UBC ISCI 422 "Models in Science"

Project 2: Model Construction – Stage 7: Report

An Agent Based Model of the Action Potential

By

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Abstract

The Hodgkin Huxley equations were the first to characterize the action potential. It was done by describing a sodium, a potassium and a leak current; they do not explicitly describe the discrete ion channels causing these currents. The number of ion channels can be directly regulated by the neuron, but since the Hodgkin Huxley model does not explicitly deal with the ion channels, it is unable to predict how this would affect the characteristics of the action potential. We created an agent based model of the action potential which simulated each ion channel individually to try and understand how changing the number of ion channels could affect the characteristics of the action potential. Here we show that the amplitude of the action potential increases, and the time until the maximum and minimum voltages decreases as the number of sodium and potassium ion channels increase. Since generating the action potential is the rate limiting step of current conduction in the axon, our data implies that increasing the number of ion channels should increase the speed at which the action potential is propagated down the nerve fibre, and that regulating the number of ion channels is critical in neurons involved in reflex arcs that must be optimized for speed.

1 Introduction

One of the most seminal works in neuroscience done to date was the work by Hodgkin and Huxley in 1952 to understand how nerve cells fire (they do so by producing an action potential). The power in their model was that they were able to boil down the complex voltage signalling patterns of the action potential to the opening and closing of a few types of ion channels. These ion channels have become the forefront of the work on the physiology of the nervous system with a huge variety of channels and their effects on action potentials characterized since the description of the classic sodium and potassium channels by Hodgkin and Huxley.

Since the Hodgkin and Huxley model was done, there have been a host of similar models for how the variety of discovered ion channels can generate different types of action potentials in different kinds of neurons. For example, thalamocortical relay neurons that are involved in sleep-wake cycles exhibit a bursting pattern of action potentials have been modelled with the I_T, I_A and I_{K2} currents (McCormick and Huguenard 1992). While these models are very effective at what they seek to describe, not one of them explicitly deal with individual ion channels, instead they are found implicitly in the equations that describe the currents. Recent discoveries show that the number of operable ion channels in the neuron membrane is not a fixed number but can be regulated by the cell. One of these methods is by phosphorylation, whereby the channel is still physically present but is inactivated and functionally absent (Park et al. 2008). Since the Hodgkin Huxley equations do not deal explicitly with the ion channels they are unable to predict the effect of changing the number of ion channels. This leaves

an unanswered question; how does changing the number of ion channels affect the characteristics of the action potential

The details of how single channels behave are well understood from what can be inferred from the Hodgkin Huxley equations to a degree that a model that deals with them explicitly can be constructed. There are 4 gates on each of the sodium and potassium channels; 3 m and 1 h gates for sodium channels, and 4 n gates for sodium channels. The channels require that all 4 gates are open to begin conducting current. The rate constants for the different gates have bee determined experimentally and are functions of voltage given by (Hodgkin and Huxley 1953).

$$\text{Opening of n gates } \alpha_n = \frac{0.01(-V-55)}{e^{\frac{-V-55}{10}}-1} \quad \text{Closing of n gates } \beta_n = 0.125e^{\frac{-V-65}{80}}$$

$$\text{Opening of m gates } \alpha_m = \frac{0.1(-V-40)}{e^{\frac{-V-40}{10}}-1} \quad \text{Closing of m gates } \beta_m = 4e^{\frac{-V-65}{18}}$$

$$\text{Opening of h gates } \alpha_h = 0.07e^{\frac{-V-65}{20}} \quad \text{Closing of h gates } \beta_h = \frac{1}{e^{\frac{-V-35}{10}}+1}$$

Patch-clamp studies have been used to measure how much current each channel conducts. When open, each sodium channel has a conductance value of 14 pS (Bezanilla 1987) while each potassium channel has a conductance value of 17 pS (Llano et al. 1988). The density of sodium channels in the membrane has been estimated to be between 166-533 channels/ μm^2 (Hille 2001).

Here we create an agent based model of the action potential using Netlogo to answer the question about how changing the number of sodium and potassium channels affects the properties of the action potential. Understanding the effects of changing the number of ion channels on the global dynamics of the action potential helps us

understand the control the cell has over the shape of the action potential its communication with other neurons.

2 Methods

In order to understand how changing the number of sodium and potassium ion channels affects the behaviour of the action potential a model is required because an experiment would be unfeasible. While the ability to change the number of ion channels in the membrane is possible with the tools currently available to molecular biologists, the changes possible are too crude to answer the question with any sort of reasonable accuracy. Building a model allows for manipulations in the number of ion channels in the membrane down to a single ion channel that would be impossible with the experimental tools currently available.

