ELECENG 4BB3:
Cellular Bioelectricity
Assignment 5

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1. Create a function `membranewithNaHT_ODE.m` based on the `nonlinearmembraneODE.m` function from Assignment #4, with an **additional** voltage-gated ion current I_{NaHT} incorporated, describing a high-threshold voltage-gated sodium channel with the following characteristics:

$$E_{\mathrm{NaHT}} = E_{\mathrm{Na}}; \qquad g_{\mathrm{NaHT}}(t) = \bar{g}_{\mathrm{NaHT}}\, w(t)\, z(t); \qquad \bar{g}_{\mathrm{NaHT}} = 40\ \mathrm{mS/cm^2}$$

$$\frac{dw}{dt} = \alpha_w [1 - w] - \beta_w w; \qquad \frac{dz}{dt} = \alpha_z [1 - z] - \beta_z z$$

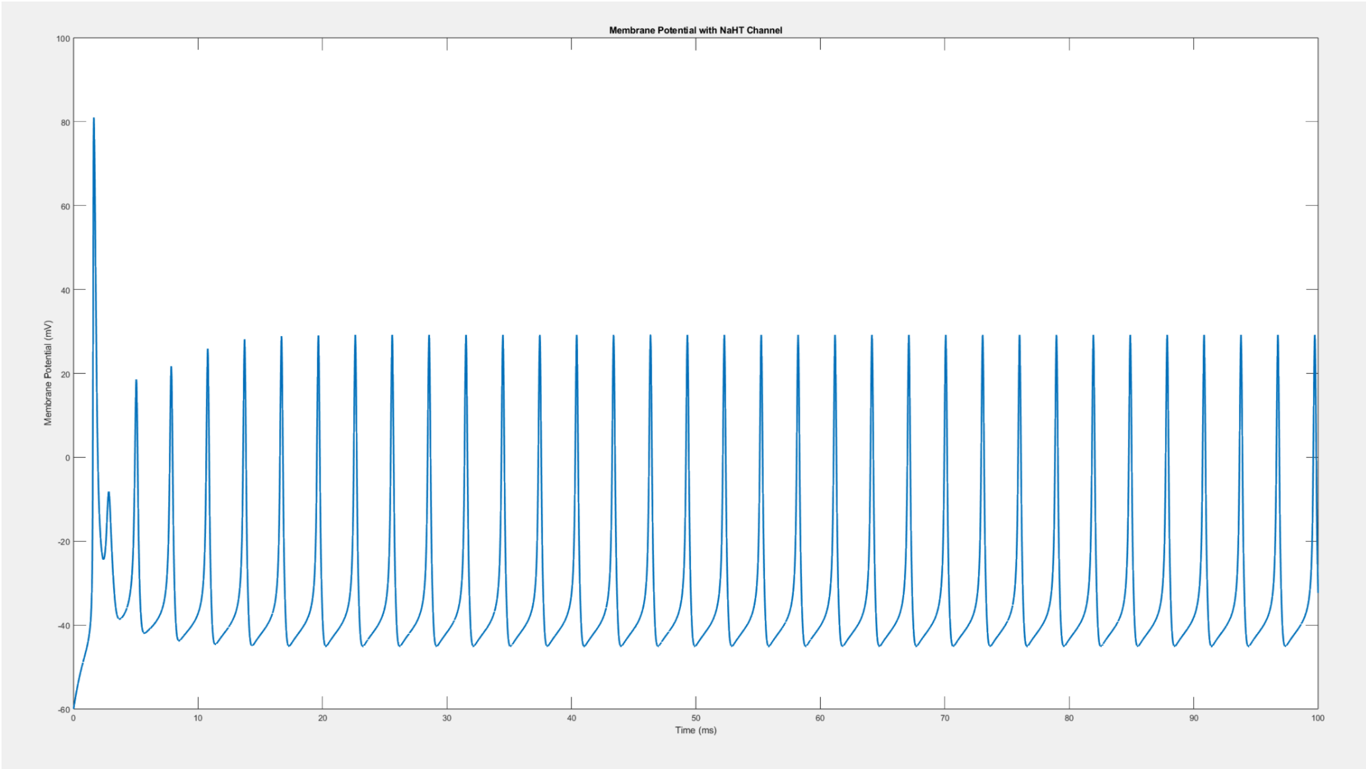
$$\alpha_w = \frac{0.0936(v_m - 55.41)}{1 - e^{(55.41 - v_m)/6.06}} \ \& \ \beta_w = \frac{0.199(51 - v_m)}{1 - e^{(v_m - 51)/9.41}}, \ \alpha_z = \frac{-0.055(27.74 + v_m)}{1 - e^{(v_m + 27.74)/9.06}} \ \& \ \beta_z = \frac{2.257}{1 + e^{(56 - v_m)/12.5}},$$

