Phase reduction and phase-based optimal control for biological systems

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1 Introduction

The purpose of this report is to present the work that has been done in the field of optimal control for biological systems, specifically in the context of the thalamocortical neuron model. This work was inspired by the paper "Phase reduction and phase-based optimal control for biological systems: a tutorial,"[1] and aimed to reproduce the results using MATLAB while also adding new insights, strategies, and improvements as original contributions. This report will provide a detailed technical account of the mathematical formulation and the main results obtained from this study.

2 Model overview and objectives

In this section, we present a model for the thalamocortical neuron that is based on the work described in [1]. While the specific details of parameter choice are described in the original article, we provide a brief overview of the model and its key features.

The thalamocortical neuron model is a dynamical system that exhibits periodic behavior with a limit cycle. In this model, the limit cycle represents the neuron's spiking behavior.

$$\dot{v} = \frac{-I_L(v) - I_{\mathrm{Na}}(v,h) - I_K(v,h) - I_T(v,r) + I_{\mathrm{b}}}{C_m} + u(t), \tag{1}$$

$$\dot{h} = \frac{h_\infty(v) - h}{\tau_h(v)}, \tag{2}$$

$$\dot{r} = \frac{r_\infty(v) - r}{\tau_r(v)} \tag{3}$$

In these equations, I_b is the baseline current, v is the transmembrane voltage, and h, r are the gating variables of the neuron which describe the modulation of the flow of ions across the neural membrane. $u(t)$ represents the applied current as the control input. It is project we will consider control problems for which the control input only directly affects a single state variable.

The objective of the project is to change the periodicity of the neuron model by using optimal control theory. Specifically, the aim is to increase the period of the model, which means that the neuron will spike slower than the original one. This can be achieved by designing a control input that affects the dynamics of the system and changes its behavior in a desired way. The optimal control approach seeks to find the input that minimizes a cost function that captures the desired behavior of the system. With no control input, these parameters give a stable periodic orbit with period $T = 8.3955$ ms.

Since we know that a limit cycle is a periodic orbit which is isolated, we can apply the phase reduction method in order to simplify the optimal control theory problem. Phase-reduced models have lower dimension than the full models from which they came, thus optimal control problems for phase-reduced models give lower-dimensional boundary value problems and thus are simpler to solve. Notice that we are now dealing with a neuron model, however the methodology that is going to be presented could be applied to all nonlinear oscillators with stable periodic orbits, which arise in many systems of physical, technological, and biological interest.

3 Phase reduction

Phase reduction is a powerful technique used to simplify the analysis of nonlinear oscillators with stable periodic orbits. Isochrones and phase response curves (PRCs) are key concepts in phase reduction.

On the one hand, isochrones are a useful tool in the analysis of phase oscillators and their synchronization properties.

An isochron of a dynamical system is a set of initial conditions, or curve in the phase space, resulting in oscillations having the same phase. By projecting the dynamics onto the isochrones, the problem can be reduced to a one-dimensional problem, greatly reducing the computational complexity. For spiking models, the phase of the system can be determined by setting a threshold in the voltage profile.

On the other hand, PRCs measure how the phase of a system changes in response to a perturbation. They characterize the response of an oscillator to a small input pulse at different phases. The PRC can be obtained through various methods, with the sweeping phase method being a common one. In this method, the oscillator is subjected to a series of perturbations at different phases within the same periodic interval, and the resulting phase shifts are recorded.

