Computation of Reduced Energy Input Current Stimuli for Neuron Phase Models

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Abstract—*A regularly spiking neuron can be studied using a phase model. The effect of an input stimulus current on the phase time derivative is captured by a phase response curve. This paper adapts a technique that was previously applied to conductance-based models to discover optimal input stimulus currents for phase models. First, the neuron phase response $\theta(t)$ due to an input stimulus current $i(t)$ is computed using a phase model. The resulting $\theta(t)$ is taken to be a reference phase $r(t)$. Second, an optimal input stimulus current $i^*(t)$ is computed to minimize a weighted sum of the square-integral 'energy' of $i^*(t)$ and the tracking error between the reference phase $r(t)$ and the phase response due to $i^*(t)$. The balance between the conflicting requirements of energy and tracking error minimization is controlled by a single parameter. The generated optimal current $i^*(t)$ is then compared to the input current $i(t)$ which was used to generate the reference phase $r(t)$. This technique was applied to two neuron phase models; in each case, the current $i^*(t)$ generates a phase response similar to the reference phase $r(t)$, and the optimal current $i^*(t)$ has a lower 'energy' than the square-integral of $i(t)$. For constant $i(t)$, the optimal current $i^*(t)$ need not be constant in time. In fact, $i^*(t)$ is large (possibly even larger than $i(t)$) for regions where the phase response curve indicates a stronger sensitivity to the input stimulus current, and smaller in regions of reduced sensitivity.*

I. INTRODUCTION

Optimal control theory provides powerful tools for finding efficient inputs that move a system output to a desired state [1]. The definition of an efficient input is determined by a user selected cost function that measures input resource usage. Optimization techniques have been applied to biological systems [2], including control of circadian rhythms [3]. Optimization techniques have also been used in neuroscience. Of particular interest here is [4], where optimization techniques are used to calculate input stimulus currents with minimized square-integral that output spikes in neuron phase models at a particular time. A subsequent work considered the controllability of the time between spikes for constrained stimuli [5]. Optimal control techniques have been successfully applied in an experimental setting to find optimal currents to control spike timing in a biological neuron [6].

The work described in this paper grew out of applying optimal control to conductance-based neuron models, such as the reduced second-order model employed by [7] as studied in [8]. The input to this neuron model is an input stimulus current $i(t)$ and the output is the neuron membrane voltage $v(t)$. For a range of current waveforms $i(t)$ the neuron output $v(t)$ was computed; the resulting $v(t)$ was considered to be a reference waveform $r(t)$. The goal of this "reduced energy input stimulus discovery method" [8, pg. 186] was to find optimal currents $i^*(t)$ that produced a neuron membrane voltage $v^*(t)$ that closely matched $r(t)$. This was accomplished by minimizing a cost function that penalized 1) the square-integral 'energy' of the input stimulus current; and 2) the error between $v^*(t)$ and $r(t)$. One notable feature of this approach is that the balance between input energy and output tracking can be varied. Better tracking between $v^*(t)$ and $r(t)$ was obtained at the expense of an increased input stimulus current energy. The results showed that significantly reduced energy input stimulus currents can provide accurate tracking of the reference waveform. This optimal control method can be applied to more complex higher dimensional conductance-based models [9]. Results of these studies were intuitively pleasing in that one might expect that a reduced energy input should be able to produce a similar response as a higher energy current in these models - once a trap is sprung, there is no need to further press the trigger. Potential applications of this method include finding reduced energy currents in electrophysiology experiments. Selecting the neuron model parameters for optimization rather than the input stimulus current might lead to more accurate models. Modification of the cost function to penalize the integral of $v(t)*i(t)$ ('real' energy) could facilitate investigation of neuron model energy efficiency in producing a desired output along the lines of [10].

The utility of the "reduced energy input stimulus discovery method" [8, pg. 186] in studying conductance-based models led the authors to apply this approach to the *neuron phase model* as pioneered by Winfree [11], [12]. While conductance-based models aspire to capture the underlying ion channel mechanisms of neuron function, a phase model is focused on higher level behavior, facilitating studies of large neuronal networks, where timing of neuron spikes is of primary interest; see [4], [12], [13] and references therein.