We are using an agent based model over a mathematical or a numerical model because it allows explicit manipulations in the number of ion channels.

2.1 Model Description

The model (described in Figure 1) was constructed in Netlogo with the 2-D plane corresponding to the surface of the cell, and each turtle corresponds to either a sodium or a potassium channel. Each channel can exist in one of two states, open or closed. When in the open conformation each channel conducts a current which changes the membrane voltage as discussed below, but while in the closed state a channel does not affect the membrane voltage. As discussed above, each channel has 4 gates (4 m gates for the potassium channels and 3 n gates, 1 h gate for the sodium channel) which open independently with first order reactions which are functions of voltage as given above.

The reason this model displays dynamic behaviour is that when a channel is open, it conducts current to change the overall voltage, which in turn affects the probabilities for opening and closing of all the other channels. When a given channel is open is conducts current which changes the membrane voltage according to

$$Q = CV$$

$$I = \frac{dQ}{dt} = C\frac{dV}{dt}$$

$$dV = \frac{I}{C}dt$$

Sodium and potassium channels conduct current in different directions; sodium conducts current into the cell to increase the voltage while potassium channels conduct current out of the cell to decrease the voltage. The current is given by Ohm's law

$$g(V - Ex) = I$$

And the overall change in voltage is given by

$$dV = \frac{g(V - Ex)}{C}dt$$

In this equation, g is the single channel conductance, Ex is the Nernst potential, and C is the membrane capacitance, all of which can be found in the Hodgkin Huxley model or more modern literature. The membrane capacitance C is given by 1 μF/cm^2, the Nernst potential for sodium is+50mV, the Nernst potential for potassium is -77mV(Hodgkin and Huxley 1952), the single channel conductance is given by 14 pS for sodium channels (Bezanilla 1987) and 17 pS for potassium channels (Llano et al. 1988). Finally, there is a leak current with a conductance of 0.3 μS/cm^2 which decreases the voltage according to the equation above.

We assume a spherical cell of radius 1μm for the domain on which to run the model. With the densities of sodium channels above, the range of channels works out to 2100-6700 sodium channels for our cell. Since we were unable to find experimental data for the number of potassium channels, we assumed that it was equal to the number of sodium channels.

The assumptions in this model are that the channel gates open and close independently of each other with first order rate equations. We also assume that each channels is identical and cannot be modulated in any way by control from the cell. Since this is a discrete model, we have to assume that the time step we have chosen (dt = 0.0023) is sufficiently small to overcome any effects that arise from the discrete time nature of the model.

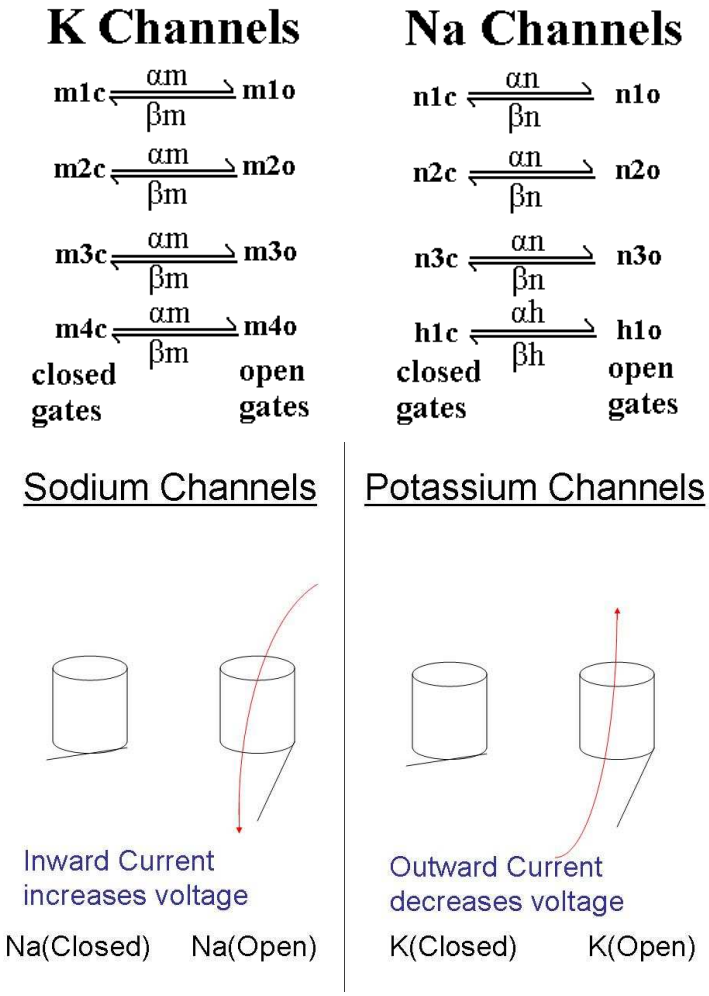

Figure 1 Na channels and K channels both have 4 gates. The opening and closing of these gates are first order reactions with rates that are functions of voltage with the equations provided (Hille 1991). Channels diffuse randomly in the 2-D plane (the membrane) until all 4 gates are open, then the channel conducts current , which changes the membrane voltage and in turn, the probabilities for opening and closing of the gates on the other channels.