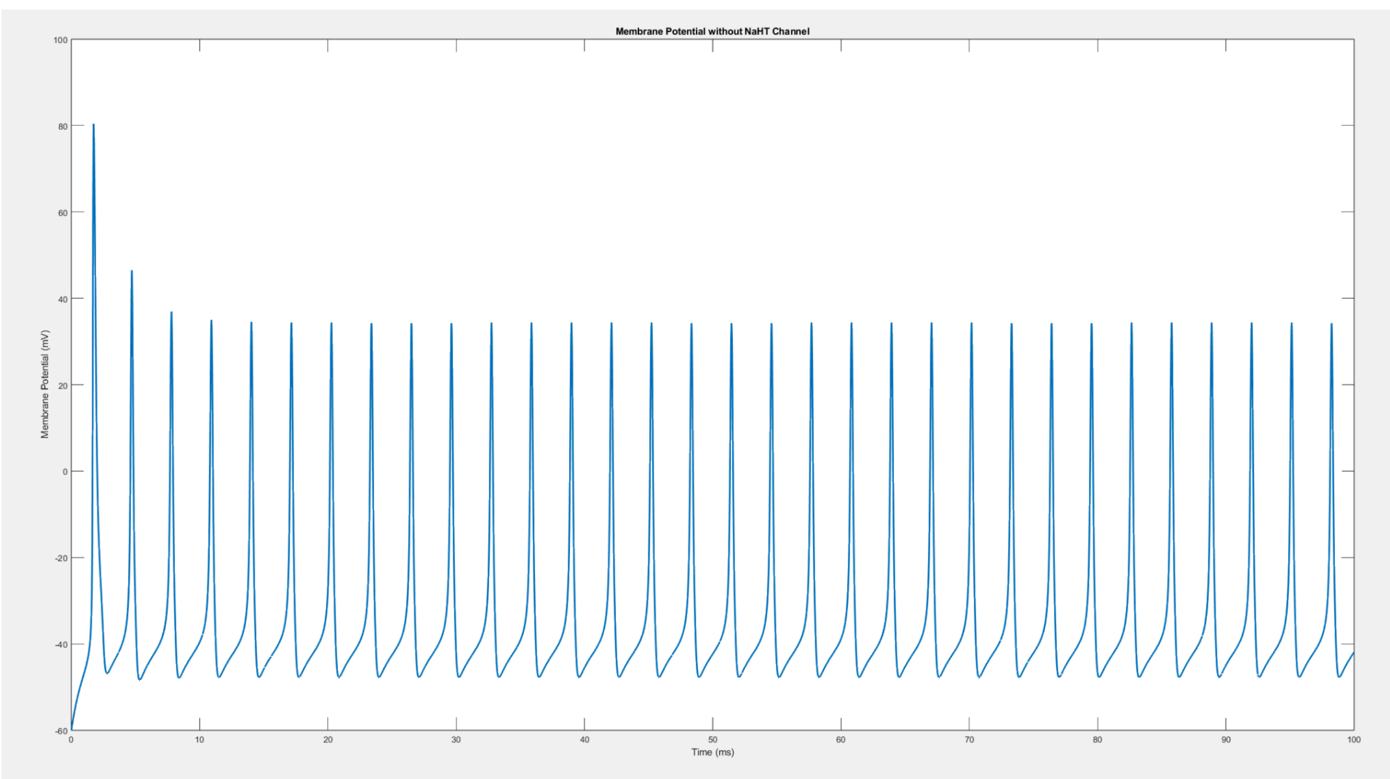
where v_m is the **relative** transmembrane potential in mV.

Note that, in addition to the higher threshold for activation compared to the standard $\mathrm{Na_V}$ channel in the model, this NaHT channel also has only a single activation particle w and slower activation & inactivation time constants. Because of the high threshold for activation for this channel, the value of V_{rest} can still be assumed to be unchanged from Assignments #1 and 4.

We will refrain from including snippets of the code here, so as to keep the report tidy. You may view our commented code to observe methodologies on how we simulated each part.

2. Create a script `actionpotential_demo_NaHT.m` that demonstrates this model's pattern of spiking in response to a long-duration positive current step, and compare it to the pattern of spiking when this channel is blocked (which can be achieved by setting $\bar{g}_{\mathrm{NaHT}} = 0$).


Membrane Potential with NaHT Channel
Membrane Potential (mV)
Time (ms)
100
80
60
40
20
0
-20
-40
-60
0
10
20
30
40
50
60
70
80
90
100


Membrane Potential without NaHT Channel
Membrane Potential (mV)
Time (ms)
100
80
60
40
20
0
-20
-40
-60
0
10
20
30
40
50
60
70
80
90
100

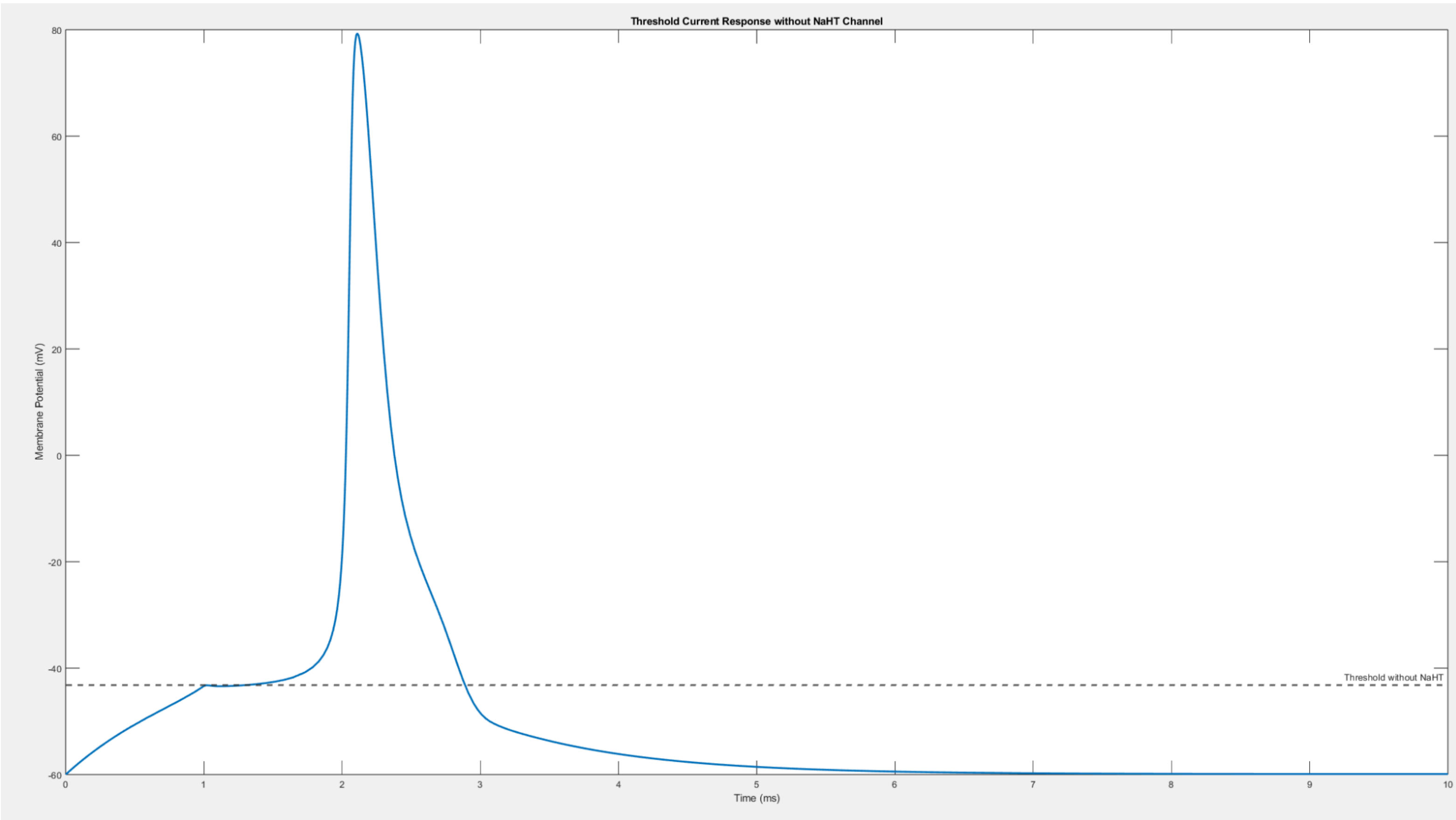
```
Spike rate WITH NaHT: 346.5569 spikes/s
Spike rate WITHOUT NaHT: 321.2236 spikes/s
fx >>
```