Specifically, this paper considers the phase model

$$\frac{d\theta}{dt} = f(\theta) + Z(\theta)i(t) \qquad (1)$$

where $\theta \in [0, 2\pi]$ is the phase of the neuron, $f(\theta)$ is the neuron "baseline dynamics" [4, pg. 358], $i(t)$ is the input stimulus current, and $Z(\theta)$ specifies a phase response curve (PRC) which mediates the effect of $i(T)$ on the neuron phase.

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The neuron fires a spike at $\theta = 0$. Simple constraints on $f(\theta)$ and $Z(\theta)$ insure that the neuron phase subsequently advances from $\theta = 0$ to $\theta = 2\pi$, at which time another spike is generated, and θ is reset to 0 [4]. Thus the model input is the stimulus current $i(t)$ and the output is the neuron phase $\theta(t)$.

Following the general approach of [8], [9], currents $i(t)$ are input to a model and the resulting phase responses $\theta(t)$ are computed. Optimal control is then used to find optimal currents $i^*(t)$ that provide varying degrees of tracking accuracy between the reference phase $r(t) = \theta(t)$ and $\theta^*(t)$ based on a varying balance between the energy of $i^*(t)$ and the tracking error. It should be expected that optimized currents will tend to have 1) larger amplitudes in regions where the PRC indicates a higher sensitivity of the phase to the input stimulus current and 2) smaller amplitudes in regions of lower sensitivity. The utility of regions with differing levels of sensitivity when computing optimal currents was noted in [6].

Section II describes a cost function tailored to incorporate both the energy of the input stimulus current and the tracking error between the actual and reference neuron phase. The results shown in Section III demonstrate that the "reduced energy input stimulus discovery method" [8, pg. 186] can be adapted to provide a range of phase tracking performance in two neuron phase models. The models considered in this paper are the Sinusoidal PRC (Section III-A) and the SNIPER PRC (Section III-B). Section IV summarizes the paper findings.

II. METHOD

This section adapts the approach to finding optimal currents in conductance-based neuron models described in [8], [9] for use with neuron phase models. As previously described, phase models provide a macromodel of neuron function that is particularly useful in studying large neuronal networks.

A. Cost Function

The goal is to discover an optimal input stimulus current $i^*(t)$ that provides a specified balance between the energy of $i^*(t)$ and the difference between a neuron reference phase $r(t)$ and the actual neuron phase $\theta(t)$ over the time interval $[0, T]$, where T is the smallest t such that $\theta(T) = 2\pi$. This balance is achieved through minimization of a cost function

$$J[i(t)] = \frac{\alpha}{2} \int_0^T [i(t)]^2 dt + \frac{1-\alpha}{2} \int_0^T [r(t) - \theta(t)]^2 dt \quad (2)$$

where the weight coefficient $\alpha \in (0, 1]$ specifies a balance between input stimulus current energy and the tracking error between $r(t)$ and $\theta(t)$. To emphasize minimization of input energy at the expense of the tracking error, a large α is selected. To emphasize reduction of the tracking error at the expense of input stimulus current energy, a small α is selected. To find an optimal input stimulus current $i^*(t)$ which minimizes J (2), the "Continuous Nonlinear Optimal

Controller with Function of Final State Fixed" method [1, pg. 134] is used. The Hamiltonian generated from (2) is

$$H(i(t), \theta(t), \lambda(t)) = \frac{\alpha}{2} [i(t)]^2 + \frac{1-\alpha}{2} [r(t) - \theta(t)]^2 + \lambda [f(\theta) + Z(\theta)i(t)] \quad (3)$$

and thus

$$\frac{d\theta}{dt} = \frac{\partial H}{\partial \lambda} = f(\theta) + Z(\theta)i(t) \quad (4)$$