2.2 Model Verification

The major test of the model is if we can recreate the action potential measured in squid giant axons and modelled by the Hodgkin-Huxley Equations, which we can. In Figure 2 we see that our model accurately recreates the action potential. We have an initial spike in voltage which maxes out close to the equilibrium potential for sodium (E_{Na}

= +50 mV) and then a falling phase past the resting potential to the equilibrium potential for potassium (E_K = -77 mV).

Furthermore, when we look behind the voltage changes at the profiles for opening of the ion channels we see what we expect. In Figure 3 we see how sodium channels open faster than the potassium channels, but then start to close reflecting a rise in the number of inactivated channels. Afterwards the number of potassium channels beings to open and then eventually close in a slow time course. These dynamics are equivalent to the changes in sodium and potassium conductance predicted by the Hodgkin Huxley equations.

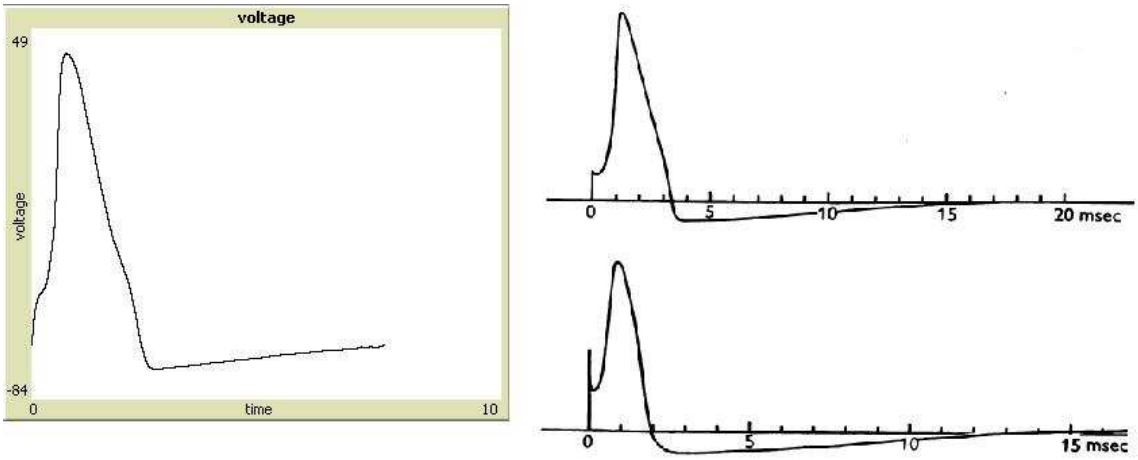

Figure 2. On the left we have our simulation, while on the top right we have the Hodgkin Huxley simulation and on the bottom right we have the experimental result (adapted from Hodgkin and Huxley 1952). The model was run with 6700 sodium and potassium channels starting from rest at -65mV and then given a depolarizing pulse to -45mV. Time is given in milliseconds

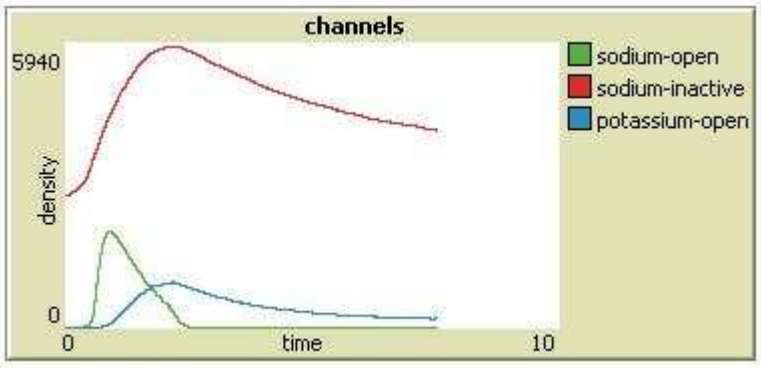

Figure 3. A graph showing the number of open sodium channels in green, number of inactive sodium channels in red and the number of open potassium channels in blue. The model was run with 6700 sodium and potassium channels starting from rest at -65mV and then given a depolarizing pulse to -45mV. Time is given in milliseconds.