Let us start with the mathematical formulation of these: Letting $\mathbf{x} = (x_1, x_2, \ldots, x_n)$, by definition

$$\left.\frac{\partial \theta}{\partial x_i}\right|_{\tilde{\mathbf{x}}^\gamma} = \lim_{\Delta x_i \to 0} \frac{\Delta \theta}{\Delta x_i}, \quad i = 1, \ldots, n \tag{4}$$

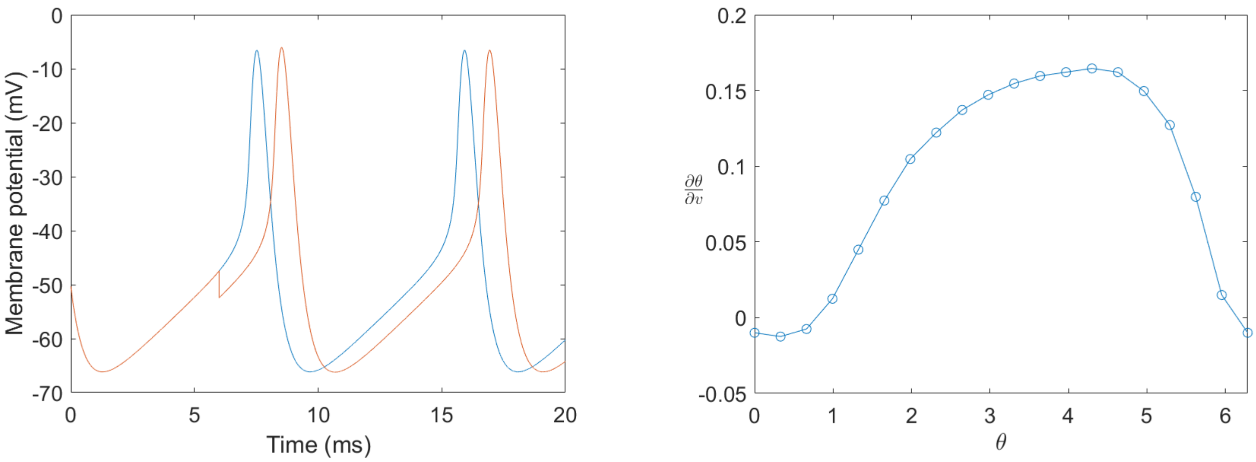
where $\Delta\theta = \theta\left(\tilde{\mathbf{x}}^\gamma + \Delta x_i \hat{i}\right) - \theta\left(\tilde{\mathbf{x}}^\gamma\right)$ is the change in $\theta(\mathbf{x})$ resulting from the perturbation $\tilde{\mathbf{x}}^\gamma \to \tilde{\mathbf{x}}^\gamma + \Delta x_i \hat{i}$ from the base point $\tilde{\mathbf{x}}^\gamma$ on the periodic orbit in the direction of the i th coordinate. Since $\dot{\theta} = 2\pi/T = w$ everywhere in the neighborhood of $\mathbf{x}^\gamma$, where the dot indicates $\frac{d}{dt}$, the difference $\Delta\theta$ is preserved under the flow; thus, it may be measured in the limit as $t \to \infty$, when the perturbed trajectory has (in fact asymptotically) collapsed back to the periodic orbit. That is, $\left.\frac{\partial \theta}{\partial x_i}\right|_{\mathbf{x}^\gamma}$ can be found by comparing the phases of solutions in the infinite-time limit with initial conditions on and infinitesimally shifted from base points on γ.

In practice, we are only interested in the first component of the PRC, that is $\frac{\partial \theta}{\partial v}\mid_{\tilde{\mathbf{x}}^\gamma}$, since the control will only be acting on v. The mathematical intuition behind this will be explain afterwards.

Thus, in order to obtain the first component of the PRC at each value of the phase θ we compute this phase shifts by comparing the perturbed and the unperturbed phase for very long times of simulation. In order to integrate the system a RK4 was manually implemented using $dt = 10^{-3}$ and $t_{end} = 500$. In our case, we disturb the system between the first and second spike. Also it was ensured from pre-selected initial conditions, that the system was really close to the limit cycle. The perturbations are made, one at each simulation, at different phases of the solution.