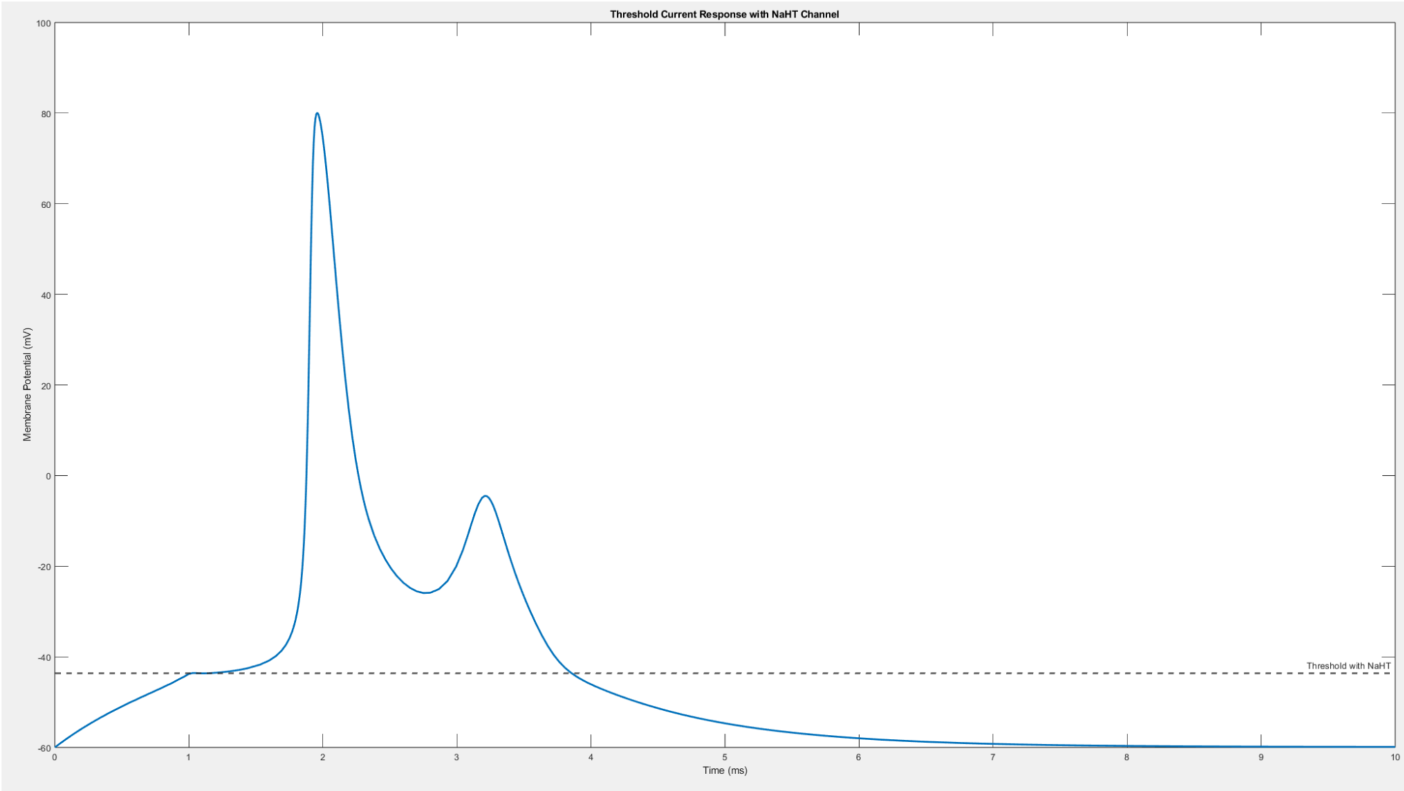
In both images, there is a repeating pattern of spikes that represent the neuronal action potentials. Here are some observations and discussion points based on the provided spike rates and visual patterns:

The presence of the NaHT channel increases the spike rate to 346.5569 spikes/s compared to 321.2236 spikes/s when the NaHT channel is blocked. This suggests that the NaHT channel contributes to a higher excitability of the neuron, allowing it to fire action potentials more frequently.

Neurons with an active NaHT channel may exhibit increased responsiveness to stimuli, as the NaHT channel can contribute to depolarization and thus lower the threshold for action potential initiation. The inclusion of the NaHT channel can alter the simulated firing patterns and rates as seen here. With the NaHT channel active, the neuron’s response to the initial pulse is immediate and pronounced, leading to a rapid depolarization that results in an action potential. In the blocked-channel model, the response may be more subdued, potentially due to the absence of the amplifying effect of the NaHT channels.

3. Create a script `thresholdcurrent_demo_NaHT.m` to demonstrate this model's threshold current in units of $\mu A/cm^2$ (to one decimal point) for a 1-ms long depolarizing current pulse, and compare it to the threshold current for a 1-ms current pulse when this channel is *blocked* ($\overline{g}_{NaHT} = 0$).





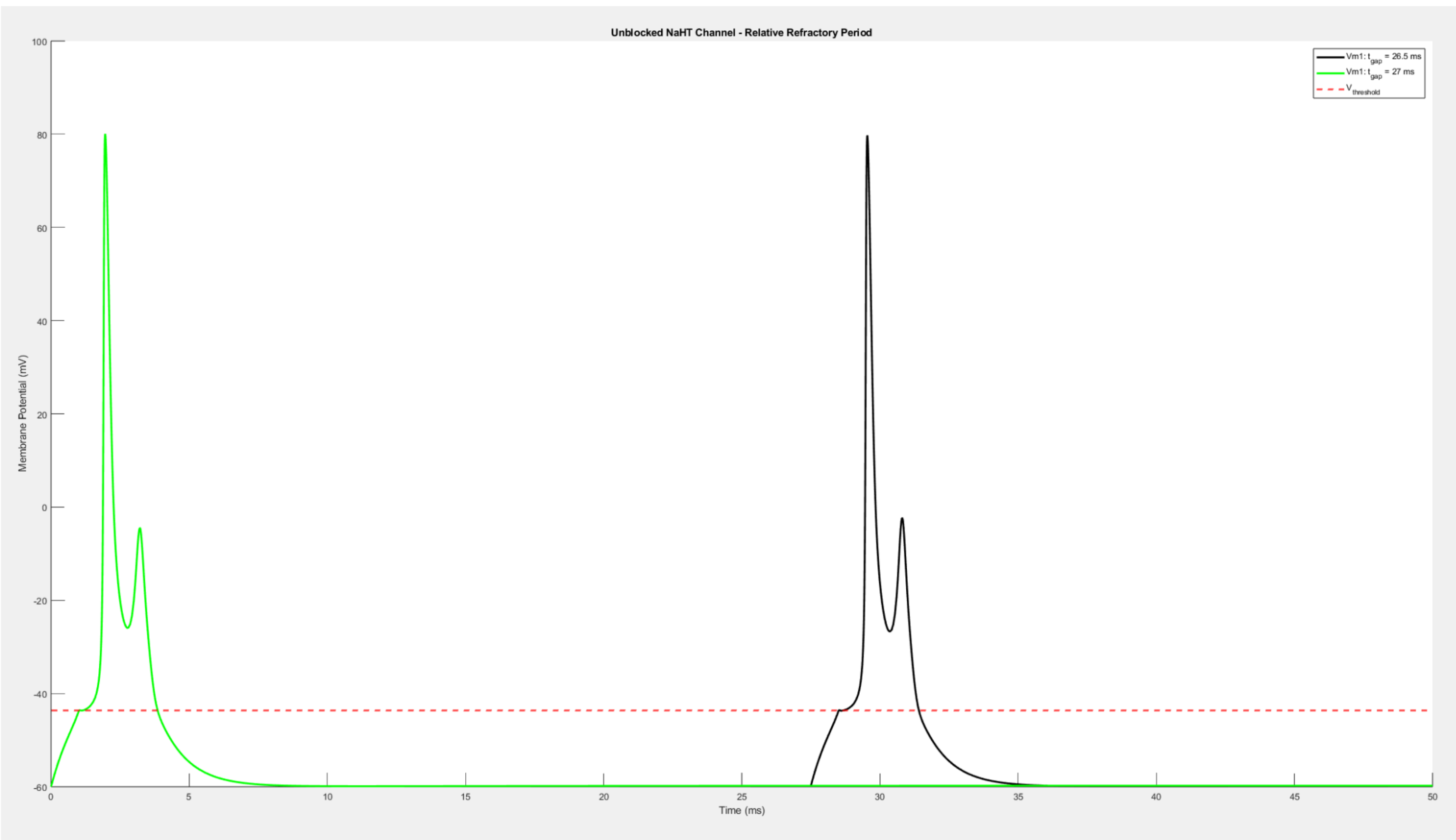

```
Threshold current with NaHT channel: 22.4 µA/cm^2
Threshold current without NaHT channel: 23.7 µA/cm^2
Threshold potential with NaHT: -43.5934 mV
Threshold potential without NaHT: -43.2337 mV
fx >>
```

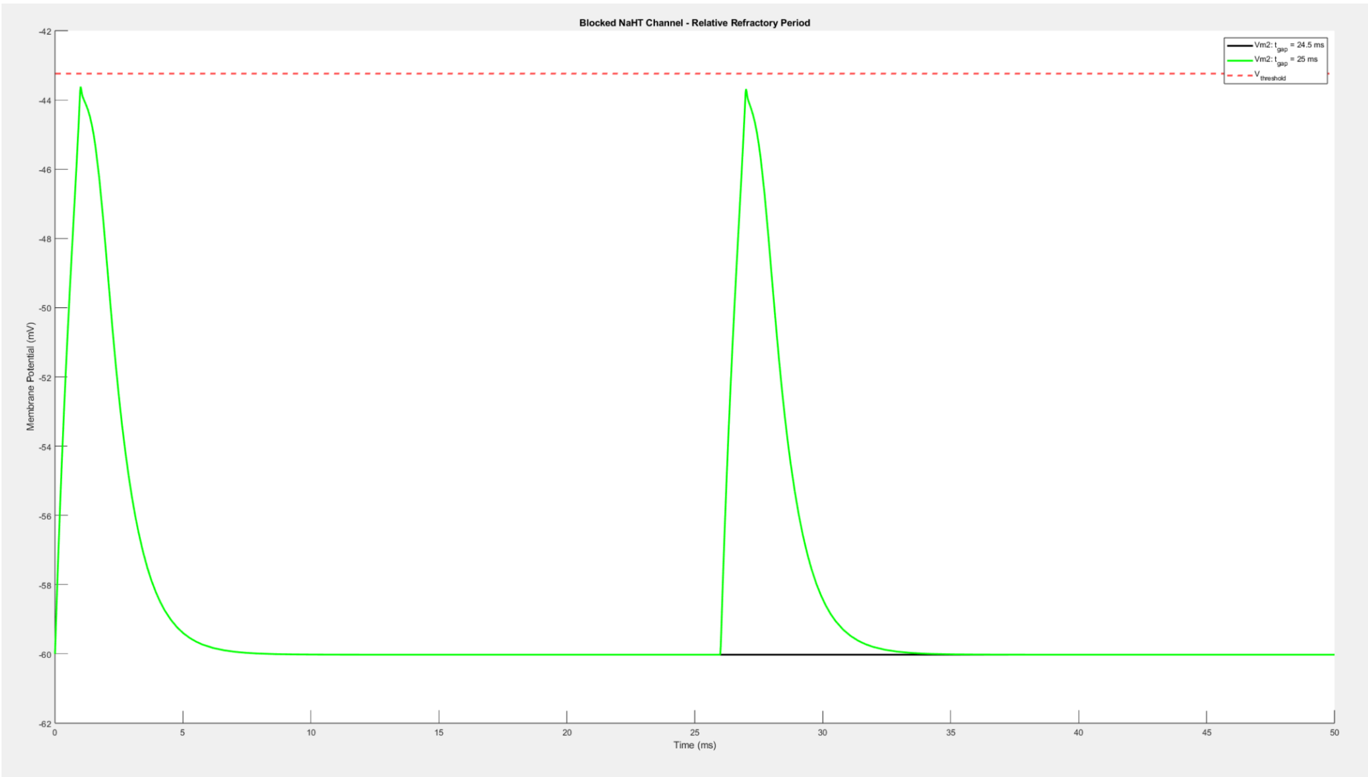
The threshold current refers to the minimum current amplitude required to depolarize the membrane potential sufficiently to initiate an action potential. In our simulation, the threshold current for the NaHT (high-threshold sodium) channel model is slightly lower (22.4 µA/cm^2) than for the blocked-channel model (23.7 µA/cm^2). This difference suggests that the presence of the NaHT channels facilitates the initiation of action potentials at lower current thresholds compared to when these channels are blocked.

The NaHT channels are designed to activate at more depolarized potentials than regular sodium channels. When they are functional (unblocked), they contribute to the membrane's excitability by providing an additional inward sodium current. This means that less external current is needed to reach the action potential threshold, hence the lower threshold current in the presence of the NaHT channels. On the other hand, when the NaHT channels are blocked, the cell relies solely on the standard channels for depolarization, which requires a higher external current to achieve the same effect.

The threshold potentials (with NaHT: -43.5934 mV, without NaHT: -43.2337 mV) are very close to each other, which suggests that the NaHT channels do not significantly alter the membrane potential at which action potentials are triggered. Instead, they affect how readily the neuron can reach that potential when stimulated. This is consistent with the role of NaHT channels in neuronal excitability, particularly in response to sustained depolarizations, where they can help generate repetitive firing by contributing to the late phase of depolarization. The presence of NaHT channels could thus be critical in neurons where rapid firing and quick responses to stimuli are essential, as they lower the threshold current necessary for action potentials to occur.

4. Create a script `refractory_demo_NaHT.m` that demonstrates the <u>relative refractory period</u> properties of the NaHT model and the blocked-channel model for a pair of 1-ms long current pulses by setting the current amplitudes equal to the appropriate threshold current value for $\bar{g}_{\text{NaHT}} = 40\ \text{mS/cm}^2$ or $\bar{g}_{\text{NaHT}} = 0$ and varying the inter-pulse gap.