There are some limitations with the accuracy of our model. The biggest is that the time it takes the voltage to recover from the after hyperpolarization phase (when the voltage is below the initial voltage) is much shorter in our model than in Hodgkin Huxley or in the measured data. As such, we will not perform any experiments on the after hyperpolarization phase.

2.3 Experiment Description

Our central research question is how changing the discrete number of ion channels in the membrane will affect the characteristics of the action potential. In order to do this we let the model run while incrementally changing the number of ion channels. We started with 2100 of each type of channel (the lower physiological estimate) and then incrementally increased the number until we reached 6700 (the upper physiological estimate). From the voltage vs. time data we generated we extracted the maximum voltage as well as time until maximum voltage and the time until minimum voltage, since these parameters are important for propagation down the nerve fibre.

In order to let the model run we started at a rest potential of -65mV with the number of channels in each state (open or closed) at equilibrium. We then introduced a sustained current to bring the membrane voltage to -45mV, which is robust enough to trigger an action potential, and then waited for the voltage changes to unfold, and finally we collected the data.

3 Results

We present here various characteristics of the action potential with an increasing number of ion channels in the membrane. The first is the maximum voltage of the action potential which is important for how fast an action potential can be propagated down the nerve fibre (Purves et al. 2004). In Figure 4 we see a saturating effect on the maximum voltage as the number of channels increases. Please note that there is a theoretical maximum on the maximum voltage of +50mV where the driving force on the sodium channels in zero so the current must be zero.

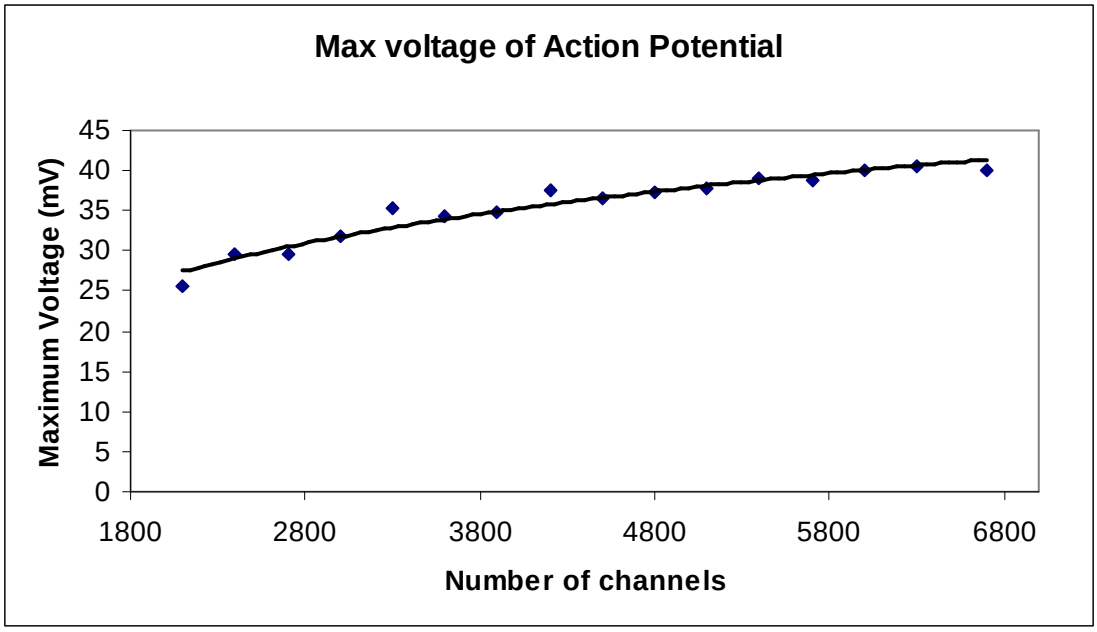

Figure 4. A graph showing the maximum voltage attained during our simulation of the action potential plotted against the number of sodium and potassium channels in the membrane. The model was run starting from rest at -65mV and then given a depolarizing pulse to -45mV. Time is given in milliseconds.

In Figure 5 and 6 we more parameters which will affect how fast the action potential is propagated down the nerve fibre, the time until the maximum voltage, and minimum voltage is attained (Purves et al. 2004). There is a saturating decrease in the time, and there must be a theoretical limit because time cannot be less than 0.