$$\frac{d\lambda}{dt} = -\frac{\partial H}{\partial \theta} = (1-\alpha)(r(t) - \theta(t)) - \lambda(f'(\theta(t)) + i(t)Z'(\theta)) \quad (5)$$

$$\frac{\partial H}{\partial i} = \alpha i(t) + \lambda Z(\theta). \quad (6)$$

The stationarity condition requires that $\frac{\partial H}{\partial i} = 0$ enabling $i(t)$ to be found using the substitution

$$i(t) = -\frac{\lambda(t)Z[\theta(t)]}{\alpha} \quad (7)$$

yielding the boundary value problem (BVP)

$$\frac{d\theta}{dt} = f(\theta) - \frac{\lambda Z(\theta)^2}{\alpha} \quad (8)$$

$$\frac{d\lambda}{dt} = (1-\alpha)(r(t) - \theta(t)) - \lambda \left(f'(\theta(t)) - \frac{\lambda Z(\theta)Z'(\theta)}{\alpha} \right) \quad (9)$$

with boundary conditions

$$\theta(0) = 0 \quad (10)$$

$$\lambda(T) = 0. \quad (11)$$

Boundary condition (11) specifies a free final state [1]. Note that the final time T is fixed. Solving the BVP (8)-(11) yields $\lambda^*(t)$. Substituting the resulting $\lambda^*(t)$ into (7) provides an optimal input stimulus current $i^*(t)$ that minimizes the cost function $J[i(t)]$ for the selected α. The neuron state resulting from substituting $i^*(t)$ into (4) and solving the differential equation is referred to as $\theta^*(t)$.

To summarize, generating an optimal solution is divided into two processes. In the first process, a stimulus current $i(t)$ is used as the input in a neuron phase model (1), yielding the output phase $\theta(t)$. The reference phase, $r(t)$, is then equated to the previously calculated $\theta(t)$. The second and final process requires numerically solving the BVP (8)-(11) for $\lambda^*(t)$ that in turn yields the optimal input stimulus current $i^*(t)$. This can be done for various values of α, placing greater emphasis on either the input stimulus current energy or the tracking error between $r(t)$ and $\theta^*(t)$. As a check, using $i^*(t)$ as the input current stimulus $i(t)$ in the original model (1) must yield $\theta^*(t)$. Fig. 1 illustrates the solution process. MATLAB$^{\text{TM}}$ was used to obtain these solutions.

III. RESULTS

This section presents results of applying the previously described method for two phase models studied in [4]: the Sinusoidal PRC Phase Model and the SNIPER PRC Phase Model.
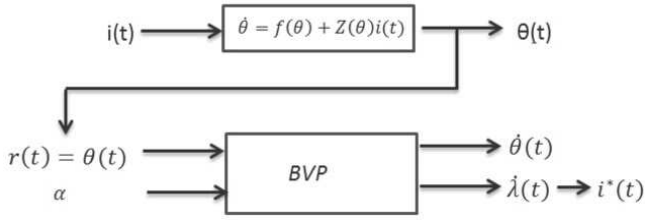
Fig. 1. Input Stimulus Current Optimization Process

A. Sinusoidal PRC

Setting $f(\theta) = \omega = 2$ and $Z(\theta) = \sin(\theta)$ in the phase model (1) yields [4]

$$\frac{d\theta}{dt} = f(\theta) + Z(\theta)i(t) = 2 + \sin(\theta)i(t). \qquad (12)$$