Refractory Search Method Explanation

The refractory period section of the code we've designed to be responsible for determining the relative refractory period for a neuronal model both with and without the high-threshold Na+ (NaHT) channels.

The initial_gap variable is the starting point for the search—it is set after the absolute refractory period, which is the time during which a second action potential cannot be triggered, regardless of stimulus strength. The max_gap is the upper limit of the search window for the relative refractory period, and the gap_increment determines how finely the search is conducted between initial_gap and max_gap.

Two anonymous functions, fun_with_NaHT and fun_without_NaHT, define the model equations for the ODE solver, ode15s, with the NaHT channel included and blocked, respectively. These functions take into account the current, pulse duration, inter-pulse gap, and maximal conductance for NaHT channels.

The while loops for both with and without NaHT channels incrementally increase the inter-pulse gap, starting from initial_gap and using gap_increment steps. At each step, the system of ODEs is solved, and the membrane potential is observed. If the membrane potential (Vm) at any time point is greater than or equal to the defined threshold (V_threshold_with_NaHT or V_threshold_without_NaHT), it indicates that an action potential has been triggered. At this point, the current gap value is recorded as the relative refractory period for that particular model.

The loops continue to run until an action potential is detected or the maximum gap (max_gap) is reached. If an action potential is triggered, the loop stops, and the current gap value is reported as the relative refractory period. If no action potential is triggered within the maximum gap range, the loop concludes, and the relative refractory period remains NaN (Not a Number), indicating that it wasn't possible to find a refractory period within the tested range.

The output of this process is printed to the MATLAB Command Window, showing the relative refractory period in milliseconds for both models. For the NaHT channel model, a shorter refractory period would suggest that the channel contributes to faster recovery after an action potential. For the blocked NaHT channel model, a longer refractory period would suggest slower recovery, which may imply that the NaHT channel plays a significant role in the neuron's ability to fire action potentials in quick succession.

Explanations of observed behavior

The chosen gaps seen above for the plots were determined empirically by testing various gaps with typical refractory periods & observed Action Potentials. The chosen gaps are used to demonstrate the model's behavior when a second pulse is applied after the indicated time intervals. If a second action potential is successfully triggered, it indicates that the gap is outside the refractory period. Channels like NaHT contribute to the refractoriness by temporarily making the neuron less excitable after an action potential. This is due to the changes in conductance and the gating particles' dynamics, which are modulated by the presence of the NaHT channel. Hence, in the presence of the NaHT channel, the neuron's ability to fire a second action potential is enhanced, resulting in a shorter refractory period compared to when the channel is blocked.

For the blocked NaHT channel condition, the membrane potential does not reach the threshold; hence, no action potential is triggered after the first one. This is the expected behavior during the refractory period of a neuron. During the absolute refractory period, no new action potential can be initiated because the Na+ channels are inactivated. This is followed by the relative refractory period where a higher-than-normal stimulus can initiate an action potential because some Na+ channels have returned to a state capable of opening.

For the unblocked NaHT channel condition, if the stimulus during the relative refractory period reaches or exceeds the threshold potential, an action potential will be triggered. The presence of the NaHT channels affects the neuron's excitability and, consequently, the relative refractory period. The NaHT channels may contribute to a shorter relative refractory period, meaning they may allow an action potential to be triggered sooner after the first one, compared to when these channels are blocked.

5. In your PDF report, include plots of your simulation results for parts 2–4 and discuss: i) what differences you see in the NaHT and blocked-channel model spiking patterns from part 2; ii) the values of the threshold currents for the NaHT and blocked-channel models from part 3; and iii) the minimum values of the inter-pulse gap for the NaHT and blocked-channel models from part 4 that place the 2^{nd} pulse outside of the relative refractory period. In each case, explain how the properties of the NaHT channel cause the observed behaviour.

The analysis for each part has been done above with the accompanying plots of the simulation results in the respective questions.

As always, thank you for taking the time to go through this & have a wonderful summer!