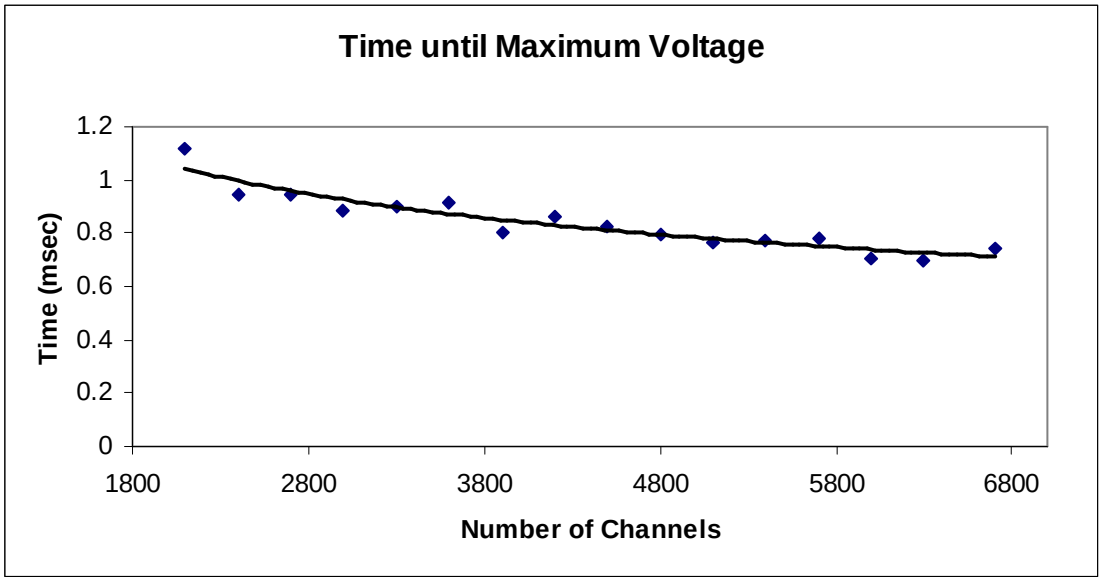

Figure 5. A graph showing the time until maximum voltage attained during our simulation of the action potential plotted against the number of sodium and potassium channels in the membrane. The model was run starting from rest at -65mV and then given a depolarizing pulse to -45mV.

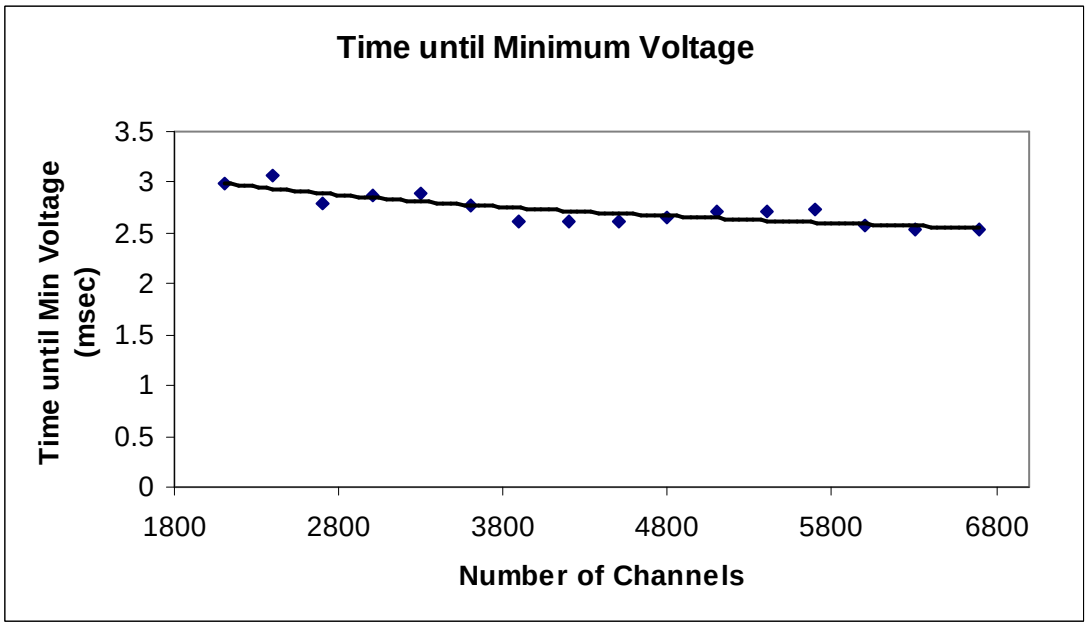

Figure 6. A graph showing the time until minimum voltage attained during our simulation of the action potential plotted against the number of sodium and potassium channels in the membrane. The model was run starting from rest at -65mV and then given a depolarizing pulse to -45mV.

In Figures 4, 5 and 6 we see some stochasticity in the data; they do not cleanly follow the fit curve. This reflects the probabilistic nature of the gating equations.

However, since we can fit a curve to these data it suggests that the probabilistic nature does not overshadow the properties of the action potential.