This phase model generates a spike at $T \approx 3.6292$s for $i(t) = 1$, where $\theta(T) = 2\pi$. Finding an optimal input stimulus current $i^*(t)$ that minimizes (2) proceeds as follows. An input stimulus current $i(t)$ is used in the phase model (12) to produce $\theta(t)$. The reference phase r(t) is set equal to $\theta(t)$, an α is selected, and $i^*(t)$ is found by minimizing (2). The optimal input stimulus current $i^*(t)$ produces $\theta^*(t)$. Fig. 2 shows $i(t)$ and $i^*(t)$ in the top row and $\theta(t)$ and $\theta^*(t)$ in the bottom row. Note that even though $i^*(t)$ has peaks that exceed $i(t)$, all discovered $i^*(t)$ have reduced energy as compared to $i(t)$. As α is decreased, the energy of the optimal current $i^*(t)$ increases, while the tracking error between $\theta(t)$ and $\theta^*(t)$ improves. With larger α, the current $i^*(t)$ has lower energy and $\theta^*(t)$ does not track $\theta(t)$ well. Fig. 3 plots the input stimulus current $i(t)$ and the optimal input stimulus current $i^*(t)$ against the neuron phase state $\theta(t)$. $Z(\theta)$ is also shown. Dips in the magnitude of $i^*(t)$ correspond to values of $\theta(t)$ for which $Z(\theta)$ is close to 0, i.e. to those values of $\theta(t)$ for which the phase model is least responsive to the current input stimulus.

B. Sniper PRC

Setting $f(\theta) = \omega = 2$ and $Z(\theta) = 1 - \cos(\theta)$ in the phase model (1) yields [4]

$$\frac{d\theta}{dt} = 2 + (1 - \cos(\theta))i(t). \qquad (13)$$

This phase model spikes at $T \approx 2.2224$s for $i(t) = 1$, where $\theta(T) = 2\pi$. Fig. 2 shows that a smaller α again produces close tracking between $r(t) = \theta(t)$ and $\theta^*(t)$. Fig. 3 shows that the optimal input stimulus current $i^*(t)$ moves to a higher magnitude when $Z(\theta)$ has a large magnitude and conversely a lower magnitude value of $i^*(t)$ is obtained when $Z(\theta)$ has a lower magnitude.

IV. CONCLUSIONS

The "reduced energy input stimulus discovery method" [8, pg. 186] previously developed for conductance-based neuron models has been adapted for use in two neuron phase models studied in [4]. This technique finds optimal input current stimuli $i^*(t)$ that result in tracking a reference phase

originally produced with an input stimulus current $i(t)$ having a larger square-integral 'energy'. The method is just as effective with phase models as with conductance-based models [8], [9]. Furthermore, this paper provides significant insight into the differences between $i(t)$ and $i^*(t)$, owing to the prominence of the phase response curve role in neuron dynamics, as described next.

The phase response curve for each considered case can be used to understand differences between the original input stimulus current $i(t)$ and the optimal input stimulus current $i^*(t)$. When the input and optimal currents are plotted against the neuron phase $\theta(t)$ and compared to the phase response curve as in Fig. 3, it is evident that the optimal stimulus current energy is 1) primarily applied where the phase response curve of the particular phase model is most sensitive; and 2) reduced where the phase response curve has reduced sensitivity. As α is decreased, the tracking between $r(t) = \theta(t)$ and $i^*(t)$ is improved, at the expense of an increase in the energy of $i^*(t)$, indicated by a broadening of the area of the optimal input stimulus current $i^*(t)$.

In this paper the output of a phase model $\theta(t)$ was used as the reference signal $r(t)$; however, it may be possible to use other functions for the reference signal $r(t)$ that span $[0, 2\pi]$. This may be useful in an experimental setting, in which a desired reference signal may obtained from a from measurements of a physical cell.

Future studies may incorporate the addition of noise to mimic other environmental factors that may affect neural phase measurements. This application of optimal control may not only be valuable in the calculation of optimal input currents in neural phase models, but in other types of phase models as well. It might be useful in the calculation of optimal input currents for dynamic clamp phase models [14]. This work may provide a framework with which to study controllability of neuron phase models, that is, the extent to which the model neuron can be forced by correct choice of input to produce a desired $\theta(t)$, in a manner similar to [13], [5].