Small perturbations (that do not cause the system to leave the regime of interest) of $\Delta v = -0.3mV$ were made at 20 points spread along the periodic orbit. Since $\Delta\theta$ has time units and is dependent on the amplitude of the perturbation the following normalization needs to be applied:

$$PRC_1 = \frac{\Delta\theta}{T|\Delta v|} 2\pi \tag{5}$$



(a) Default dynamics of the dynamical system in the limit cycle (blue). Effects of a perturbation $\Delta v = -5mV$ in the trajectory (orange).

(b) PRC or sensitivity curve.

Figure 1

In order to carry on, we consider the standard phase reduction for the oscillator given by

$$\frac{\mathrm{d}\theta}{\mathrm{d}t} = \omega + Z(\theta)u(t) \tag{6}$$

where ω is the oscillator's natural angular frequency, $Z(\theta)$ is the component of the phase response curve in the $x_1(v)$ direction, and $u(t)$ is the control stimulus. We take $Z(\theta)$ to be an interpolated version of the PRC using cubic splines in a fine grid will be used in order to be more precise without compromising computational power.

If we consider the product $Z(\theta)u(t)$ as a scalar product we realise that since $\mathbf{u(t)} = [u(t), 0, 0]$ it only made sense to compute the first component of the PRC, since the others would be multiplied by 0 and would be of little or no practical value in our calculations.

4 Optimal control

In order to achieve the objective of increasing the period of the thalamocortical neuron model, we will utilize optimal control theory. Optimal control theory is a mathematical framework that aims to find the best control inputs to a system that minimize a given cost function. This is done by solving the Euler-Lagrange equations, which describe the dynamics of the system and the optimal control input that minimizes the cost function. The cost function represents the objective of the optimal control problem, and the solution is obtained by introducing Lagrange multipliers to enforce the dynamics system. In this section, we will formulate the optimal control problem for the thalamocortical neuron model and solve it using the Euler-Lagrange equations.

When formulating an optimal control problem, we typically define the system dynamics, the control inputs, and a cost function that we want to minimize subject to some constraints. In many cases, this leads to a double boundary value problem, which means we have constraints at both the initial and final times.

The cost function that we are going to impose penalizes the use of what is called 'control energy' and has the following expression

$$G[u(t)] = \int_0^{T_1} [u(t)]^2 dt \tag{7}$$

with T_1 being the periodicity we want to achieve with the controlled system. Subsequently, we want to impose periodicity for the solutions with this value, thus we want to impose $\theta(0) = 0$ and $\theta(T_1) = 2\pi$.

One has to realise that there are some limitations on the value of T_1 since the PRC is locally defined around the limit cycle of the original system. As a result of this, the whole methodology presented below yields a good result for $T_1 = 1.2T$ but not for $T_1 = 2T$. This would not be a problem if we somehow knew the analytical expression of the PRC globally.

$$C[u(t)] = \int_0^{T1} \underbrace{\{[u(t)]^2 + \lambda(t)\} \left(\frac{d\theta}{dt} - \omega - Z(\theta)u(t)\right)}_{L} dt \tag{8}$$

The Lagrange-Euler equations are derived by considering the functional $C[u(t)]$ as a function of the system's state variables, and then minimizing it with respect to these variables subject to constraints. This approach allows us to obtain the optimal control strategy that minimizes the cost of our system, given the constraints and dynamics of the system.

$$\frac{\partial \mathcal{L}}{\partial u} = \frac{\mathrm{d}}{\mathrm{d}t}\left(\frac{\partial \mathcal{L}}{\partial \dot{u}}\right), \quad \frac{\partial \mathcal{L}}{\partial \lambda} = \frac{\mathrm{d}}{\mathrm{d}t}\left(\frac{\partial \mathcal{L}}{\partial \dot{\lambda}}\right), \frac{\partial \mathcal{L}}{\partial \theta} = \frac{\mathrm{d}}{\mathrm{d}t}\left(\frac{\partial \mathcal{L}}{\partial \dot{\theta}}\right) \tag{9}$$

$$u(t) = \frac{\lambda(t)Z(\theta(t))}{2}, \tag{10}$$

$$\frac{\mathrm{d}\theta}{\mathrm{d}t} = \omega + Z(\theta)u(t) = \omega + \frac{\lambda(t)[Z(\theta)]^2}{2}, \tag{11}$$

$$\frac{\mathrm{d}\lambda}{\mathrm{d}t} = -\lambda(t)Z'(\theta)u(t) = -\frac{[\lambda(t)]^2 Z(\theta)Z'(\theta)}{2} \tag{12}$$