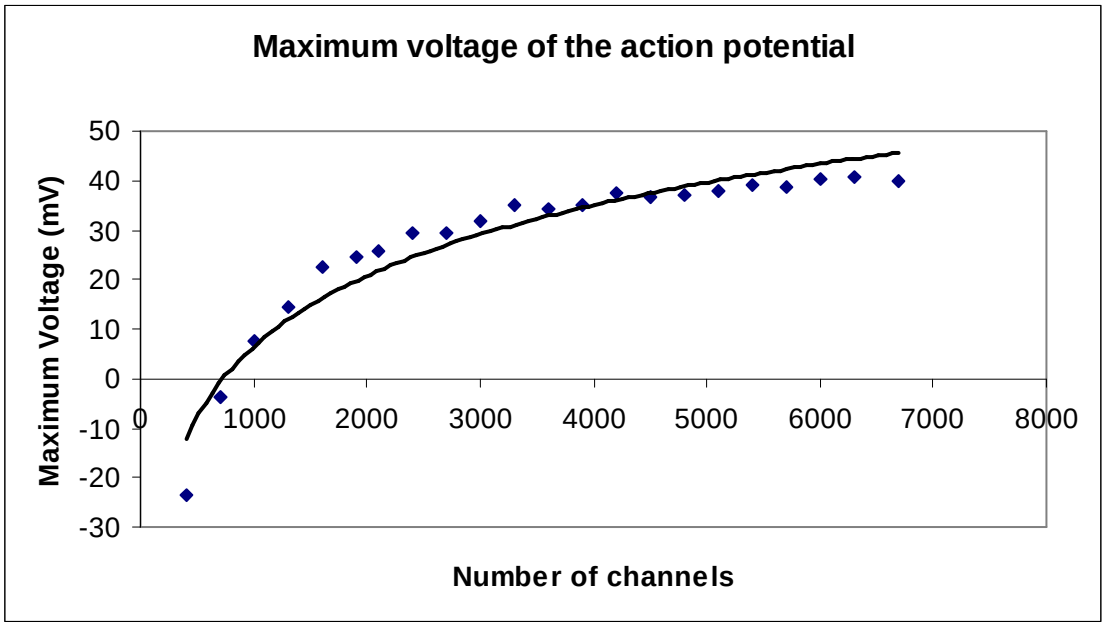

Figure 7. A graph showing the time until minimum voltage attained during our simulation of the action potential plotted against the number of sodium and potassium channels in the membrane. The model was run starting from rest at -65mV and then given a depolarizing pulse to -45mV.

In Figure 7 we see the effect on the maximum voltage of the action potential if we extend the number of ion channels into non-physiologically relevant numbers of ion channels. It is important to note that the slope of the change is much larger in these regions and so there is a much greater effect on changing the number of ion channels into the range that physiologically occurs.

4 Discussion

Here we have seen that increasing the number of ion channels in the membrane (and holding the number of sodium and potassium channels equal) has increased with saturation the maximum voltage attained during the action potential and decreased with saturation the time until the maximum voltage and minimum voltage is attained. These

properties have strong implications on how fast an action potential is conducted down the nerve fibre. A higher maximum voltage means that the voltage is conducted further down the nerve by passive mechanisms before it must be replenished by another action potential (Purves et al. 2004). The decrease until the maximum voltage and until the minimum voltage reflects a shortening of the time it takes to fire an action potential. Since generating the action potential is the most time intensive process in neuronal signalling a decrease in the time required to generate it should speed up action potential propagation down the nerve fibre (Purves et al. 2004).

Together these results suggest that cellular regulation of the number of ion channels in the membrane (Park et al. 2008) can have a physiological effect on the speed of action potential propagation down the nerve fibre. The more ion channels that are available, the faster the action potential is propagated because the maximum voltage is higher, and thus it propagates further, and the time it takes to fire the action potential is decreased. Speeding up the propagation of the action potential is critical in neurons involved in reflex arcs and can be mediated by other processes such as increasing the diameter of the axon and myelination.

While the changes we saw were significant, we must make note that the changes we saw for non-physiological values of the ion channels were much greater. This would imply that the level of control that the cell has on the number of ion channels in the membrane has been selected to have only a small effect. The highest fitness must occur within a narrow range, but big enough that dynamic changes in response to environmental stimuli could have a large enough effect to significantly change the speed at which the neuron in question responds at.

We encountered a few difficulties in the making and study of this model. The most obvious is the noise in our data likely originating from the probabilistic nature of our equations. The easiest way to deal with this would be to run multiple trials on the program with the different number of channels. However, due to computational and time limits we leave this for future directions; it may be worthwhile optimizing the program code before doing this.