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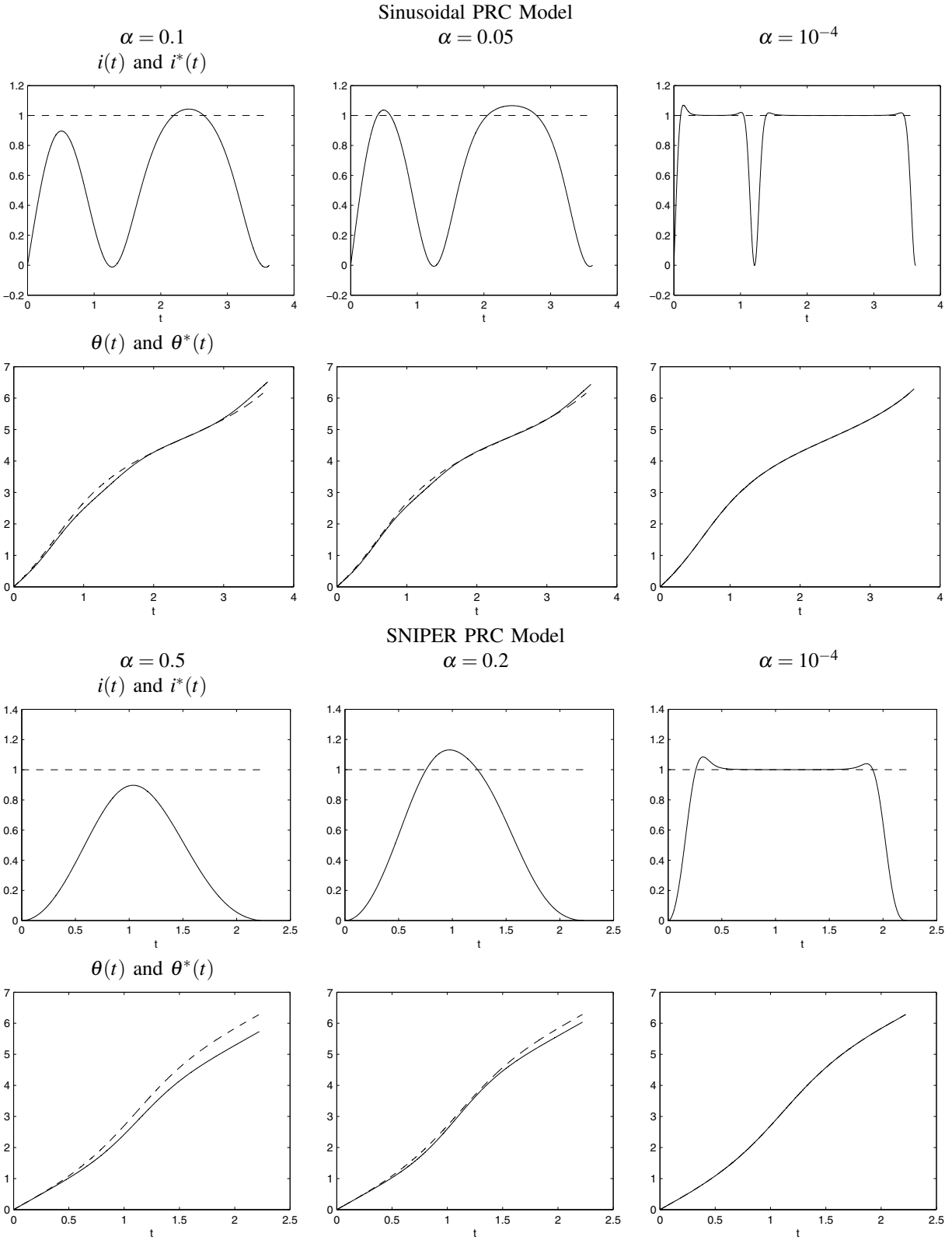
Fig. 2. Results for the Sinusoidal PRC Model with $\alpha = \{0.1, 0.05, 10^{-4}\}$ and $T = 3.6292$s and the SNIPER PRC Model with $\alpha = \{0.5, 0.2, 10^{-4}\}$ and $T = 2.2224$s. In each case the constant $i(t)$ (dashed) produces the reference phase $r(t) = \theta(t)$ (dashed). The computed optimal input stimulus current $i^*(t)$ (solid) results in $\theta^*(t)$ (solid). As α is decreased, the tracking between $r(t) = \theta(t)$ and $\theta^*(t)$ is improved at the expense of an increase in the energy of $i^*(t)$.

