

Controlling neural clustering using delayed inputs [★]

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Abstract: Coupled Hodgkin-Huxley neurons are considered when finite-speed signal propagation introduces time delays into the coupling. Bifurcations of the fully synchronous and partially synchronized cluster states are studied by varying the coupling delay. Based on these investigations a controller is constructed that uses delayed inputs to destroy full synchrony and stabilize clustering. A generalization of such a controller may be useful to drive neural systems away from pathological synchronous states associated with Parkinson's disease. *Copyright ©IFAC 2009*

Keywords: Hodgkin-Huxley model, signal transmission delay, bifurcation, event-based act-and-wait control

1. INTRODUCTION

Neural systems have been studied mathematically for more than half a century and they are well characterized at the component level; see Hodgkin and Huxley (1952). Still, their emergent rhythmic behavior is not fully understood. One of the key properties of these systems is that finite signal transmission times introduce time delays into the couplings that can lead to very rich behavior; see Campbell (2007); Schöll et al. (2009); Ermentrout and Ko (2009); Coombes and Laing (2009).

A robust rhythm that often can be found in neural networks is full synchrony, where all neurons fire together. This can lead to pathological tremors associated with Parkinson's disease; see Elble and Koller (1990). To eliminate this behavior one may use nonlinear delayed feedback and inject current to the brain at multiple sites; see Hauptmann et al. (2007). When the injected signals are phase shifted with respect to each other and the neurons that are close to an electrode entrain their rhythms to the injected signal, the overall synchronous behavior is destroyed.

In this paper we consider a different approach. By varying the time delay in the coupling between neurons, we search for regimes where certain cluster states are stable but the fully synchronous state is unstable. Based on this analysis we are able to construct delayed control algorithms that can destabilize full synchrony while stabilizing a cluster state. So instead of imposing an artificially chosen rhythm on the system we choose one of its natural rhythms and control the corresponding state using mild model-engineered inputs. To mimic the effect of delayed coupling between spiking neurons we propose an 'act-and-wait' type of controller with short 'act period' and long 'wait period';

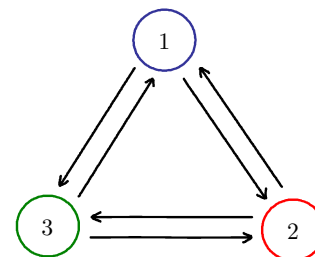


Fig. 1. Sketch of three mutually coupled neurons.

see Insperger (2006). To ensure that the input signal is phase locked (with the appropriate phase difference) to the natural rhythm of the neural system, the control algorithm is made 'event-based' as in Danzl and Moehlis (2007).

We remark that coupling delays arise in many other networked dynamical systems due to finite-time information propagation. Examples include artificial neural networks (Bonnin et al. (2007)), gene regulatory networks (Novák and Tyson (2008)), car-following models (Orosz and Stépán (2006)), and coupled chemical oscillators (Kiss et al. (2007)).

2. MODELLING

In this paper we consider the simple case of three neurons. To model the dynamics of individual neurons, i.e. to describe the biophysical state of their somas, we use the Hodgkin-Huxley model described in Hodgkin and Huxley (1952). We consider that neurons are coupled to each other by direct electrotonic coupling (gap junctions) and we assume all-to-all coupling; see the sketch in Fig. 1. Furthermore, we incorporate axonal delays in the coupling, that is, the time required to transmit the electric signals from the soma along the axon to the point where the axon connects to another neuron. For simplicity all coupling delays are assumed to be equal.

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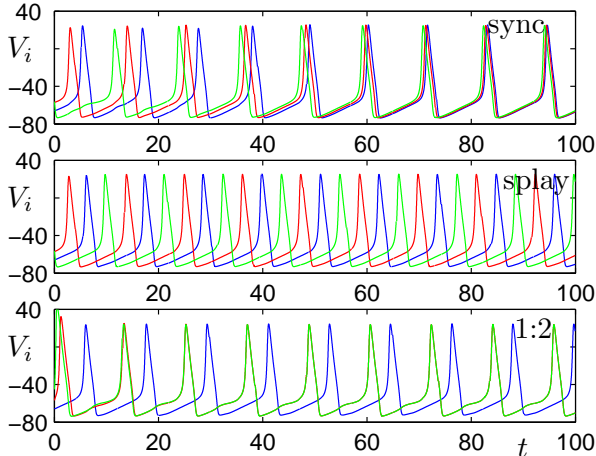


Fig. 2. Voltage time series of neurons for stable oscillatory solutions with different clusterings: full synchrony (for $\tau = 0$), splay state and 1:2 cluster state (both for $\tau = 6$). Observe that spikes are evenly spaced in the splay state but not in the 1:2 state.

We remark that for synaptic coupling one may also consider synaptic delays that would correspond to the time required for the release of chemicals at the synapse. Moreover, axons do not connect directly to the soma of the other neuron but to its dendritic tree. The time until the signal reaches the soma along the dendrite is a source of another delay. For more details on synaptic and dendritic delays see Campbell (2007); Ermentrout and Ko (2009).

The time evolution of the states of three neurons is given by the following delay differential equations

$$\begin{aligned} \dot{V}_i(t) = & \frac{1}{C} \left(I - g_{\text{Na}} m_i^3(t) h_i(t) (V_i(t) - V_{\text{Na}}) \right. \\ & \left. - g_{\text{K}} n_i^4(t) (V_i(t) - V_{\text{K}}) - g_{\text{L}} (V_i(t) - V_{\text{L}}) \right) \\ & + \varepsilon \sum_{j=1, j \neq i}^3 (V_j(t - \tau) - V_i(t)) + \frac{\delta}{C} u_i(t), \quad (1) \end{aligned}$$

$$\dot{m}_i(t) = \alpha_m(V_i(t))(1 - m_i(t)) - \beta_m(V_i(t))m_i(t),$$

$$\dot{h}_i(t) = \alpha_h(V_i(t))(1 - h_i(t)) - \beta_h(V_i(t))h_i(t),$$

$$\dot{n}_i(t) = \alpha_n(V_i(t))(1 - n_i(t)) - \beta_n(V_i(t))n_i(t),$$

for $i = 1, 2, 3$. Here the dot represents the derivative with respect to time t (measured in ms) and V_i is the voltage of the i -th neuron (measured in mV). (From now on we do not spell out the dimensions of quantities.) The dimensionless quantities $m_i, h_i, n_i \in [0, 1]$ are called gating variables, and they characterize the ‘openness’ of the sodium and potassium ion channels embedded in the cell membrane.

The first equation in (1) is based on a simple electric circuit model of the membrane where $g_{\text{Na}}, g_{\text{K}}, g_{\text{L}}$ are conductances, and $V_{\text{Na}}, V_{\text{K}}, V_{\text{L}}$ are reference voltages for the sodium and potassium ion channels and for the so-called ‘leakage current’. The quantity C represents the capacitance of the membrane while I is a constant injected current that drives the neurons to tonic spiking. For numerical values of these parameters see (A.1) in Appendix A.

The term proportional to ε represents the electrotonic coupling between neurons. The coefficient ε is the coupling strength and τ is the transmission delay described above.

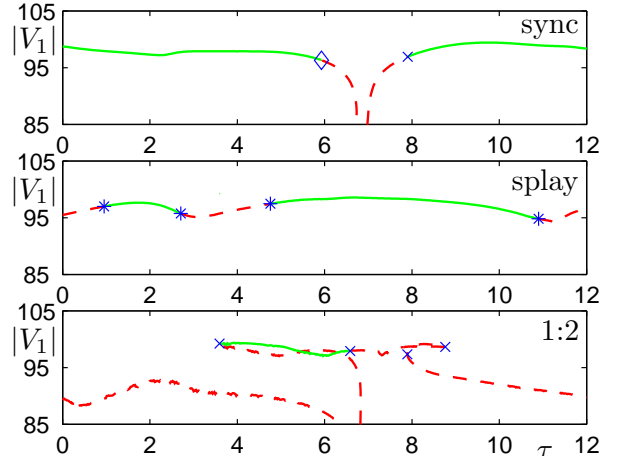


Fig. 3. Bifurcation diagrams for the synchronized state, the splay state and the 1:2 cluster state. The peak-to-peak voltage amplitude of the first neuron $|V_1|$ is plotted as the coupling delay parameter τ is varied. Stable and unstable oscillations are shown as solid green and dashed red curves, respectively. Blue crosses, blue diamonds and blue stars represent fold, period doubling and Neimark-Sacker bifurcations, respectively.

We will vary this parameter in Section 3 and study the qualitative changes of the dynamics. The coupling is assumed to be weak, i.e. $\varepsilon \ll 1$. The term proportional to δ represents the control signal. The coefficient δ is the magnitude of the injected current and $u_i(t)$ describes the time variation of the input such that $\max_t |u_i(t)| = 2$ for $i = 1, 2, 3$. Since we wish to apply mild inputs we require that the order of magnitude of the input is on the order of magnitude of the coupling. That is, $\delta = \mathcal{O}(\varepsilon|V|)$ where $|V|$ represents the peak-to-peak amplitude of voltage oscillations. For parameters (A.1) we have $|V| \approx 100$. In this paper we use the coefficients

$$\varepsilon = 0.05, \quad \delta = 12.5. \quad (2)$$

The last three equations in (1) are based on measurements, and the nonlinear functions $\alpha_m(V), \alpha_h(V), \alpha_n(V), \beta_m(V), \beta_h(V), \beta_n(V)$ are given by (A.2) in Appendix A.

3. BIFURCATION STUDIES

In this section we study the dynamics of system (1) without input ($\delta = 0$) by using numerical continuation techniques, in particular the package DDE-Biftool; see Roose and Szalai (2007). These allow us to follow branches of oscillatory solutions as function of parameters and to study both stable and unstable solutions. Here we vary the time delay τ and investigate the stability and bifurcations of oscillatory solutions with different clustering properties to obtain a picture of the qualitative changes of the emergent dynamics.

To characterize what kind of cluster states may emerge in the system, we recall some general principles of weakly coupled oscillatory networks; see Ermentrout and Ko (2009); Izhikevich (1998). System (1) for $\varepsilon = \delta = 0$ (with parameters (A.1,A.2)) describes independent neurons that are spiking periodically (with period $T_p \approx 10.43$). If the coupling is sufficiently weak, that is, $\varepsilon \ll 1$ and the delays are sufficiently small, i.e. $\varepsilon \tau 2\pi/T_p \ll 1$, oscillations persist in the coupled system and the coupling only changes

the relative timing of the spikes. In this case one can reduce the system to a phase model where each neuron is described by a scalar phase variable. Consequently, the time evolution of the system can be described with three ordinary differential equations.

Analyzing the phase model as in Ashwin and Swift (1992); Brown et al. (2003), one may conclude that there may exist three types of different clustering behavior: full synchrony (when neurons spike together), splay state (when no neurons spike together), and 1:2 state (when only two neurons spike together); these are shown in Fig. 2. Since we consider identical neurons the spikes are evenly spaced in the splay state. The phase difference between the singleton and the pair in the 1:2 state is determined by the properties of the neurons and coupling, and in general does not lead to evenly spaced spikes. We note that there are two different splay states distinguished by the order of spikes, and there are three different 1:2 states distinguished by which two neurons synchronize.

In this paper we do not carry out phase reduction but study the above cluster states in the full Hodgkin-Huxley model with delayed coupling. (In fact, the delays we consider do not necessarily satisfy $\varepsilon\tau 2\pi/T_p \ll 1$.) The different cluster states shown in Fig. 2 are linearly stable. In the top panel $\tau = 0$ and the system approaches the fully synchronous state. In the middle and bottom panels $\tau = 6$ but different initial conditions are considered. Recall that the initial conditions for delay differential equations are functions in the interval $t \in [-\tau, 0]$ (that are chosen to be constant functions here). In the middle panel the system approaches a splay state, while in the bottom panel it approaches a 1:2 state.

We use the states approached in Fig. 2 as initial states for numerical continuation in which we vary the time delay τ . The corresponding results are shown in Fig. 3 where the peak-to-peak voltage amplitude of the first neuron $|V_1|$ is shown. Branches of stable and unstable oscillations are shown as solid green and dashed red curves, respectively. Oscillations are stable if all the (infinitely many) Floquet multipliers are located inside the unit circle. The bifurcations shown in Fig. 3 correspond to parameters where multipliers cross the unit circle.

Blue crosses represent fold bifurcations where a real multiplier crosses the unit circle at $+1$. This bifurcation either makes the branch fold back or results in extra branches of periodic orbits. For example, the fold bifurcation point of the synchronized solution coincides with one of the fold points of the 1:2 solution, i.e. the 1:2 branch arises from a symmetry breaking bifurcation of the fully synchronous state. Blue diamonds correspond to period doubling bifurcations where the a real multiplier crosses the unit circle at -1 . These bifurcations lead to extra branches of periodic orbits with doubled period that are not studied here. Finally, blue stars represent Neimark-Sacker bifurcations where a pair of complex conjugate multipliers crosses the unit circle. These bifurcations also result in extra branches of quasiperiodic oscillations that are not studied in this paper.

For the synchronized and the 1:2 states, part of the branches are not shown (they are out of the window). These parts correspond to low-amplitude oscillatory so-

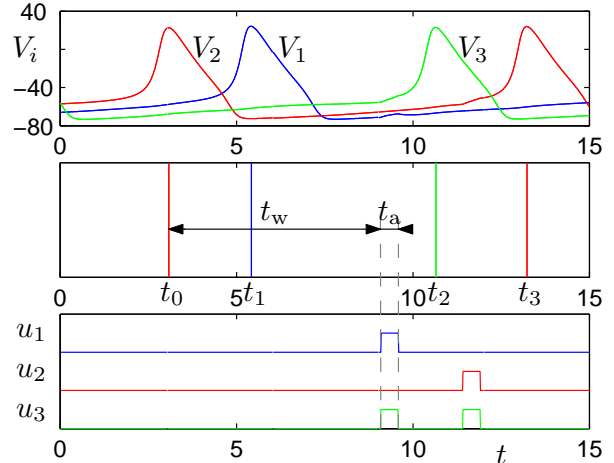


Fig. 4. Construction of the controller: a time t_w after a neuron spikes a constant input of duration t_a is injected to the other two neurons; see (3). From top to bottom: the voltage oscillations of neurons; the recorded spike times; the input signals. Notice the relation between the act and wait times $t_a \ll t_w$.

lutions where the clusterings still persist but the phase oscillator approach breaks down.

4. EVENT BASED ACT-AND-WAIT CONTROLLER

In this section we construct a controller based on the dynamics studied in the previous section. We fix the time delay to be zero ($\tau = 0$), so the fully synchronous state is globally stable in the uncontrolled system. We propose a control algorithm that is able to destroy full synchrony and stabilize cluster states.

As was shown in Section 3, neurons communicate with spikes and introducing time lags into this communication can change the emergent behavior of the system. To mimic the effects of delayed couplings we construct an ‘act-and-wait’ controller where the ‘act time’ t_a is much smaller than the ‘wait time’ t_w , i.e. $t_a \ll t_w$; see Insperger (2006). In this paper we use the act time $t_a = 0.5$ and vary the wait time t_w .

We measure when a neuron spikes (its voltage reaches the maximum), wait a time t_w and then inject an input current of magnitude δ to the other two neurons for a time t_a . We do this to mimic the effect of delayed spikes. Since the wait time is measured from the spike, this is an example of ‘event-based’ control; see Danzl and Moehlis (2007). Considering the initial condition $u_i(0) = 0$ for $i = 1, 2, 3$, the control rules can be formalized as follows.

$$\begin{aligned} &\text{If neuron } i \text{ spikes at } t = t_0 \text{ then} \\ &u_j^+(t_0 + t_w) = u_j^-(t_0 + t_w) + 1 \\ &u_j^+(t_0 + t_w + t_a) = u_j^-(t_0 + t_w + t_a) - 1 \\ &\text{for all } j \neq i. \end{aligned} \quad (3)$$

This is demonstrated in Fig. 4. Indeed, signals may accumulate if two neurons spike together so $\max_t |u_i(t)| = 2$ for $i = 1, 2, 3$.

To be able to quantify the emergent state of the system we define a scalar observable called the order parameter. Describing the phase of oscillations at an arbitrary moment of time is a complicated process and can only be

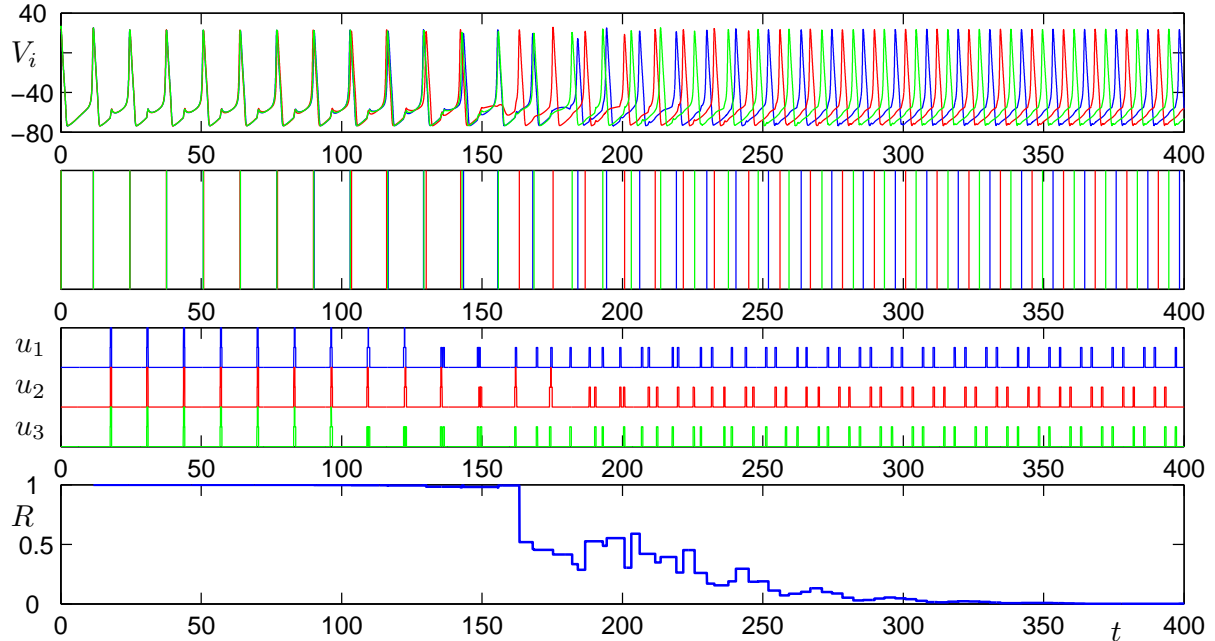


Fig. 5. Controlling the emergent behavior of neurons: driving the system from full synchrony to a splay state. From top to bottom: the voltage oscillations of neurons; the recorded spike times; the input signals; the order parameter (4). The time delay is $\tau = 0$ while the wait time of the controller is $t_w = 6$.

done when phase reduction is possible. However, we are only interested in the phase relations of the spikes. Assume that the last four spikes arrived at $t_0 \leq t_1 \leq t_2 \leq t_3$ such that spikes at t_0 and t_3 were produced by the same neuron while the other two spikes were produced by the other two neurons; see the middle panel of Fig. 4. Now we can define the order parameter

$$R = \frac{1}{3} \left| e^{i2\pi \frac{t_1-t_0}{t_3-t_0}} + e^{i2\pi \frac{t_2-t_0}{t_3-t_0}} + e^{i2\pi} \right|. \quad (4)$$

This quantity needs to be updated when a new spike arrives at t_4 using the update rule $t_0 \leftarrow t_1$, $t_1 \leftarrow t_2$, $t_2 \leftarrow t_3$, $t_3 \leftarrow t_4$. Note that for the fully synchronous state $R = 1$ and for the splay state (with evenly spaced spikes) $R = 0$. For the 1:2 state (with general phase difference between the singleton and the pair) one obtains $1/3 \leq R < 1$. The minimum $R = 1/3$ is reached when the spikes of the singleton and the pair are evenly spaced.

We demonstrate the control algorithm (3) in Fig. 5. Considering the bifurcation diagrams in Fig. 3 we chose $t_w = 6$ (since for $\tau = 6$ the fully synchronous state is unstable while the splay state is stable). The initial conditions are such that the system is very close to full synchrony. (Recall that this state is globally stable for $\tau = 0$ without inputs.) The applied inputs destroy full synchrony and lead the system to a splay state. The order parameter, shown in the bottom panel of Fig. 5, quantifies these changes as it goes from $R \approx 1$ to $R \approx 0$. Indeed, setting the initial conditions further away from the fully synchronous state gives faster convergence.

To test the robustness of the proposed algorithm we vary the wait time t_w and check the asymptotic behavior through the asymptotic values of the order parameter (taken at $t = 400$). The results are shown in Fig. 6 where the approached states are identified in each regime. One

may observe the abrupt changes in the dynamics as t_w is varied. The regimes of qualitatively different behaviors are well pronounced. Comparing this figure to Fig. 3 one may notice remarkable analogy: the wait time t_w serves as an effective time delay. That is how the inputs can stabilize the cluster states.

Observe that for 1:2 state we have $R \approx 1/3$, that is, spikes of the singleton and the pair are almost evenly spaced. Also notice that a new splay-like state (splay*) appears with unevenly spaced spikes. This state is not present in the symmetric system without inputs, but the inputs destroy the symmetry and the non-symmetric splay state may arise. In this state the order parameter (4) does not approach a particular value but keeps oscillating, resulting in the ‘noisy’ appearance of the curve in this regime. We remark that the splay state may not appear for certain initial conditions for $t_w \approx 2$ (the system remains synchronous) but the splay state always appears for $t_w \approx 6$.

5. CONCLUSION AND DISCUSSIONS

In this paper we constructed an event-based act-and-wait controller that is able to drive a neural system away from the fully synchronous state to cluster states. The controller provides the system with mild model-engineered inputs while still being robust and tunable. The design was based on bifurcation studies of the uncontrolled system with signal transmission delays and on the analogy between the transmission delay and the tunable control parameter called the wait time.

We tested our ideas for the uncontrolled system with zero delay in the coupling. Initial investigations show that the controller also works for non-zero coupling delay for certain windows of the waiting time. In the future we would also

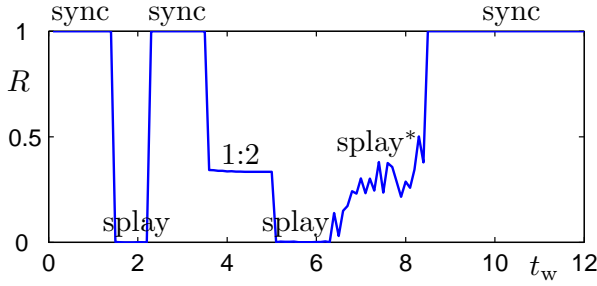


Fig. 6. The asymptotic value of the order parameter R as a function of the wait time t_w (for $\tau = 0$). The states where the system is driven by the controller are written in each regime. The splay* state is a splay-like state where the spikes are not evenly spaced.

like to vary the coupling strength and the input magnitude to test the robustness of the controller. The controller gives non-zero input even when the system reaches the chosen cluster state, while it would be desirable that the input signal approaches zero in this case. An appropriate feedback law is required to achieve this, which should also be tested for stability and robustness.

We would also like to test these control ideas in real biological systems. To do so it is necessary to study larger networks with synaptic couplings and different network topologies. We remark that the time resolution required in the wait time is about 0.5 ms, corresponding to a sampling frequency of 2 kHz, which is satisfied by most digital controllers. However, biological systems are usually noisy and may require the use of the state-of-art Kalman filtering; see Ullah and Schiff (2009).

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Appendix A. PARAMETERS FOR THE HODGKIN-HUXLEY MODEL

Here we define the parameters

$$\begin{aligned} g_{\text{Na}} &= 120 \text{ [mS/cm}^2\text{]} & V_{\text{Na}} &= 50 \text{ [mV]} \\ g_{\text{K}} &= 36 \text{ [mS/cm}^2\text{]} & V_{\text{K}} &= -77 \text{ [mV]} \\ g_{\text{L}} &= 0.3 \text{ [mS/cm}^2\text{]} & V_{\text{L}} &= -54.4 \text{ [mV]} \\ I &= 20 \text{ [\mu A/cm}^2\text{]} & C &= 1 \text{ [\mu F/cm}^2\text{]} \end{aligned} \quad (\text{A.1})$$

and the functions

$$\begin{aligned} \alpha_m(V) &= \frac{0.1(V+40)}{1 - e^{-\frac{V+40}{10}}}, & \beta_m(V) &= 4e^{-\frac{V+65}{18}}, \\ \alpha_h(V) &= 0.07e^{-\frac{V+65}{20}}, & \beta_h(V) &= \frac{1}{1 + e^{-\frac{V+35}{10}}}, \\ \alpha_n(V) &= \frac{0.01(V+55)}{1 - e^{-\frac{V+55}{10}}}, & \beta_n(V) &= 0.125e^{-\frac{V+65}{80}}. \end{aligned} \quad (\text{A.2})$$

used in the Hodgkin-Huxley model (1).