Further difficulties arose regarding the level of inactivation of the sodium channels. In figure 3 you can see that the number of inactivated sodium channels rises much faster than the number of open sodium channels, probably because only 1 gate needs to close to inactivate while 3 gates need to open to become open. Some experiments suggest that inactivation is coupled to activation, whereby the inactivation gate cannot close until the channel opens (Kuhn and Greeff 1999). Future directions of the model may rework the code to consider this.

Finally, we should note here that we have always changed the number of sodium and potassium channels together keeping them equal in number. It may be interesting to change them independently of each other and generating more data to produce a full 3-D surface for the maximum voltage, time until maximum voltage, and time until minimum voltage with sodium and potassium channels as the x and y axes. This is beyond our computational power and we doubt it will have much effect on our conclusion

4.1 Summary

Here we have shown that increasing the number of sodium and potassium channels concurrently increases the maximum voltage attained during the action potential and the time until the maximum voltage and minimum voltage decreases. A higher

maximum voltage leads to further passive conductance of the voltage signal before needing to be regenerated by an action potential, and lower time until the maximum and minimum voltage mean that the action potential occurs more rapidly. The changes in amplitude were greatest in the intervals of numbers of ion channels that were not physiologically relevant, implying that evolution has selected for a strong limit on the amount of cellular control of the shape of the action potential. Since generating the action potential is the rate limiting step, our model suggests that increasing the number of sodium and potassium channels concurrently will lead to a faster rate of conduction of the depolarizing signal down the nerve fibre. This mechanism is important because it joins well studied mechanisms like myelination and increasing the diameter of the axon as a method for increasing the speed of voltage conduction in neurons which are required for quick motor reflexes. Since the number of ion channels in the membrane can be changed reversibly by a cell, it suggests that the mechanism we present here is a novel reversible regulation on the speed of action potential conduction, since changes in the size of the axon and myelination are not reversible.

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References

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Purves, D., Augustine G. J. et al. (2004). Neuroscience. Sinauer Press.