Phase Plots
$Z(\theta)$, $i(t)$, $i^*(t)$ vs. $\theta(t)$

Sinusoidal PRC Model
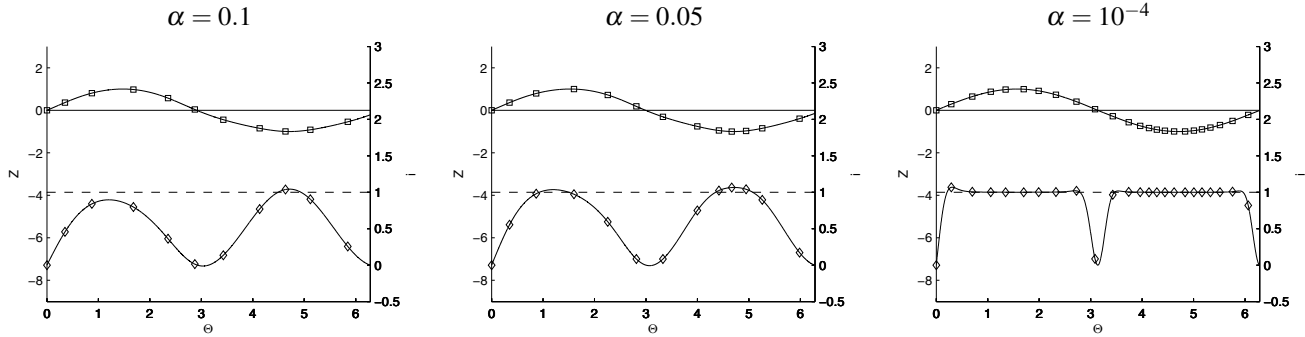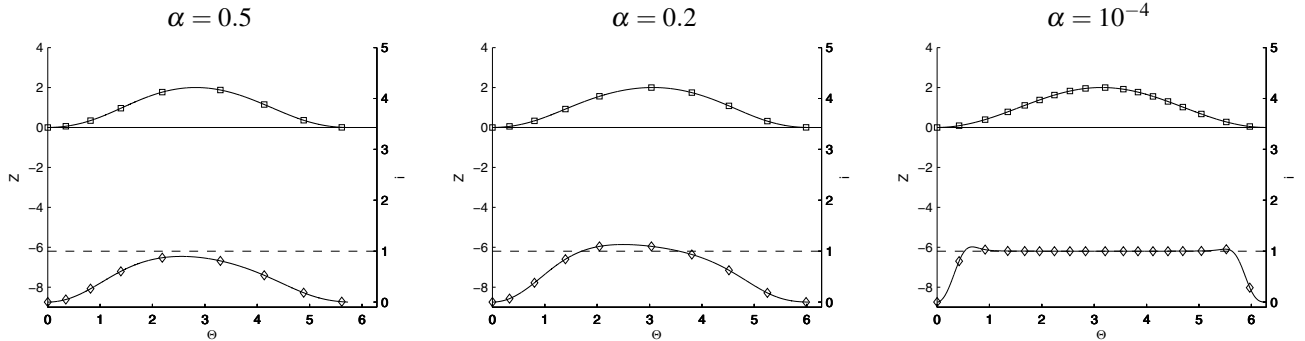

SNIPER PRC Model

Fig. 3. Input stimulus current $i(t)$ (dashed curve), optimal input stimulus current $i^*(t)$ (solid $\Diamond$ curve, bottom), and $Z(\theta)$ (solid $\Box$ curve, top) plotted against the neuron phase state $\theta(t)$ for the two considered models. The left y-axis is the scale for $Z(\theta)$ while the right y-axis is the scale for the stimulus currents. The magnitude of the optimal input stimulus current $i^*(t)$ is reduced as compared to the original current $i(t)$ in regions where the magnitude of $Z(\theta)$ is close or equal to zero.

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