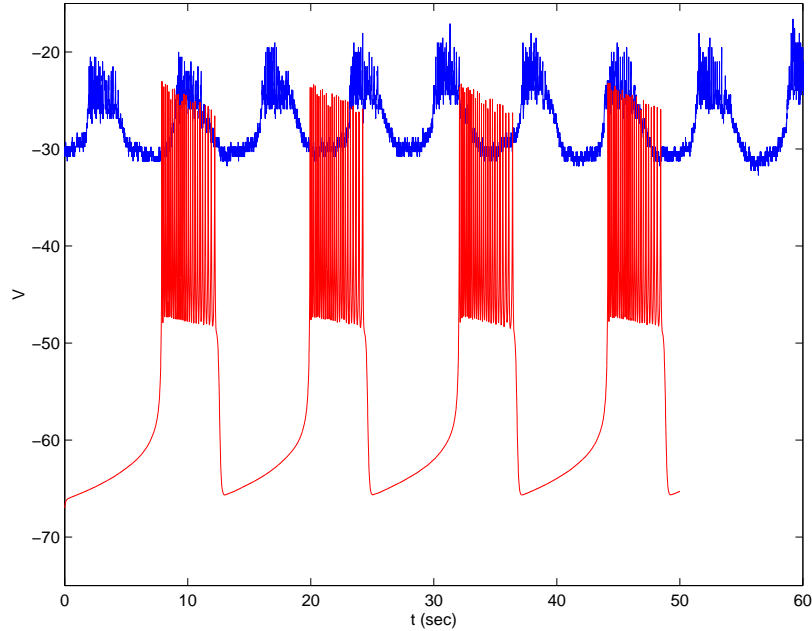


FIG. 3. Membrane potential of a pancreatic β -cell in mV. The top trace shows the membrane potential measured experimentally when the cell was bathed in a 10mM glucose solution. The bottom trace shows a theoretical prediction using the Sherman-Rinzel-Keizer model with parameter values chosen from [8]. For these standard parameter values, theory and experiment differ greatly. The object is to find parameter values for which theory and experiment agree in some measure.

where p is an averaging parameter indicating the width of the window over which the averaging is performed.

A discrete differentiation operation D was used to compute derivatives. For example,

$$(4.17) \quad D(V_e) = \frac{V_e(t_{k+1}) - V_e(t_k)}{\Delta t} \simeq \frac{dV_e}{dt}(t_k).$$

To compute Λ at a given λ , $\frac{dV_e}{dt}$ was approximated by $(DS)(V_e)$, $\frac{d^2V_e}{dt^2}$ by $(DSDS)(V_e)$ and so forth.

Unlike the computations of Λ from the experimental data, the computation of the penalty function requires a (more computational costly) numerical integration of the model equations. However, this computation needs only be performed once when minimizing M with respect to the phase and scaling parameters λ defined in (4.7). After $V_{\lambda_0}(t)$ has been found by numerically integrating the model equations

for $\lambda = \lambda_0 = (1, 1, 0, 0)$, $V_\lambda(t)$ for other λ is easily computed from the relations (4.5)-(4.6) without further integrations. As a result, however, the time grid for $V_\lambda(t)$ in the numerical integration may not match the experimental time grid $\{t_k\}$ making it necessary to interpolate (via cubic splines) $V_\lambda(t)$ values at $t = t_k$ so that the penalty function defined above may be approximated via

$$(4.18) \quad \mathcal{P} = \|V_e(t) - V_\lambda(t)\|_{L^2[0,T]}^2 \simeq \sum_k (V_e(t_k) - V_\lambda(t_k))^2 \Delta t.$$

A sliding window “width” of $p = 40$ was used to compute the measure $M(\lambda)$ from the data and a numerical integration of the SRK model. The functional $M(\lambda)$ was then minimized using the Nelder-Mead simplex algorithm ([3, 6]) using the initial value $\lambda = (1, 1, 0, 0)$. After several iterations, the algorithm yielded the parameter values $\lambda = \lambda_m = (\delta_t, \delta_v, \phi_t, \phi_v) = (1.72, 2.94, -2.7, -9.32)$. In Figure 4, the experimental data $V_e(t)$ is plotted against the scaled and phased theoretical prediction $V_{\lambda_m}(t)$. It is apparent that this choice of λ has significantly improved the correlation of phase and scaling (compared to Figure 3).

5. Discussion. As has already been demonstrated, a large class of excitable cell models are controllable in the sense that there exists an input $I(t)$ which illicitly any (smooth) response $v(t)$. This does not mean that these models are simultaneously controllable in the other dependent variables \vec{w} . Nevertheless, the implications are still broad and interesting. For example, the predicted controllability in the FitzHugh-Nagumo model implies that there is an input $I(t)$ such that $v(t)$ equals the first component of the Lorenz attractor. It is therefore not a surprise that forced excitable cell models exhibit such a rich variety of behaviors. At this early stage, it is not clear how (or if) the invertibility of these models can be used as a tool to examine these behaviors.

From the results in section 4, however, it is evident that the inversion can be used for parameter estimation purposes. What is most relevant in the procedure described and demonstrated there is that $\vec{w}(t)$ need not be measured experimentally to obtain parameter estimates. It is very probable that there are several improvements which can be made in the procedure implemented on the SRK model. There are many ways to de-noise data, minimize functionals and make derivative estimates from data. All of these play a role and the crude approach taken on the SRK model was primarily demonstrative. A future goal for work in this area will be find an integral formulation for Λ so that derivate estimates can be avoided. Lastly, although de-noising will always be an issue, it may be less so in neuronal systems since electrical measurements on neurons tend to be cleaner than those made on endocrine cells.

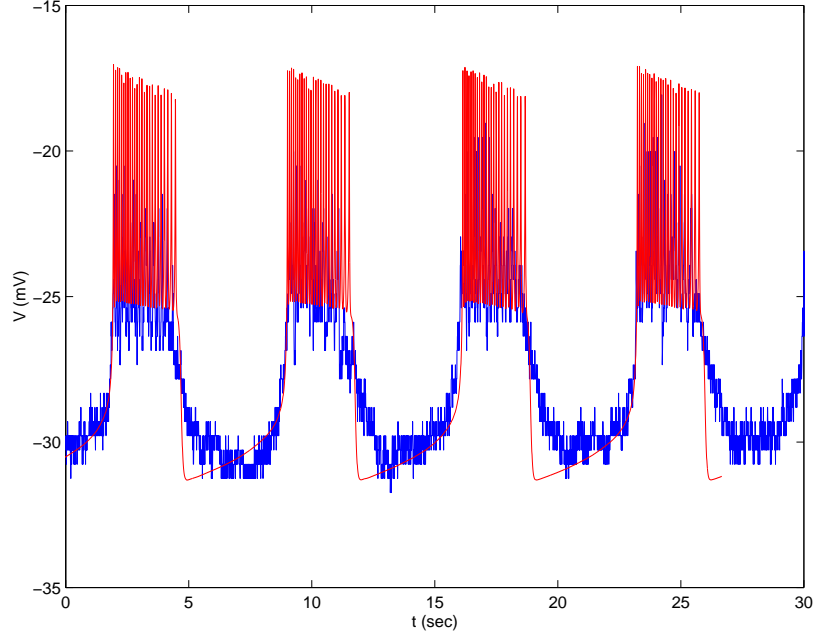


FIG. 4. Comparison of experimental data and SRK model prediction for different model parameters. The scaling and phase parameters used to make the theoretical prediction agree better with the experimental trace when $\lambda = (\delta_t, \delta_v, \phi_t, \phi_v) = (1.72, 2.94, -2.7, -9.32)$. This choice was determined using the algorithm described in the text.

6. Appendix I. I: SRK function definitions

$$(6.1) \quad I_{Ca-v}(v) = \bar{g}_{Ca} m_{\infty}(v) h_{\infty}(v) (v - v_{Ca})$$

$$(6.2) \quad I_K(v, n) = \bar{g}_K n (v - v_K)$$

$$(6.3) \quad I_{K-Ca}(v, c) = \bar{g}_{K-Ca} \frac{c}{K_d + c} (v - v_K)$$

$$(6.4) \quad m_{\infty}(v) = \frac{1}{1 + \exp[(v_m - v)/S_m]}$$

$$(6.5) \quad h_{\infty}(v) = \frac{1}{1 + \exp[(v - v_h)/S_h]}$$

$$(6.6) \quad n_{\infty}(v) = \frac{1}{1 + \exp[(v_n - v)/S_n]}$$

$$(6.7) \quad \tau_n(v) = \frac{\bar{\tau}_n}{\exp[(v - v_b)/S_a] + \exp[-(v - v_b)/S_b]}$$

Standard parameter values in SRK model:

Parameter	(units)	SRK value
v_{Ca}	(mV)	110
v_K	(mV)	-75
\bar{g}_{Ca}	(pS)	1400
\bar{g}_K	(pS)	2500
\bar{g}_{K-Ca}	(pS)	30000
V_{Cell}	(μm^3)	1150
C_m	(fF)	5310
K_d	(μM)	100
k_{Ca}	(ms^{-1})	.03
α	(mole coul $^{-1}(\mu m^3)^{-1}$)	4.5062×10^{-6}
f		.001
v_b	(mV)	-75
v_h	(mV)	-10
v_m	(mV)	4
v_n	(mV)	-15
S_a	(mV)	65
S_b	(mV)	20
S_h	(mV)	10
S_m	(mV)	14
S_n	(mV)	5.6
$\bar{\tau}_n$	(ms)	37.5

In the SRK model, the parameter $\alpha = 1/(2V_{Cell}F)$ where F is Faraday's constant.

7. Appendix II. Elimination of (n, c) from SRK Model

In this section we reduce the modified SRK model equations to a single third order differential equation in $v(t)$. For simplicity, set $F(v) = I_{Ca-V}(v)$. The potential equation

$$(7.1) \quad C_m \frac{dv}{dt} = -F(v) - g_K n(v - v_K) - g_{KCa} c(v - v_K)$$

is equivalent to

$$(7.2) \quad H_0 \left(v, \frac{dv}{dt} \right) + \vec{K}_0(v) \cdot \vec{w} = 0$$

where $\vec{w} = (n, c)$, $\vec{K}_0 = (K_{01}, K_{02})^T$ and

$$(7.3) \quad H_0 = C_m \frac{dv}{dt} + F(v)$$

$$(7.4) \quad \vec{K}_0 = (g_K(v - v_K), g_{KCa}(v - v_K))$$

Using the procedure discussed in section 2 with $I = 0$,

$$(7.5) \quad H_1 \left(v, \frac{dv}{dt}, \frac{d^2v}{dt^2} \right) + \vec{K}_1 \left(v, \frac{dv}{dt} \right) \cdot \vec{w} = 0$$

where $\vec{K}_1 = (K_{11}, K_{12})^T$ and

$$(7.6) \quad H_1 = C_m \frac{d^2v}{dt^2} + F' \frac{dv}{dt} + \frac{g_K n_\infty}{\tau_n} (v - v_K) - f \alpha g_{K-Ca} F (v - v_K)$$

$$(7.7) \quad \vec{K}_1 = \left(g_K \frac{dv}{dt} - \frac{g_K}{\tau_n} (v - v_K), g_{K-Ca} \frac{dv}{dt} - f g_{K-Ca} k_{Ca} (v - v_K) \right)$$

To find H_2 and $\vec{K}_2 = (K_{21}, K_{22})^T$ in

$$(7.8) \quad H_2 \left(v, \frac{dv}{dt}, \frac{d^2v}{dt^2}, \frac{d^3v}{dt^3} \right) + \vec{K}_2 \left(v, \frac{dv}{dt}, \frac{d^2v}{dt^2} \right) \cdot \vec{w} = 0$$

differentiate (7.5) in t :

$$(7.9) \quad \frac{dH_1}{dt} + \frac{d\vec{K}_1}{dt} \cdot \vec{w} + \vec{K}_1 \cdot \left(\frac{n_\infty - n}{\tau_n}, f(-\alpha F - k_{Ca}c) \right)$$

Thus,

$$(7.10) \quad H_2 = \frac{dH_1}{dt} + \frac{K_{11}n_\infty}{\tau_n} - K_{12}f\alpha F$$

$$(7.11) \quad \vec{K}_2 = \frac{d\vec{K}_1}{dt} - \left(\frac{K_{11}}{\tau_n}, K_{12}fk_{Ca} \right)$$

where

$$(7.12) \quad \frac{dH_1}{dt} = C_m \frac{d^3v}{dt^3} + F' \frac{d^2v}{dt^2} + F''(v) \left(\frac{dv}{dt} \right)^2$$

$$(7.13) \quad -f\alpha g_{K-Ca} F'(v)(v - v_K) \frac{dv}{dt} - f\alpha g_{K-Ca} F \frac{dv}{dt}$$

$$(7.14) \quad \left(\frac{g_K n'_\infty}{\tau_n} (v - v_K) - \frac{g_K n_\infty}{\tau_n^2} \tau'_n (v - v_K) + \frac{g_K n_\infty}{\tau_n} \right) \frac{dv}{dt}$$

and

$$(7.15) \quad \frac{d\vec{K}_1}{dt} = \begin{pmatrix} g_K \frac{d^2v}{dt^2} + \left[\frac{g_K}{\tau_n} \tau'_n (v - v_K) - \frac{g_K}{\tau_n} \right] \frac{dv}{dt} \\ g_{K-Ca} \frac{d^2v}{dt^2} - f g_{K-Ca} k_{Ca} \frac{dv}{dt} \end{pmatrix}$$

Next, solve for $(n, c)^T$ using (7.2),(7.5) to find

$$(7.16) \quad n = n^* = \frac{K_{02}H_1 - K_{12}H_0}{\det K}$$

$$(7.17) \quad c = c^* = \frac{K_{11}H_0 - K_{01}H_1}{\det K}$$

where

$$(7.18) \quad \det K = K_{01}K_{12} - K_{02}K_{11}$$

Substituting these into (7.8), one obtains a single third order equation for $v(t)$:

$$(7.19) \quad \Lambda \equiv H_2 \left(v, \frac{dv}{dt}, \frac{d^2v}{dt^2}, \frac{d^3v}{dt^3} \right) + \vec{K}_2 \left(v, \frac{dv}{dt}, \frac{d^2v}{dt^2} \right) \cdot (n^*, c^*)^T = 0$$

8. Acknowledgment. I would like to express my deep regret and sadness at recent passings of Teresa Chay and Joel Keizer. Their influence on my work has been immense. Indeed, even in this manuscript Joel Keizer's influence can be noted in the references.

Also, I would like to thank David Mears at the National Institutes for Health for sharing his data on pancreatic beta-cells so that I could complete the last section of this paper.

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