We then realise that the control variable $u(t)$ can be obtain as a post-process and the dynamical system we have to solve in order to be able to obtain it only involves $\lambda(t)$ and $\theta(t)$ restricted to

$$\theta(0) = 0,$$
$$\theta(T_1) = 2\pi$$

By implementing a RK4 and analysing the final value of θ for different values of the only degree of freedom we have, $\lambda(0) = \lambda_0$, we get more insight of what we are aiming for. We want the value of λ_0 that ensures periodicity in the solutions of the controlled system.

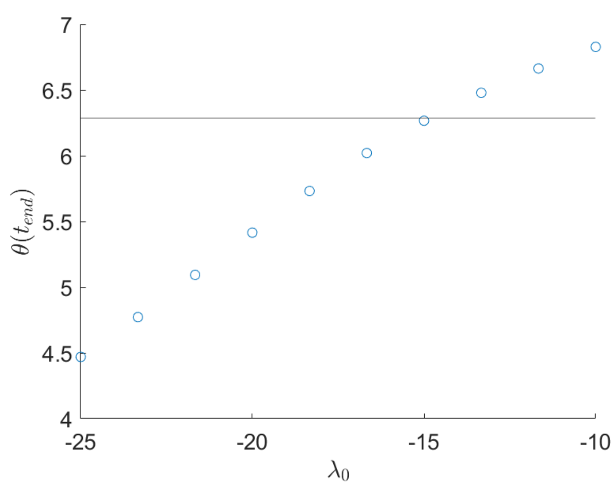


Figure 2: $\theta(t_{end})$ as a function of λ_0.

In [1], they implement a poor shooting method in order to obtain an approximation of the solution. In contrast, we have developed a newton method by means of the variational equations, which is going to be precisely described.

First, we define the equation which we want to find the root to.

$$\theta(T_1) - 2\pi = \phi(\lambda_0) \tag{13}$$

The update rule of the newton iterator is

$$\lambda_0^{n+1} = \lambda_0^n - \frac{\phi(\lambda_0^n)}{\phi'(\lambda_0^n)} \tag{14}$$

Then, we proceed to obtain the relationships that are going to lead to obtain $\phi'(\lambda_0^n)$. We need to derivate the entire system.

$$\begin{cases} \dfrac{d\dot{\theta}}{d\lambda_0} = \dfrac{d\dot{\theta}}{d\lambda}\dfrac{d\lambda}{dt}\dfrac{dt}{d\lambda_0} + \dfrac{d\dot{\theta}}{d\theta}\dfrac{d\theta}{d\lambda_0} + \dfrac{d\dot{\theta}}{d\lambda}\dfrac{d\lambda}{d\lambda_0} \\ \dfrac{d\dot{\lambda}}{d\lambda_0} = \dfrac{d\dot{\lambda}}{d\lambda}\dfrac{d\lambda}{dt}\dfrac{dt}{d\lambda_0} + \dfrac{d\dot{\lambda}}{d\theta}\dfrac{d\theta}{d\lambda_0} + \dfrac{d\dot{\lambda}}{d\lambda}\dfrac{d\lambda}{d\lambda_0} \\ \dfrac{d\theta}{d\lambda_0}(0) = 0 \\ \dfrac{d\lambda}{d\lambda_0}(0) = 1 \end{cases} \tag{15}$$

For seek of clarity, we introduce the following change of variables.

$$x = \frac{d\theta}{d\lambda_0}$$
$$y = \frac{d\lambda}{d\lambda_0}$$

The system now reads:

$$\begin{cases} \dot{x} = x(t)\lambda(t)Z(\theta)Z'(\theta) + y(t)\dfrac{Z^2(\theta)}{2} \\ \dot{y} = -x(t)\lambda^2(t)(\dfrac{Z'^2(\theta)}{2} + \dfrac{Z(\theta)Z''(\theta)}{2}) - y(t)\lambda(t)Z(\theta)Z'(\theta) \\ x(0) = 0 \\ y(0) = 1 \end{cases} \tag{16}$$

where the following notation has been followed:

$$\dot{} = \frac{d}{dt}$$
$$' = \frac{d}{d\theta}$$

From this point, it is straightforward to see that

$$x(T_1) = \frac{d\theta}{d\lambda_0}(T_1) = \frac{d}{d\lambda_0}(\theta(T_1) - 2\pi) = \phi'(\lambda_0) \tag{17}$$

Thus, solving this variational equations together with the main system will give us all the ingredients we need in order to update the newton solver for λ_0.

In order to solve the system we set $T_1 = 1.2T$. By setting the tolerance to 10^{-9} this method quadratically converges to the following solution in just 9 iterations departing from a favorable initial guess.

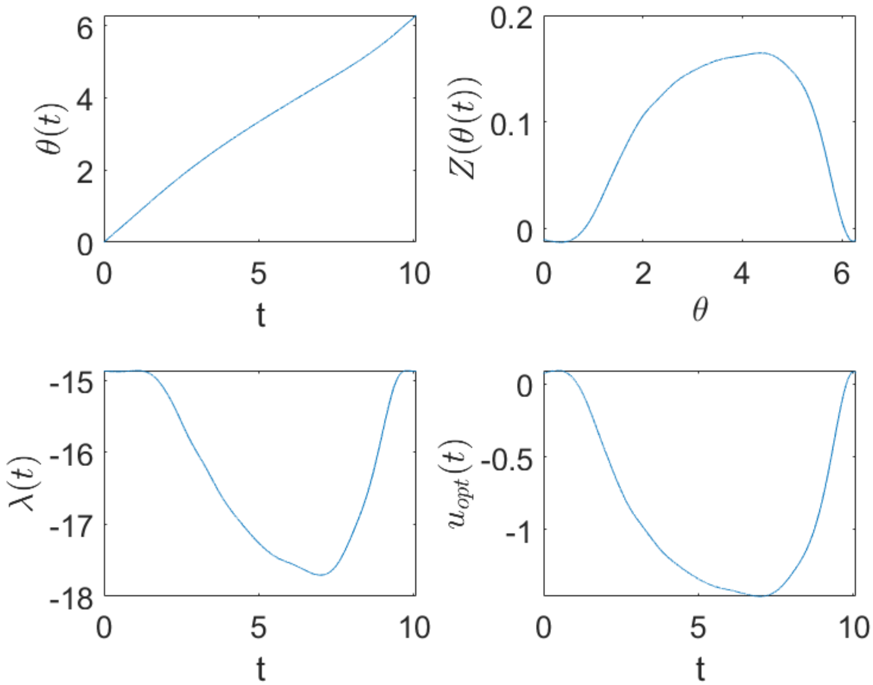


Figure 3: Different quantities after solving the control problem.

We can now make some comments of the solution. As expected, by aiming to a greater period, the intensity that is inputted to the system as the control variable is negative. It is also interesting to see how the ω profile has not dramatically changed from it's originally linear shape (because in the uncontrolled system ω is constant, so integrating one gets a linear function).

Despite the optimal control approach has many advantages over standard control theory, like the incorporation of constraints on the system or the capability to handle complex dynamics and disturbances without any feedback loop, there is a trade-off between achieving a desired system behavior and minimizing the control effort.

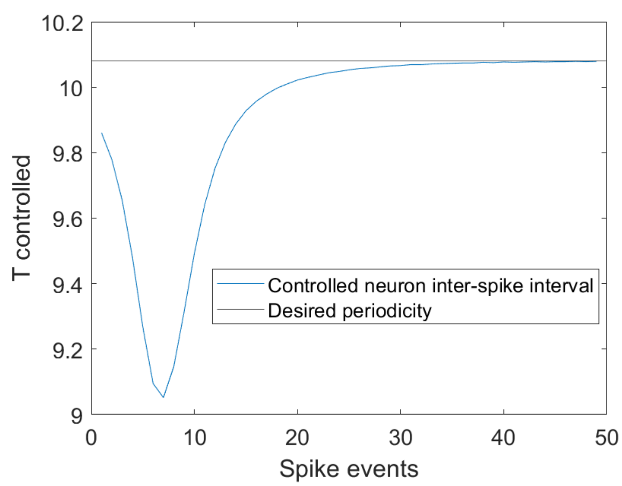
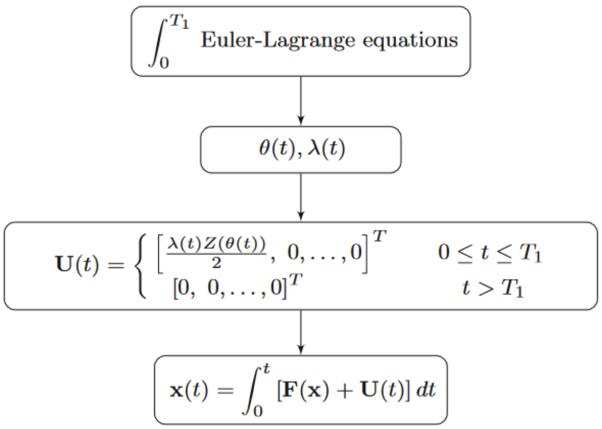
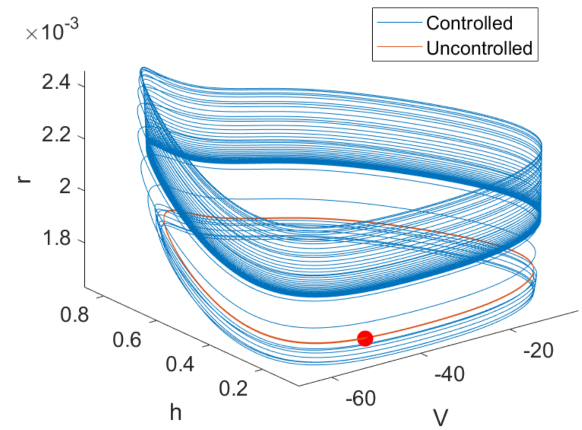


Figure 4: Inter-spike interval of the controlled system.

After obtaining the solution of $u(t)$ for one period, we can repeat it many times and stick them all together. By looking at the performance we realise that the optimally controlled system approaches asymptotically the desired value T_1.



(a) Flowchart describing the energy-optimal control algorithm based on standard phase reduction.



(b) Original space trajectories for the controlled and the uncontrolled system. Red dot indicates the initial conditions, situated in the original limit cycle.

Figure 5

As a final comment in this section it is important to point out that different constraints could have been applied in the formulation of the problem. When one has several constraints numerical parameters can be added to the problem that regulate the effect of each of the restriction, thus leading to different solutions. They act as a regularization parameter in the field of Machine Learning.

However in this case, adding a parameter α in front of the energy consumption term does not change the shape of the optimal $u(t)$.

5 Comparison with a standard control

This section discusses a comparison between the performance of a constant control and an optimal control in achieving a desired system behavior. The constant control is determined by computationally finding the value of a parameter that makes the neuron spike with a desired period, while the optimal control is determined through optimization. The constant control achieves perfect performance by nature, while the optimal control achieves the control objective asymptotically.

In order to first determine the expression of the constant control, one must realise that the most important parameter that tunes firing rate in a spiking model tends to be the external intensity. Thus, we can computationally determine the value of I_b that makes the neuron spike with period exactly T_1. The value for $u(t)$ can be determined following a similar strategy as in Figure 2.

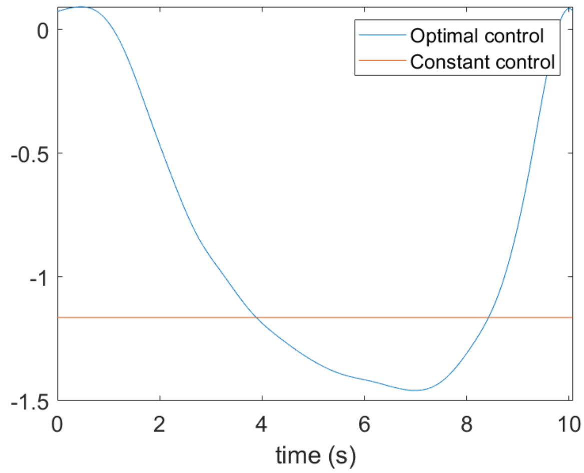


Figure 6: Control functions over T_1 s.

By using trapezoidal integration the constant control consumes 13.6374 units of control energy while the optimal control only consumes 10.7155 units. Thus, it achieves the same results using much less energy. However, its trade-off can be observed in Figure 7. The constant control has an imminent perfect performance by nature. In contrast, the optimal control achieves the control objective asymptotically, which can be recalled from Figure 4.

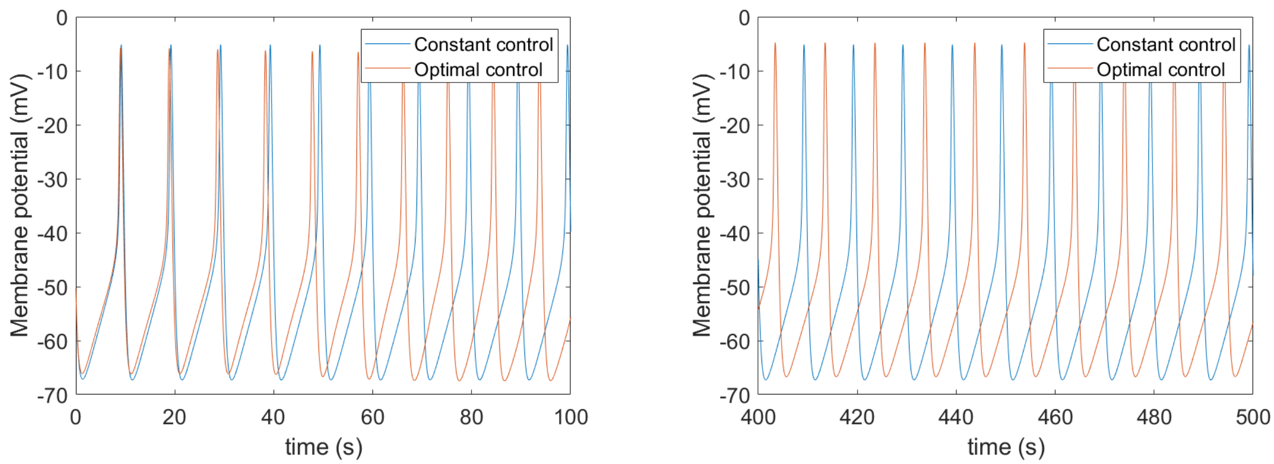


Figure 7: Control comparison for different time intervals.

This effect can be appreciated by checking how the inter-spike interval of the optimally controlled system is off with the system controlled by the constant control at early stages. However, the inter-spike interval or period at later stages is almost the same for both systems. For this time the control system has already reached the desired periodicity.

6 Implementation of the Newton Shooting Method

```
alpha = 1;    % Regulates the energy constraint. Defaul is set to 1.

% Define main parameters
dt = 10^-3;
tol = 10^-8;
it_max = 14;
```

```
T_original =  8.3995;
w = 2*pi/T_original;
T1 = 1.2 * T_original;
t_end = 100;

%% PRC and simple drawis



figure()
neuron_simple(0,0,dt,20,1,5);
neuron_simple(6,-5,dt,20,1,5);


[phase_diff] = sweeping_phase_method(20,dt);

%% Control in phase space

% I interpolate (precision) and get the derivative of Z. I need the same
% resolution of t than of theta.
tsppan = [0 T1]; % ms. Long simulation to be able to compare phases to infinity
t = tsppan(1):dt:tspan(2);

theta = linspace(0,2*pi,20);
theta_int = linspace(0,2*pi,length(t)+2);  %interpolated domain
Z = spline(theta,phase_diff,theta_int);

dtheta = theta_int(2)-theta_int(1);
Z_dot = diff(Z)/dtheta;
Z_dot_dot = diff(Z_dot)/dtheta;

theta_int = theta_int(1:end-2);
Z = Z(1:end-2);
Z_dot = Z_dot(1:end-1);


% Solve the coupled system + Implement Newton to do shooting.

lambda0 = -15;
fun = tol + 1;  % in order to inicialize
it = 0;

while it <= it_max && abs(fun) > tol
    y = zeros(length(t),2);      % Sistema
    x = zeros(length(t),2);      % Variational system
    y(1,:) = [0 lambda0]; % Initialize the first row with the initial conditions
    x(1,:) = [0 1];

    dydt = @(t, theta_ix, lambda) [w + (lambda * Z(theta_ix)^2)/ (2*alpha);
                -(lambda^2*Z(theta_ix)*Z_dot(theta_ix))/(2*alpha)];

    for i = 1:length(t)-1

        theta = y(i,1);
        lambda = y(i,2);
        [~, theta_ev_ind] = min(abs(theta_int-mod(theta,2*pi)));
```

```
        k1 = dt*dydt(t(i), theta_ev_ind, lambda);
        [~, theta_ev_ind_k1] = min(abs(theta_int-mod(theta + k1(1)/2,2*pi)));
        k2 = dt*dydt(t(i)+dt/2, theta_ev_ind_k1, lambda + k1(2)/2);
        [~, theta_ev_ind_k2] = min(abs(theta_int-mod(theta + k2(1)/2,2*pi)));
        k3 = dt*dydt(t(i)+dt/2, theta_ev_ind_k2, lambda + + k2(2)/2);
        [~, theta_ev_ind_k3] = min(abs(theta_int-mod(theta + k3(1),2*pi)));
        k4 = dt*dydt(t(i)+dt, theta_ev_ind_k3, lambda + k3(2));
        y(i+1,:) = y(i,:) + (1/6)*(k1 + 2*k2 + 2*k3 + k4)';

        % Solving variational equations for convergence of newton's method.
        v1 = x(i,1);
        v2 = x(i,2);
        x(i+1,:) = [v1 v2] + dt * 1/alpha * [lambda * Z(theta_ev_ind) * Z_dot(theta_ev_ind) *
                       -(lambda^2 * v1)/2 * (Z_dot(theta_ev_ind)^2 + Z_dot_dot(theta_ev_ind
    end

    df = x(int16(T1/dt),1);
    fun = y(int16(T1/dt),1) - 2*pi;

    lambda0 = lambda0 - fun/df;
    it = it + 1;
end

% Find Z(theta(t)). I have everything as a function of theta_ind (fine grid 0.2pi)
theta_t_ind = zeros(1,length(y(:,1)));
for i = 1:length(y(:,1))
    [~, theta_t_ind(i)] = min(abs(theta_int-y(i,1)));
end

theta_t = theta_int(theta_t_ind);
Z_theta_t = Z(theta_t_ind);

u_opt = (y(:,2).*Z_theta_t')/(2*alpha);
```

References

[1] Bharat Monga et al. “Phase reduction and phase-based optimal control for biological systems: a tutorial”. In: *Biological cybernetics* 113.1-2 (2019), pp. 11–46.