Appendix A: Netlogo Source Code

```
breed [ sodium ]
breed [ potassium ]

sodium-own [
  h1
  m1
  m2
  m3
  open
]

potassium-own [
  n1
  n2
  n3
  n4
  open
]

globals [
  voltage
  Eleak
]

to setup
  ; this is a comment
  clear-all
  set voltage initialvoltage
  set Eleak -50
  create-sodium initialsodiumchannels
  ask sodium [
    set color green
    set xcor random 100
    set shape "circle"
    set h1 true ; h gate open
    set m1 false ; m gates closed
    set m2 false
    set m3 false
    set open false
  ]
  create-potassium initialpotassiumchannels
  ask potassium [
    set color blue
```

```
    set ycor random 100
    set shape "circle"
    set n1 false
    set n2 false
    set n3 false
    set n4 false
    set open false
  ]
end

to move
; one turtle moves forward and "wiggles" randomly
  forward 1
  right random 90
  left random 90
end

to go
  tick-advance time-step
  ask sodium [
    move
    ;open/close h1
    if not h1 [
    openh1
    ]
    if h1 [
    closeh1
    ]

    ;open/close m1
    if not m1 [
    openm1
    ]
    if m1 [
    closem1
    ]
    ;open/close m2
    if not m2 [
    openm2
    ]
    if m2 [
    closem2
    ]
    ;open/close m3
    if not m3 [
    openm3
```

```
    ]
    if m3 [
    closem3
    ]

    ;for counting purposes
    ifelse m1 and m2 and m3 and h1
      [ set open true
      ; gamma in mS since voltage is in mV
      set voltage (voltage + -1.11e-1 * (voltage - 50) * time-step)

      set shape "circle 2"
      ]
      [ set open false
      set shape "circle" ]

  ;Ileak
  set voltage (voltage + -0.015 * (voltage - Eleak) * time-step)
  set voltage (voltage - -0.015 * (initialvoltage - Eleak) * time-step) ; this is to hold it at
the initial voltage

  ]
  ask potassium [
    move

    ;open/close n1
    if not n1 [
    openn1
    ]
    if n1 [
    closen1
    ]
    ;open/close n2
    if not n2 [
    openn2
    ]
    if n2 [
    closen2
    ]
    ;open/close n3
    if not n3 [
    openn3
    ]
    if n3 [
    closen3
    ]
```

```
   ;open/close n4
   if not n4 [
   openn4
   ]
   if n4 [
   closen4
   ]

   ;for counting purposes
   ifelse n1 and n2 and n3 and n4
     [ set open true
     set shape "circle 2"
     set voltage (voltage + -0.25e-1 * (voltage + 77) * time-step)
     ]
     [ set open false
     set shape "circle"
     ]
  ]
  do-plot
end

; sodium gating equations
to openm1
  if ((random-float 1) < ((2.5 - 0.1 * (voltage + 65)) / (e ^ (2.5 - 0.1 * (voltage + 65)) - 1)
* time-step)) [
    set m1 true ]
end

to closem1
  if ((random-float 1) < (4 * e ^ ((- voltage - 65)/ 18) * time-step)) [
    set m1 false ]
end

to openm2
  if ((random-float 1) < ((2.5 - 0.1 * (voltage + 65)) / (e ^ (2.5 - 0.1 * (voltage + 65)) - 1)
* time-step)) [
    set m2 true ]
end

to closem2
  if ((random-float 1) < (4 * e ^ ((- voltage - 65)/ 18) * time-step)) [
    set m2 false ]
end

to openm3
```

```
  if ((random-float 1) < ((2.5 - 0.1 * (voltage + 65)) / (e ^ (2.5 - 0.1 * (voltage + 65)) - 1)
* time-step)) [
    set m3 true ]
end

to closem3
  if ((random-float 1) < (4 * e ^ ((- voltage - 65)/ 18) * time-step)) [
    set m3 false ]
end

to openh1
  if ((random-float 1) < (0.07 * e ^ ( (- voltage - 65)/ 20) * time-step)) [
    set h1 true
    ;set shape "cow"
    set color green
    ]
end

to closeh1
  if ((random-float 1) < (1 / (e ^ (3 - 0.1 * (voltage + 65)) + 1)) * time-step) [
    set h1 false
    ;set shape "bug"
    set color red
    ]
end
;end sodium gating equations

;start potassium gating equations

to openn1
  if ((random-float 1) < ((0.1 - 0.01 * (voltage + 65)) / (e ^ (1 - 0.1 * (voltage + 65)) - 1) *
time-step)) [
    set n1 true ]
end

to closen1
  if ((random-float 1) < (0.125 * e ^ ((- voltage - 65)/ 80) * time-step)) [
    set n1 false ]
end

to openn2
  if ((random-float 1) < ((0.1 - 0.01 * (voltage + 65)) / (e ^ (1 - 0.1 * (voltage + 65)) - 1) *
time-step)) [
    set n2 true ]
end
```

```
to closen2
  if ((random-float 1) < (0.125 * e ^ ((- voltage - 65)/ 80) * time-step)) [
    set n2 false ]
end

to openn3
  if ((random-float 1) < ((0.1 - 0.01 * (voltage + 65)) / (e ^ (1 - 0.1 * (voltage + 65)) - 1) *
time-step)) [
    set n3 true ]
end

to closen3
  if ((random-float 1) < (0.125 * e ^ ((- voltage - 65)/ 80) * time-step)) [
    set n3 false ]
end

to openn4
  if ((random-float 1) < ((0.1 - 0.01 * (voltage + 65)) / (e ^ (1 - 0.1 * (voltage + 65)) - 1) *
time-step)) [
    set n4 true ]
end

to closen4
  if ((random-float 1) < (0.125 * e ^ ((- voltage - 65)/ 80) * time-step)) [
    set n4 false ]
end
;end potassium channel gating

;opencount stuff


to-report sodium-open
  report count sodium with [open]
end

to-report sodium-inactive
  report count sodium with [not h1]
end

to-report potassium-open
  report count potassium with [open]
end

;to-report prey-density
 ; report count prey / world-width / world-height
;end
```

```
;to-report predator-density
;  report count predator / world-width / world-height
;end

to do-plot
  set-current-plot "sodium channels" ;which graph to plot in
  set-current-plot-pen "sodium-open" ;which colour to use
  plotxy ticks sodium-open
  set-current-plot-pen "sodium-inactive" ;which colour to use
  plotxy ticks sodium-inactive
  set-current-plot-pen "potassium-open"
  plotxy ticks potassium-open


  set-current-plot "voltage"
  set-current-plot-pen "voltage"
  plotxy ticks voltage
end
```

Grading Rubric

Both instructors will grade your work independently according to the criteria below (may not have equal weight). The final grade will be assigned by normalizing each instructor's evaluations (over all submissions) to have the same mean and variance (decided based on overall class performance), and averaging both instructors' normalized grades.

	Raw Score		
	Instructor:	Instructor:	
Criterion			**Comments**
Student worked independently without requiring too much instructor assistance.			
Motivation and research question clear and interesting from a scientific perspective.			
Model clearly explained.			
Model original and ambitious.			
Assumptions are thoroughly considered and well justified.			
Experiments are appropriate to answer research question.			
Experimental results clearly explained.			
Thoroughly explores implications of results and insights gained in regard to research question.			
The page limits were satisfied.			
Total =			Final Grade: