Building a Mathematical Model of the Merkel Cell

Paulina Czarnecki

Courant Institute of Mathematical Sciences, NYU

AM-SURE 2019

Mentors: Dr. Calina Copos and Dr. Jennifer Crodelle

August 5, 2019

Abstract

Merkel cells are cells located in the skin that are responsible for transducing a light touch into an electrical signal used to communicate with the nervous system. Merkel cells generate action potentials through the in- and out- flow of positively charged ions through protein channels. As experimental data on these cells and their ion channels is relatively recent, the Merkel cell's electrophysiological behavior has yet to be modeled. This project aims to build a mathematical model that will capture action potentials in response to an applied current or indentation. The model's results are compared to experimental measurements of a Merkel cell's response to electrical and physical stimuli. We find that our model can capture the qualitative behavior of a Merkel cell in response to stimulus.

---

1   Introduction

1.1   Biological Background on the Merkel Cell

Merkel cells are located in the skin just under the epidermis and are innervated by sensory neurons. In response to light touch, Merkel cells fire action potentials that are used to communicate with neurons, ultimately sending a message to the brain [1]. This message encodes information about the touch, including features like texture and curvature [1]. The role of the Merkel cell is largely unknown, though scientists have some evidence that Merkel cells are involved in texture discrimination and light touch sensation [2]. Furthermore, pathological conditions in the Merkel cells can create numbness or extreme pain at light touch [3]. When a force indents the surface of the skin, Merkel cells must translate the force into an electrical signal to communicate with the coupled neurons.

Channels in the Merkel cell that respond to pressure, called Piezo2 protein channels, allow an influx of nonspecific positively charged particles into the cell when they open (Fig. 1 (1)) [1]. The influx of ions increases the potential across the cell membrane, prompting calcium channels to open, further depolarizing the Merkel cell (Fig. 1 (2)) [4]. The calcium-driven action potential in the Merkel cell causes the release of neurotransmitters to the gap between the Merkel cell and its afferent fiber [1]. With this signal from the

Merkel cell, as well as its own depolarization from its own mechanoreceptive Piezo2 channels and calcium channels, the afferent neuron begins to fire action potentials that eventually transmit information about the touch to the brain [5–7].
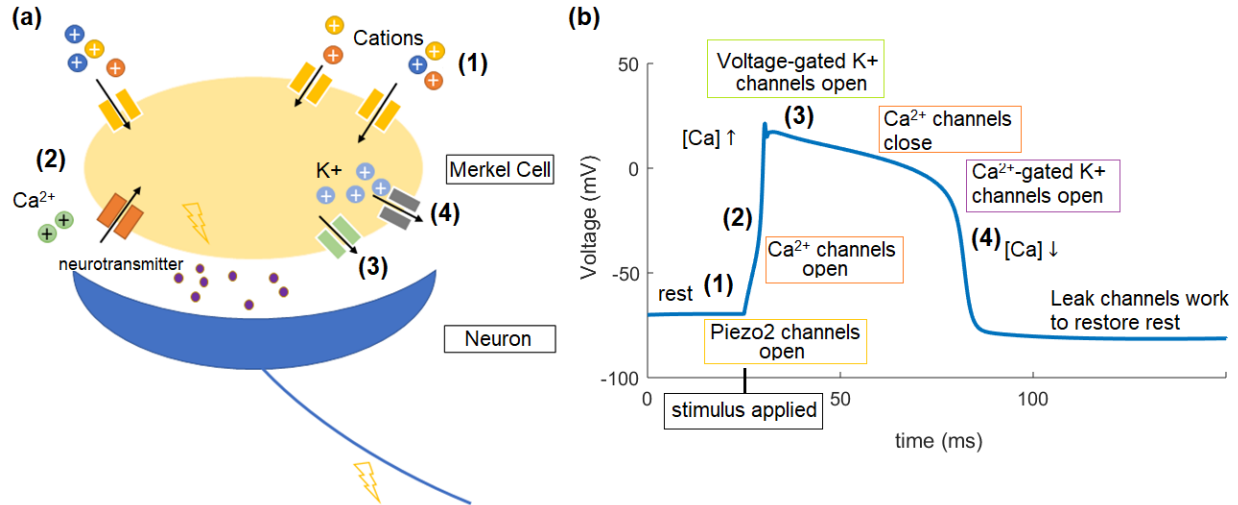

Figure 1: (a) Schematic of the Merkel cell, with an attached neuron. The orange Piezo2 channels allow in nonspecific cations; the red calcium channels allow calcium to flow in; the gray calcium-dependent potassium channel and the green voltage-gated potassium channel allow potassium to exit the cell. (b) Merkel cell activity during an action potential. The cell is at rest at -70 mV at $t = 0$ ms. A stimulus is applied at $t = 25$ ms, causing Piezo2 channels to open and allow an influx of positive ions into the cell (1). In response to the rising voltage, calcium channels open to allow calcium into the cell (2). At the peak of the action potential, voltage-gated potassium channels open and allow positively-charged potassium to exit the cell, lowering the membrane potential (3). The voltage-gated calcium channels close in response to the decreasing voltage (3). Finally, calcium-gated potassium channels open, allowing more potassium to flow out of the cell and drive the cell membrane potential down (4). Leak channels work to restore a resting potential of -70 mV.

In experiments, scientists attempt to understand the Merkel cell-neurite system by inhibiting the Merkel cell, or ion channels involved in creating action potentials, and studying the subsequent response to a voltage or pressure stimulus. By blocking calcium channels, which work to induce depolarization and generate action potentials, they inhibit the Merkel cell's depolarization. Under this treatment, neither the Merkel cell nor the connected neuron fire action potentials [3]. A sodium channel inhibitor does not stop the cells from firing action potentials, implying that a sodium current is not necessary to the working of the Merkel cell [3]. Mice with genetically knocked out Piezo2 channels respond like wild-type mice to all stimulation except for a light touch, where they do not respond at all, implying Piezo2 channels are necessary for the processing of this type of stimulus [1]. At the cellular level, mechanosensitive response is not detected in Merkel cells that did not develop Piezo2 protein channels, and the attached neuron fired a shorter burst of action potentials as compared to wild-type cells [1, 5]. Finally, skin that did not develop Merkel cells at all similarly displays a shorter sustained firing phase in the innervated neuron [4]. Researchers conclude that Merkel cells are

sufficient for producing action potentials in neurons and necessary to the sustained phase of the firing activity in the afferent neuron, and that they are particularly important in the sensation of light touch [1, 2, 4].

1.2   The Role of Protein Channels in Merkel Cells

Piezo2 channels are voltage- and pressure-gated channels that allow an influx of nonspecific positively charged ions into the cell in response to a mechanical force; they are essential in transforming a physical sensation into an electrical message [8, 9]. These channels are found in Merkel cells but not in other skin cells [4, 7, 10], and they are found across different species, from humans to rodents to protists [4]. Piezo2 channels are necessary for mechanotransduction in the Merkel cell; without them, Merkel cells do not exhibit action potentials [3]. In fact, in mice genetically engineered to develop Merkel cells without Piezo2 channels, the electrical response to light touch displays a significantly altered firing pattern from wild type, implying some characteristics of the touch are not correctly encoded [7, 10]. Thus, Piezo2 channels are thought to be the main mechanism of mechanotransduction in Merkel cells [4, 7, 10].

In Merkel cells, calcium flow into the cell causes the increase in membrane potential that creates an action potential. Merkel cells also have voltage and calcium gated potassium channels, called BKCa channels. When a Merkel cell responds to touch, calcium channels open to allow an influx of positively charged calcium ions. This triggers the opening of BKCa channels as the membrane potential rises and the cell depolarizes. The potassium channels allow potassium ions to escape the cell and limit the amplitude of the calcium spikes, but extend the duration of the calcium action potential. Potassium channels open and the outward flow of positively charged potassium ions drives down the membrane potential and repolarizes the cell. Finally, the influx of calcium into the cell triggers the internal release of calcium stores, called a Calcium Induced Calcium Release. This internal release of calcium is thought to amplify the calcium signal, as it is similar to calcium mediated neurotransmitter release in other types of cells [11].

1.3   Project Goals

In this project, our goal is to create a mathematical model to describe the electrical activity of the Merkel cell. We plan to piece together equations for the Piezo2 channels, calcium channels, and various potassium channels to create a Hodgkin Huxley-like model of the Merkel cell. Given an input of an external electrical drive or an indentation, the model will generate action potentials that have a voltage trace comparable to experiments.

2   Model

Previous models of touch sensation typically do not consider cellular level biology such as ion flow. Instead, the model receives an input that signifies touch and outputs a spiking pattern that researchers compare to the firing of attached neurons [6, 12–14]. Many of these models consider afferent neurons as the main sites of mechanotransduction [6, 13]. Others consider the Merkel cell-neurite complex as a generator current that elicits a response in the attached afferent neurons [14]. While these models make important strides in

predicting the neuron's response to touch and learning about the encoding of information in the pattern of the action potentials, these previous models do not consider the Merkel cell's response at the individual scale [6, 12–14]. Here, we aim to model the Merkel cell's electrical response to both electrical and physical stimulation by considering the response of its ion channels.

2.1 The Merkel Cell Model

The model is based on a Hodgkin Huxley formulation, which we use because each term is easy to interpret and has a clear biological meaning. A current across the cell membrane is written in the form $I_x = g_x m_x^p h_x^q (V - E_x)$ for each ion $x \in \{\text{Leak, K, Ca, CaK, Piezo2}\}$. Here, g represents the maximal conductance of the given ion, m is the probability of the activation gates of the channel being open, h is the probability of the inactivation gates being open, V is the membrane potential, and E is the reversal potential, or the membrane potential at which the given ion is at equilibrium. Calcium, potassium, calcium-dependent potassium, and Piezo2 channels each have their own terms of this form. The current across the cell membrane is the sum of all the individual ion currents and an applied drive. This applied drive, denoted I_{drive}, is a step current that is either zero or a constant in time. The total current is given by

$$C\frac{dV}{dt} = -I_{Leak} - I_K - I_{Ca} - I_{CaK} - I_{Piezo2} + I_{drive}. \tag{1}$$

2.2 Leak Current

The leak current, or the term that captures cell activity in the absence of external input, is given by

$$I_{Leak} = g_L(V - E_L). \tag{2}$$

As in the other current terms, g_L is the maximal conductance of this channel and E_L is the reversal potential. Since the leak channels drive cell voltage towards rest, E_L is chosen to be -70 mV. All parameters are found in Table 1.

2.3 Potassium

The potassium current generated by vovltage-gated potassium channels is given by

$$I_K = g_K n^4 (V - E_K). \tag{3}$$

Here, g_K is the maximal conductance of the potassium channel, n is probability the gate is open (Eq. 4), and E_K is the reversal potential of Potassium in the Merkel cell. Exact parameter values and their citations can be found in Table 1.

The probability that the potassium channel is open is governed by

$$\frac{dn}{dt} = \frac{n_\infty - n}{\tau_n}, \tag{4}$$

4

where the steady-state activation is given by (modified from [15])

$$n_\infty = \frac{1}{1 + \exp\left(\frac{-(V-3)}{12}\right)}, \tag{5}$$

and the timescale τ_n is

$$\tau_n = \frac{1}{5(\alpha_n + \beta_n)}.$$

Here, α_n and β_n are nonlinear rates of opening and closing of the potassium channel subunits. These potassium activation gate rate equations are given by

$$\alpha_n = \frac{0.02(-(V+10))}{\exp\left(\frac{-(V+10)}{5} - 1\right)},$$

$$\beta_n = 0.5\exp\left(\frac{-(V+20)}{40}\right),$$

where α_n is the opening rate of the potassium channel subunits and β_n is their closing rate (modified from [15]).

2.4   Calcium

Since the Merkel cell exhibits electrical spiking behavior due to the dynamics of calcium, the model assumes some dependence on the calcium concentration inside the cell [16]. In particular, the calcium channel inactivation gate (h, Eq. 12), the calcium-dependent potassium channel (m_{CaK}, Eq. 17), and the calcium reversal potential (E_{Ca}, Eq. 7) have terms dependent on calcium.

The calcium current through voltage-gated calcium channels is given by

$$I_{Ca} = g_{Ca}m_{Ca}^2 h_{Ca}(V - E_{Ca}). \tag{6}$$

The maximal conductance of the calcium channels is given by g_{Ca}, m_{Ca} is the calcium activation (Eq. 9), h_{Ca} is the inactivation (Eq. 12), and E_{Ca} is the calcium reversal potential (Eq. 7) (parameters in Table 1).

In classical Hodgkin Huxley, the ion reversal potentials are taken to be constant. This implies that the proportion of the ion's concentration inside to the concentration outside the cell remains constant. However, in cells that exhibit calcium spikes, the calcium activity is very dynamic, and it is unrealistic to take the internal calcium concentration to be constant [16–18]. Thus in our model the calcium reversal potential is also dependent on the internal calcium concentration [Ca], and is governed by the Nernst potential [17, 18]:

$$E_{Ca} = 1000\left(\frac{RT}{zF}\ln\left(\frac{[Ca]_e}{[Ca]}\right)\right). \tag{7}$$

The 1000 factor is a conversion factor from volts to millivolts, R is the ideal gas constant, T is the temperature in Kelvins, z is the valence of calcium (which is 2), F is Faraday's constant, $[Ca]_e$ is the external calcium
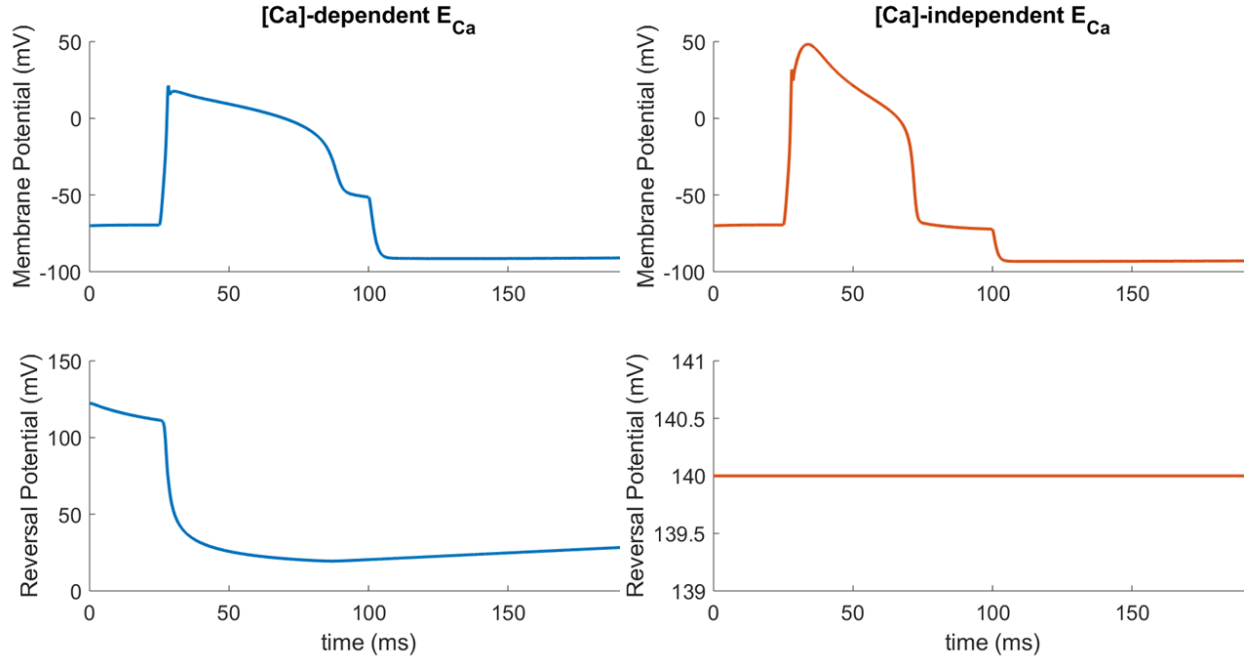
Figure 2: A Merkel cell action potential generated by our model. The indentation is a step current that takes a constant value of 3 μm for 25 ms $< t <$ 100 ms and zero elsewhere. The maximal conductance g_P is 3. (left) A calcium-dependent reversal potential [16, 17] is plotted with the associated action potential. (right) A constant calcium reversal potential E_{Ca} [15] is plotted with its associated action potential.

concentration (considered a constant), and [Ca] is the internal calcium concentration (Table 1) [16–18]. This internal calcium concentration is governed by the equation

$$\frac{d[\text{Ca}]}{dt} = -0.0002 I_{Ca} - \frac{[\text{Ca}] - 0.00024}{150}, \tag{8}$$

where [Ca] is the calcium concentration inside the cell [15].

The calcium activation is governed by the equation

$$\frac{dm_{Ca}}{dt} = \frac{m_{Ca\infty} - m_{Ca}}{\tau_{mCa}}, \tag{9}$$

where

$$m_{Ca\infty} = \frac{1}{1 + \exp\left(\frac{-(V+22.3)}{10}\right)}, \tag{10}$$

and

$$\tau_{mCa} = 1 + (V+30)(0.014). \tag{11}$$

Eq. 10 is from [16], and Eq. 11 from [15].

The calcium channel also has an inactivation variable described by the differential equation [16]

$$\frac{dh_{Ca}}{dt} = \frac{h_{Ca\infty} - h_{Ca}}{\tau_h}. \tag{12}$$

The steady-state activation is

$$h_{Ca\infty} = 0.15 + \frac{0.85}{1 + \left(\frac{[Ca]}{k_{hL}}\right)^3}, \tag{13}$$

and the timescale is given by

$$\tau_{hCa} = 11.5 + \frac{0.7}{0.017\left(1 + \left(\frac{[Ca]}{k_{hL}}\right)^3\right)}. \tag{14}$$

Here, k_{hL} is a parameter that signifies the calcium concentration at which the probability of the h gate of being open was 0.5; this value is chosen to be the calcium concentration where this occurs for our model (Table 1) [16].

2.5 Calcium Dependent Potassium

The Merkel cell has potassium channels that are both voltage- and calcium- regulated. The total calcium-dependent potassium current is given by

$$I_{CaK} = g_{CaK} m_{CaK} (V - E_K). \tag{15}$$

The maximal conductance of the calcium-dependent potassium channel is g_{CaK}, m_{CaK} is the probability that the activation gate is open (Eq. 16), and E_K is the potassium reversal potential (Table 1).The calcium-dependent potassium channels have only an activation variable

$$\frac{dm_{CaK}}{dt} = \frac{m_{CaK\infty} - m_{CaK}}{\tau_{CaKm}}, \tag{16}$$

which is taken to be dependent on the internal calcium concentration [Ca] (Eq. 8), from [15]:

$$m_{CaK\infty} = \frac{[Ca]}{[Ca] + 2}, \tag{17}$$

$$\tau_{CaKm} = \frac{100}{[Ca] + 2}. $$

2.6 Piezo2 Channels

The Piezo2 protein channels are mechanosensitive channels that respond to an input of indentation or force and elicit an electrical current through the nonselective inward flow of positive ions. To model this mathematically, we construct equations in a similar form as the other ion channels. The total Piezo current is given by

$$I_{Piezo2} = g_P m_P (V - E_P). \tag{18}$$

7

The conductance g_P is chosen to best reflect behavior shown in experiments [10]. The reversal potential E_P is chosen to be large and positive, to reflect the excitatory nature of Piezo2 channel activity. The exact values are described in Table 1. The probability of the Piezo2 channel opening is described by the activation term m_P:

$$\frac{dm_P}{dt} = \frac{m_{P\infty} - m_P}{\tau_P}.$$

Here, $m_{P\infty}$ is a function of an applied indentation d. This indentation d is considered on a scale of 0 - 5 μm, where 0 μm signifies no indentation and the probability of the Piezo2 channels opening is 0. This range is chosen because it is representative of ranges used in experiments, where scientists measure the Merkel cell's response to an applied indentation [10]. The probability of the channel opening reaches 1 at an applied indentation of 5 μm [10]. In experiments, the Merkel cell begins generating an action potential at values of indentation of about 2.5 μm [10]. Thus the probability of the Piezo2 channel being open is chosen to be $\frac{1}{2}$ at an indentation of 2.5 μm. To fit the steady-state activation $m_{P\infty}$ to experiments, we use a slope factor of 0.25, which yields the following equations:

$$m_{P\infty} = \frac{1}{1 + \exp\left(\frac{-(d-3.5)}{0.25}\right)}, \tag{19}$$

$$\tau_P = 1.$$

All steady-state activation variables are graphed in Fig. 3.

Name	Value	Eq.	Reference
C	1 μF/cm^2	1	[15]
g_K	3 mS/cm^2	1, 3	N/A
E_K	-95 mV	1, 3, 15	[15]
g_L	0.15 mV	1, 2	N/A
E_L	-70 mV	1, 2	N/A
g_{Ca}	5 mS/cm^2	1, 6	[16]
g_{CaK}	5 mS/cm^2	1, 15	N/A
g_P	3 mS/cm^2	1, 18	N/A
E_P	55 mV	1, 18	N/A
k_{hL}	0.3 mM	13, 14	[16]
z	2	7	[16–18]
F	$9.648 \cdot 10^4$ J/Kmol	7	[16–18]
R	8.314 C/mol	7	[16–18]
T	305.65 K	7	[16–18]
Ca_e	2.6 mM	7	[16]

Table 1: Parameters used in the model, as determined either in papers or fit as described in the Model section. Choices of parameter with no citation are justified in the Discussion section.

2.7   Simulation and Parameters

After fitting together the ion channel equations as described above, the activation for each of the ion channels behave as in Fig. 3. The steady-state probabilities of being open for the activation variables (n_∞, $m_{Ca\infty}$, $m_{CaK\infty}$, $m_{P\infty}$) are zero at rest (low voltage, low internal calcium concentration, low indentation) and increase in the probability of being open as their input variables increase. Conversely, h_∞ is initially open and decreases its probability of being open as the internal calcium concentration increases. The general form of these equations is $\frac{1}{1+\exp\frac{V-x}{k}}$, where x gives the value of the input (voltage, internal calcium concentration, indentation) at which the probability of that gate being open is 0.5, and k controls the slope of the curve (form from [16]).

The applied external drive I_{drive} is a step function that is either 0μm/cm^2 or some constant nonzero value. Matlab's fourth order Runge-Kutta time integrator, ode45, is used to solve the system of equations to obtain a voltage trace by integrating Eq. 1 and all other coupled ODEs. Default settings of ode45 are used. Initial conditions provided to the integrator are 0 for all variables except for $h_{Ca}(t=0)=1$, $[Ca](t=0)=0.00024$ mM, and $V(t=0)=-70$ mV. This is done to ensure the Merkel cell begins the simulation at a resting membrane potential and an internal calcium concentration of zero. Other parameters can be found in the parameter table (Table 1).
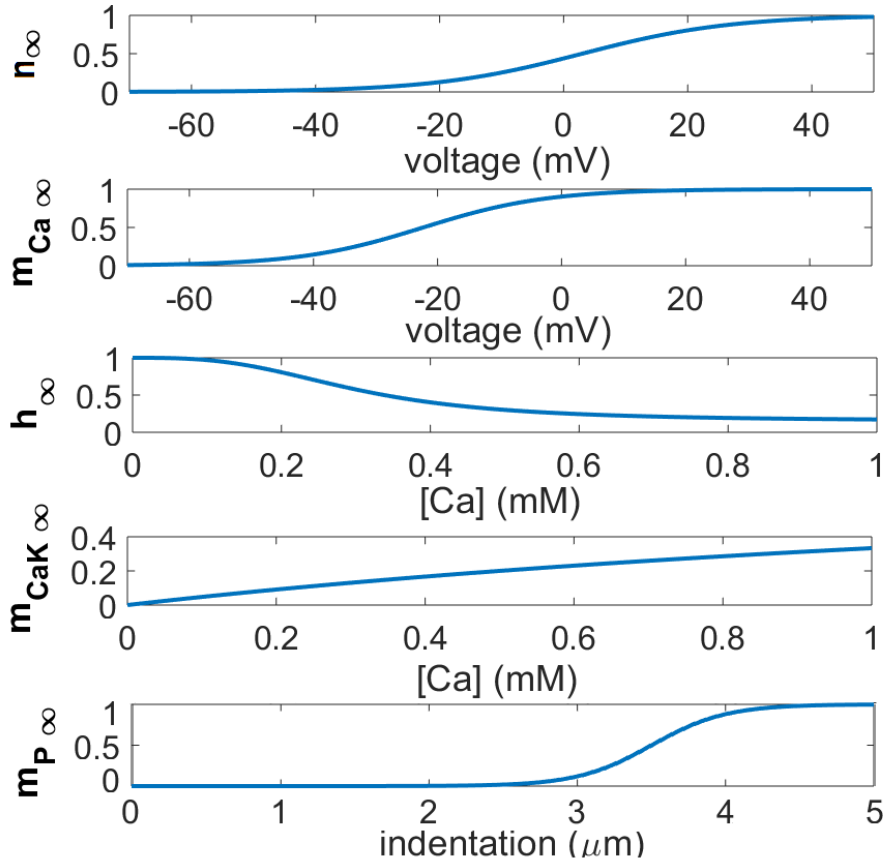
Figure 3: Plots of open probability associated with: the potassium channel as a function of voltage (Eq. 5), the calcium channel as a function of voltage (Eq. 10), the calcium inactivation as a function of internal calcium concentration (Eq. 13), the calcium-dependent potassium channel as a function of internal calcium concentration (Eq. 17), and the Piezo2 channel as a function of indentation (Eq. 19). The voltage-dependent equations are plotted for a span of -70 mV to 50 mV (Eqs. 5, 10); the internal calcium concentration-dependent equations are plotted for calcium concentrations of 0 mM to 1 mM (Eqs. 17, 13), and the indentation-dependent activation is plotted for a range of 0 μm to 5 μm (Eq. 19). $p(open)$ indicates the probability the given channel is open for a given input value. All ranges are seen in experiments.

3   Results

By solving Eq. 1 over time (in ms), we observe calcium spikes of similar wave form to those measured experimentally (Fig. 4) [10]. The calcium action potential reaches a peak of about 20 mV, has a duration of about 50 ms from its peak to its return to rest. The duration and amplitude of the spike were consistent with measurements of real Merkel cells [3, 10]. The gating variables m_{Ca} (Eq. 9), h_{Ca} (Eq. 12), m_{CaK} (Eq. 16), and n_K (Eq. 4), are governed by differential equations of the form $\frac{dx}{dt} = \frac{x_\infty - x}{\tau_x}$. Each of the activation variables

x_∞ are plotted in Fig. 3. The gating variables illustrate how calcium drives the voltage of the cell up quickly. Potassium is activated with an increase in voltage, contributing to the sharp initial peak and the slow shut down of the action potential, finally returning the cell to rest.
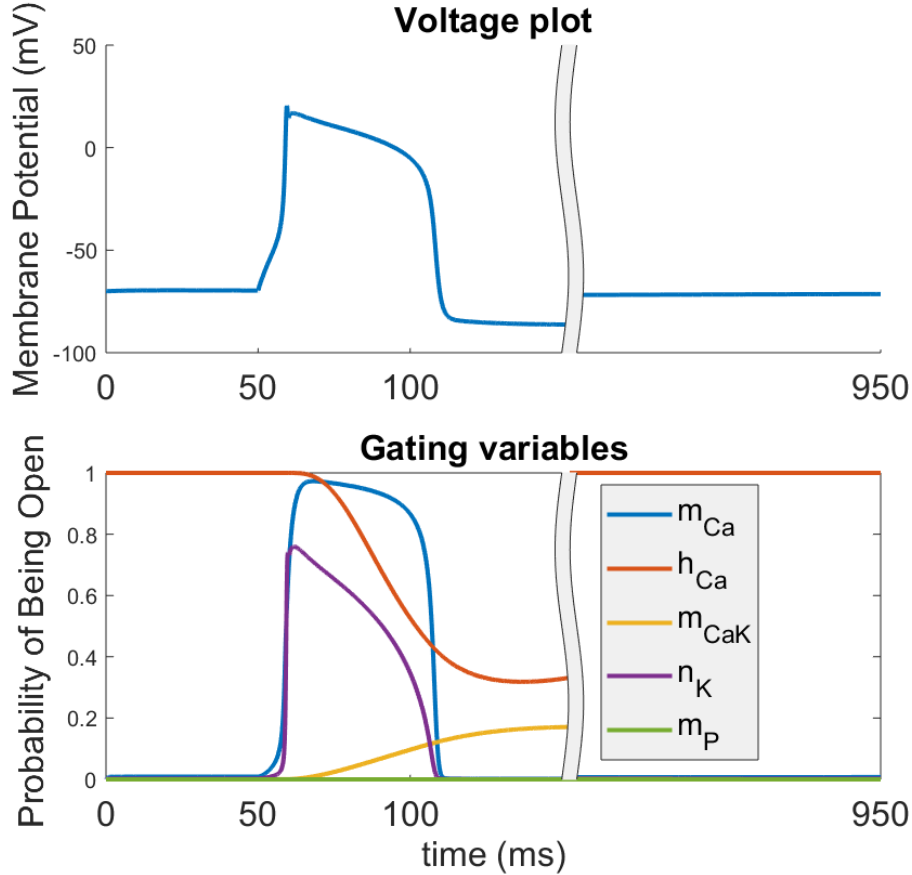

Figure 4: Single calcium-driven action potential and associated gating variables. The input drive was a constant 5 μA/cm^2 beginning at $t = 50$ ms. (top) The voltage trace of the resulting action potential. (bottom) The calcium activating gate m_{Ca} (Eq. 9), calcium inactivating gate h_{Ca} (Eq. 12), the calcium dependent potassium activation m_{CaK} (Eq. 16), and the potassium channel activating gate n_K (Eq. 4). Conductance g_P and indentation d are set to 0 to study the effect of an applied current.

The model's action potential responds to an injected current similarly to the experimental setup in Fig. 5a [10]. A step current was injected into the model as the I_{drive} parameter in Eq. 1; the applied current and resulting voltage trace in time are shown in Fig. 5b. The current is 0 μA/cm^2 until $t = 25$ ms, then instantly turns on to a given drive value, and stays constant until time $t = 75$ ms, where it shuts back off to 0 μA/cm^2. The values of I_{drive} are chosen over a range such that the cell does not reach a spike threshold at the lowest end of this range and spikes for higher values, so that ultimately the figure resembles the experiment [10]. At low levels of injected current ($I_{drive} < 1.6$ μA/cm^2), the Merkel cell does not fire an action potential. Similarly, in experimental recordings of a Merkel cell, for low levels of injected current (input current < 15 pA), the cell does not spike [10]. When the current is turned up higher, the cell does spike. This is an artifact of the

Hodgkin Huxley formulation, as it results in an all-or-nothing response; the strength of the cell's response does not depend on the strength of the input. Since the drive current is simply an added constant in Eq. 1, it adds to the rate at which the cell changes voltage. At low levels of input drive, once the cell has reached a threshold voltage of -55 mV, the voltage-dependent gating variables take over and the cell commences its action potential. Even when the current is turned off in the middle of the action potential, the action potential is not interrupted, unlike in the experimental recording (Fig. 5a, [10]). Even when I_{drive} is increased further in the model ($I_{drive} = 20$ μm/cm^2), turning off the drive current during the action potential does lead to a more dramatic decrease in voltage (as seen in Fig. 5b). Unlike in Fig. 5a, these changes in the step of applied current are not uniform.
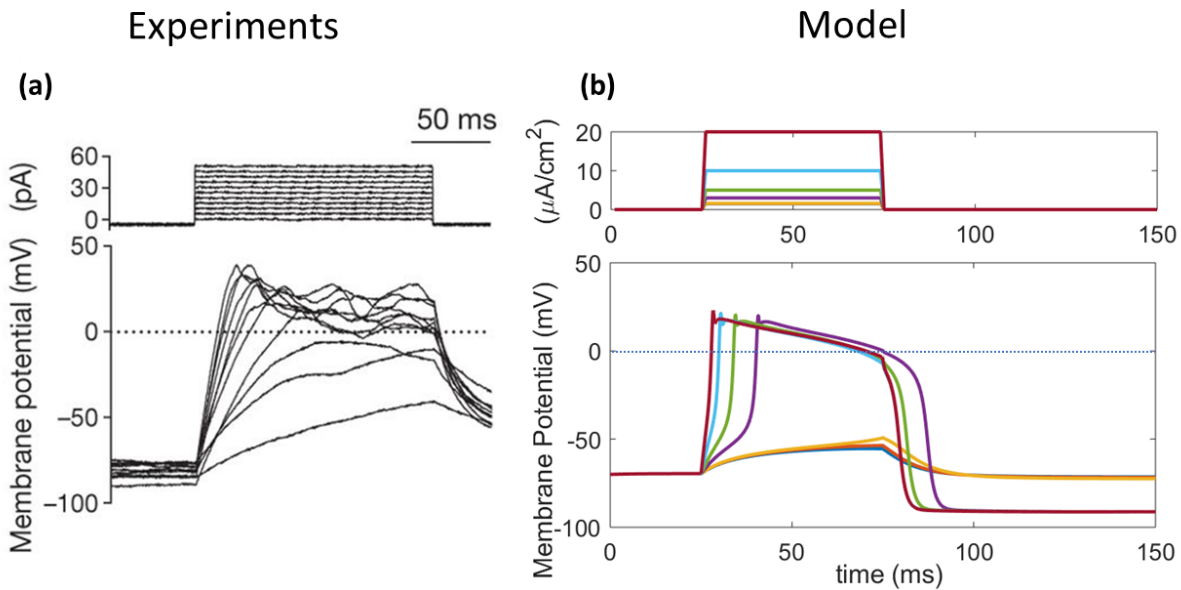

Figure 5: (a) Experimental measurements of a Merkel cell's membrane potential response to an applied electrical step current as measured in Woo et al., 2014 [10]. The applied current, in pA (top) and the Merkel cell's measured response (bottom) are recorded over a period of about 200 ms. (b) The model response to different magnitudes of step current. The current is applied for 50 ms, from $t = 25$ ms to $t = 75$ ms (top). The maximal conductance of the Piezo2 channel, g_P, is set to zero here, to observe only the response of the cell to a constant drive and no pressure (bottom). The mode cell reaches resting potential (-70 mV) on a timescale of hundreds of ms after firing (see Fig. 4).

In Fig. 5, the experimental measurements in literature [10] are noisier than the behavior exhibited by the model, as the model does not include any noise. Furthermore, once the cell's voltage passed a threshold of about -55 mV in the simulation, cutting out the external I_{drive} did not work to cease the activity of the action potential, unlike in the experimental response (Fig. 5a) [10]. This is due to the dependence of the action

potential on the gating variables, and the gating variables' strong response to the membrane potential and the internal calcium concentration.
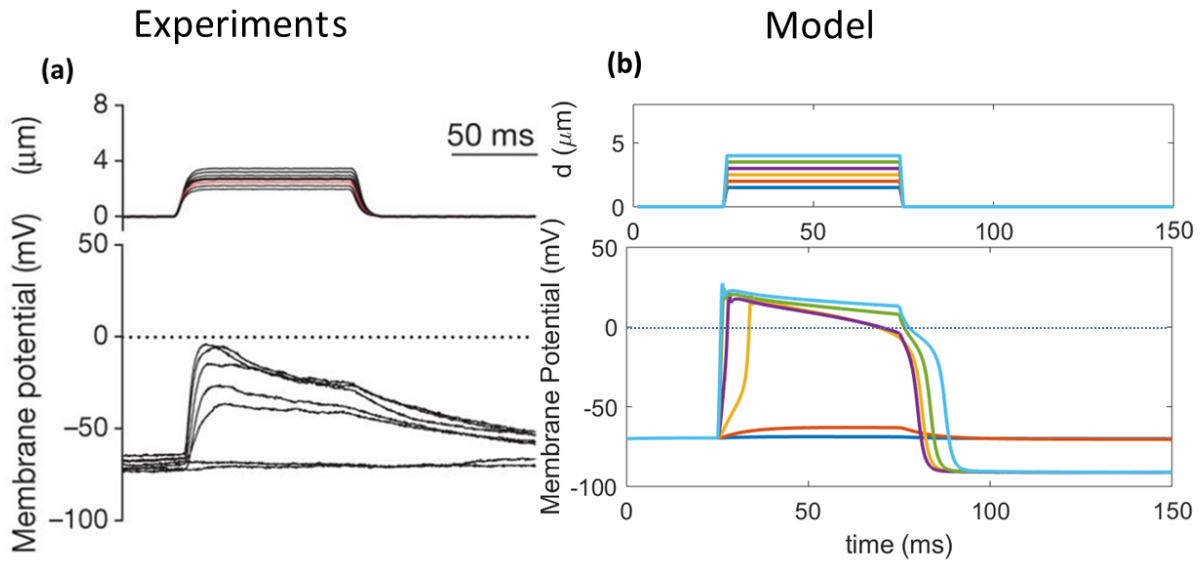

Figure 6: (a) The experimentally measured response of the Merkel cell (in mV, bottom panel) to a given indentation (in μm, top panel) [10]. (b) Comparable reactions of the model to input step current. The indentation d (Eq. 19), in μm, is plotted in the top panel; the corresponding current due to the Piezo channel term (Eq. 18 in the middle panel, and the resulting voltage trace, in mV, in the final panel. The indentation was set to 0 until 25 ms, then was on at a constant value for 50 ms, and turned back off to 0 at $t = 75$ ms.

Merkel cells' response to a constant indentation have also been measured experimentally [10]. In these experiments, a constant indentation of about 2 μm to 4 μm was applied to the cell for a time period of about 150 ms [10]. The cell did not fire at the two lowest values of this indentation (as seen in Fig. 6). Once the indentation magnitude passed the firing threshold of about -55 mV, the cells fired immediately when the indentation was applied [10]. When the applied force ceases, the cell's voltage slowly trails off (Fig. 6a), in contrast to the cell receiving an input current but no indentation (Fig. 5a).

To replicate the cell's response to indentation rather than an applied current, we create a Piezo2 channel term in the Hodgkin-Huxley format (Eqs. 19, 18). This term replaces I_{drive}, where an input of indentation (d) in μm takes the place of a constant drive. The I_{Piezo2} term takes this applied force and transforms it into an excitatory current similarly to how Piezo2 protein channels have been reported to behave in the cell [4, 10, 19, 20]. The values of d necessary to elicit spiking or non-spiking behavior in the model cell are similar to those of Woo et al., 2014 [10]. The model cell does not spike at values of $d < 2.5$ μm, as Eq. 19 is constructed such that Piezo2 channels have a probability of 0.5 to be open at $d = 2.5$ μm. The model cell does spike for higher values. Unlike in-vitro measurements, the model does not exhibit the trailing

voltage decay after the applied force was turned off. The model's action potential is on the same timescale as the experimental measures, and it either spikes or does not spike for similar values of d as measured experimentally.

4   Discussion and Future Work

In this project, I extend the Hodgkin Huxley model to encompass the electrophysiological behavior of a Merkel cell. In order to do this, the behavior of calcium in the cell must be incorporated in the Hodgkin Huxley system of equations. The calcium current depends on an activation variable, an inactivation variable, a conductance, and a calcium-dependent reversal potential. The calcium dynamics are pieced together from two different papers, where Patel et al., 2013 modeled a locust's antennal lobe and Felix-Martinez et al., 2015 studied the modeling of calcium current in the pancreas. The reversal potential is chosen to be calcium dependent because the ratio of calcium concentration outside the cell to the concentration inside the cell cannot be considered a constant [16, 17]. If it were to be considered constant, we would take $E_{Ca} = 140$ mV [15]. As seen in Fig. 2, the dynamic calcium reversal potential is siginficantly different from a constant excitatory potential.

The Piezo2 channel equations are chosen so that the membrane potential will respond in the same way as experiments. In Woo et al., 2014, the Merkel cell's response is measured in response to an indentation on a scale of about 2 μm to about 4 μm (see Fig. 6a)). Initially, the value of d where the probability of this channel being open is 0.5 is set to be $d = 2.5$. However, in order to elicit the pattern we see in literature using this midpoint, we must set g_P to be 0.08 mS/cm^2. As we can see in Table 1, maximal conductance values for other ion channels range from 3 mS/cm^2 to 5 mS/cm^2. Thus, to be more representative of physical ion channels, we choose $g_P = 3$ mS/cm^2 and shifted the activation variable to have a probability of being open of 0.5 at a value of $d = 3.5$ μm, so that we obtain the same qualitative response to indentation as experiments. After adjusting the slope factor so that the probability of the gate being open is zero at $d = 0$ μm, we are left with Eq. 19. The potassium reversal potential is also adjusted (Table 1) to be of the same order of magnitude as this current. The leak conductance g_L is chosen so that a cell at rest with no applied current or indentation will stay at rest, and the leak current reversal potential E_L is chosen to be -70 mV so that the leak current drives the voltage towards rest. The calcium-dependent conductance g_{CaK} is chosen to be of the same order of magnitude as the calcium conductance g_{Ca}. These values are chosen so that we see spiking behavior when we apply an appropriate input. In the calcium equations, k_{hL} is defined as the concentration of internal calcium at which the probability of the calcium inactivation gate $h_{Ca\infty}$ is 0.5 [16]. Based on this definition, the value of k_{hL} is chosen for our model using our own gating variable simulations. Finally, the Piezo2 channel reversal potential E_P is chosen as large and positive at 55 mV. This value signifies the Piezo2 current is driving the voltage up towards 55 mV and reflects the excitatory nature of the channel's behavior. There are several differences between the response of an action potential we obtain from the model as compared to an action potential measured in a Merkel cell. In Fig. 5, the model's response to an applied current with no activity from the Piezo2 channel is compared to experimental measures of a Merkel cell in response to an applied drive. Unlike in experiments, we are unable to obtain the trailing voltage trace once the applied current is turned

off; the gating variables driving the voltage trace are dependent on membrane potential, internal calcium concentration, or time. They are not dependent on the external applied drive, and thus the membrane potential does not react strongly to shutting off the drive. However, the length of the action potential is comparable to literature (about 50 ms, on the same order of magnitude as [10]). Furthermore, the amplitude and the shape of the action potential are similar to literature [10]. Finally, steepness of the slope in membrane potential increases as the magnitude of the input increases, as in [10].

We also compare our cell's response to indentation to the measured response in a Merkel cell in Fig. 6. Here we encounter two differences between the model and experiments. First, in experiments, the amplitude of the action potential increases as the magnitude of the indentation increases. We are unable to replicate this behavior in the model due to the formulation of the model. Hodgkin Huxley is an all-or-nothing model, and the magnitude of the response does not depend on the magnitude of the stimulus. The qualitative spiking/non-spiking behavior in the model is similar to that of experiments [10]. Second, unlike in experiments, the model does not exhibit the trailing voltage trace after the indentation is stopped. This is due to the way the calcium and potassium ion channels are described mathematically; their probabilities of opening and closing are dependent on voltage and calcium concentration. The calcium gating variable m_{Ca} timescale governs the duration of the action potential, and it is dependent only on membrane potential V, which is governed by the gating variables once it crosses the threshold. However, the length of the action potential as well as its general shape are similar as in [10].

In the future, we would like to address these limitations. First, we would like to see if adjusting the shape of the gating variables would change the shape of the action potential in response to a stimulus. For example, currently, the timescale of the action potential is almost entirely dependent on the calcium activation variable m_{Ca} (see Fig. 4). We hope that readjusting the gating variables so that the timescale is dependent on the intersect between m_{Ca}, h_{Ca}, and n_K, as in the neuronal Hodgkin Huxley model, rather than just on m_{Ca}, would create a more realistic description of the Merkel cell's behavior.

Furthermore, we know there are other processes influencing the membrane potential in the Merkel cell that we have not modeled. One such process is calcium-induced calcium release (CICR). We know that Merkel cells have internal stores of calcium in the cell. When calcium channels open and calcium flows into the cell, the cell releases these stores to increase the internal calcium concentration [11]. The purpose of this mechanism in the Merkel cell is unclear; some hypothesize that it is meant to amplify the magnitude of the Merkel cell's response, or that it is used to trigger the release of neurotransmitter to communicate with the afferent neuron [11]. We hope that by including it in our model, we could provide evidence for one of these theories.

We also hope to investigate the coupling between the Merkel cell and the afferent neuron. From past works, we know that Merkel cells release neurotransmitters to the afferent neurons to communicate [3–5, 7]. We hope that by modeling the afferent neuron and its connection to the Merkel cell, we can learn something about how these cells communicate.

5 Acknowledgements

References

[1] Seung-Hyun Woo, Ellen A Lumpkin, and Ardem Patapoutian. Merkel cells and neurons keep in touch. *Trends in cell biology*, 25(2):74–81, 2015.

[2] Stephen M Maricich, Kristin M Morrison, Erin L Mathes, and Brittany M Brewer. Rodents rely on merkel cells for texture discrimination tasks. *Journal of Neuroscience*, 32(10):3296–3300, 2012.

[3] Ryo Ikeda, Myeounghoon Cha, Jennifer Ling, Zhanfeng Jia, Dennis Coyle, and Jianguo G Gu. Merkel cells transduce and encode tactile stimuli to drive aβ-afferent impulses. *Cell*, 157(3):664–675, 2014.

[4] Masashi Nakatani, Srdjan Maksimovic, Yoshichika Baba, and Ellen A Lumpkin. Mechanotransduction in epidermal merkel cells. *Pflügers Archiv-European Journal of Physiology*, 467(1):101–108, 2015.

[5] Qiufu Ma. Merkel cells are a touchy subject. *Cell*, 157(3):531–533, 2014.

[6] Yi Dong, Stefan Mihalas, Sung Soo Kim, Takashi Yoshioka, Sliman Bensmaia, and Ernst Niebur. A simple model of mechanotransduction in primate glabrous skin. *Journal of neurophysiology*, 109(5):1350–1359, 2012.

[7] Srdjan Maksimovic, Masashi Nakatani, Yoshichika Baba, Aislyn M Nelson, Kara L Marshall, Scott A Wellnitz, Pervez Firozi, Seung-Hyun Woo, Sanjeev Ranade, Ardem Patapoutian, et al. Epidermal merkel cells are mechanosensory cells that tune mammalian touch receptors. *Nature*, 509(7502):617, 2014.

[8] Bertrand Coste, Bailong Xiao, Jose S Santos, Ruhma Syeda, Jörg Grandl, Kathryn S Spencer, Sung Eun Kim, Manuela Schmidt, Jayanti Mathur, Adrienne E Dubin, et al. Piezo proteins are pore-forming subunits of mechanically activated channels. *Nature*, 483(7388):176, 2012.

[9] Charles D Cox, Chilman Bae, Lynn Ziegler, Silas Hartley, Vesna Nikolova-Krstevski, Paul R Rohde, Chai-Ann Ng, Frederick Sachs, Philip A Gottlieb, and Boris Martinac. Removal of the mechanoprotective influence of the cytoskeleton reveals piezo1 is gated by bilayer tension. *Nature communications*, 7:10366, 2016.

[10] Seung-Hyun Woo, Sanjeev Ranade, Andy D Weyer, Adrienne E Dubin, Yoshichika Baba, Zhaozhu Qiu, Matt Petrus, Takashi Miyamoto, Kritika Reddy, Ellen A Lumpkin, et al. Piezo2 is required for merkel-cell mechanotransduction. *Nature*, 509(7502):622, 2014.

[11] Rebecca Piskorowski, Henry Haeberle, Mayuri V Panditrao, and Ellen A Lumpkin. Voltage-activated ion channels and ca 2+-induced ca 2+ release shape ca 2+ signaling in merkel cells. *Pflügers Archiv-European Journal of Physiology*, 457(1):197, 2008.

[12] RN Miftakhov and DL Wingate. Electrical activity of the sensory afferent pathway in the enteric nervous system. *Biological cybernetics*, 75(6):471–483, 1996.

[13] Sung Soo Kim, Arun P Sripati, and Sliman J Bensmaia. Predicting the timing of spikes evoked by tactile stimulation of the hand. *Journal of neurophysiology*, 104(3):1484–1496, 2010.

[14] Gregory J Gerling, Lingtian Wan, Benjamin U Hoffman, Yuxiang Wang, and Ellen A Lumpkin. Computation predicts rapidly adapting mechanotransduction currents cannot account for tactile encoding in merkel cell-neurite complexes. *PLoS computational biology*, 14(6):e1006264, 2018.

[15] Mainak J Patel, Aaditya V Rangan, and David Cai. Coding of odors by temporal binding within a model network of the locust antennal lobe. *Frontiers in computational neuroscience*, 7:50, 2013.

[16] Gerardo J Félix-Martínez and J Rafael Godínez-Fernández. Modeling ca2+ currents and buffered diffusion of ca2+ in human β-cells during voltage clamp experiments. *Mathematical biosciences*, 270:66–80, 2015.

[17] G Bard Ermentrout and David H Terman. *Mathematical foundations of neuroscience*, volume 35. Springer Science & Business Media, 2010.

[18] Wulfram Gerstner and Werner M Kistler. *Spiking neuron models: Single neurons, populations, plasticity*. Cambridge university press, 2002.

[19] Mirko Moroni, M Rocio Servin-Vences, Raluca Fleischer, Oscar Sánchez-Carranza, and Gary R Lewin. Voltage gating of mechanosensitive piezo channels. *Nature communications*, 9(1):1096, 2018.

[20] Kyung Chul Shin, Hyun Ji Park, Jae Gon Kim, In Hwa Lee, Hawon Cho, Chanjae Park, Tae Sik Sung, Sang Don Koh, Sang Woong Park, and Young Min Bae. The piezo2 ion channel is mechanically activated by low-threshold positive pressure. *Scientific reports*, 9(1):6446, 2019.
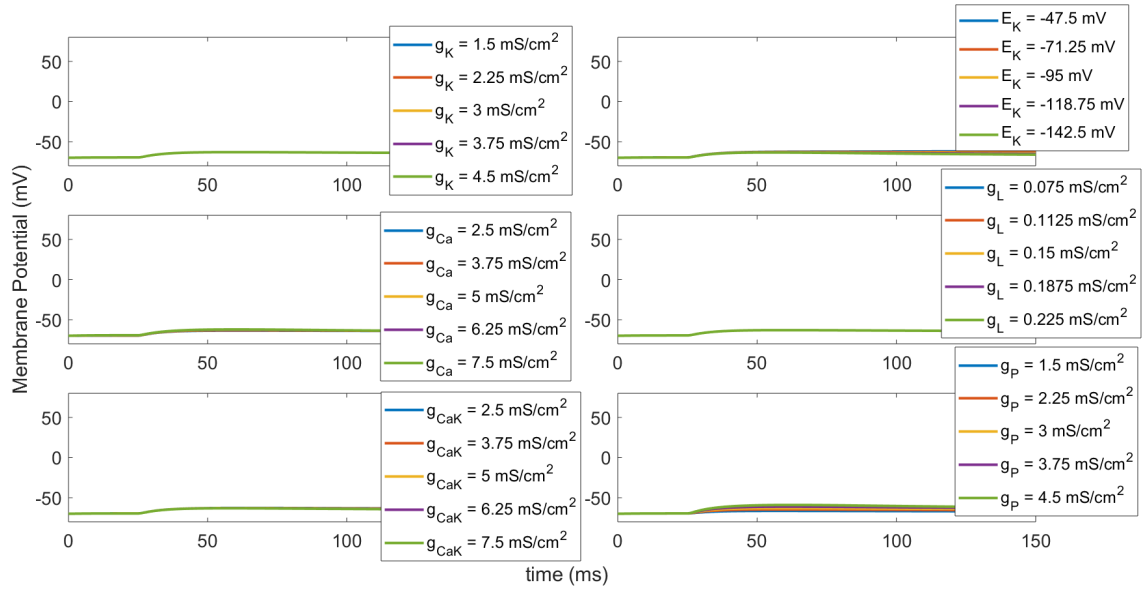
6   Supplementary Information

Figure S1: These figures are used to study the pre-threshold behavior of the Merkel cell model by modifying reversal potential and conductance values by 25 and 50 percent. An indentation of 2μm is applied at $t = 25$ ms and is constant until the end of the simulation. Unless modified for that plot, all parameter values are as in Table 1.
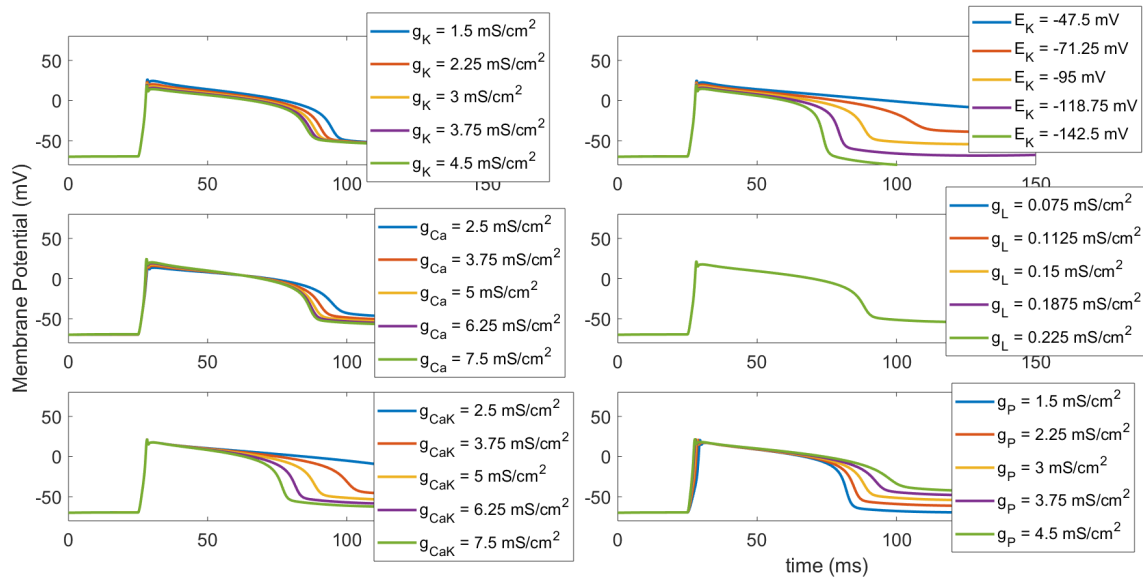

Figure S2: These figures are used to study the spiking behavior of the Merkel cell model by modifying reversal potential and conductance values by 25 and 50 percent. An indentation of 3μm is applied at $t = 25$ ms and is constant until the end of the simulation. Unless modified for that plot, all parameter values are as in Table 1.
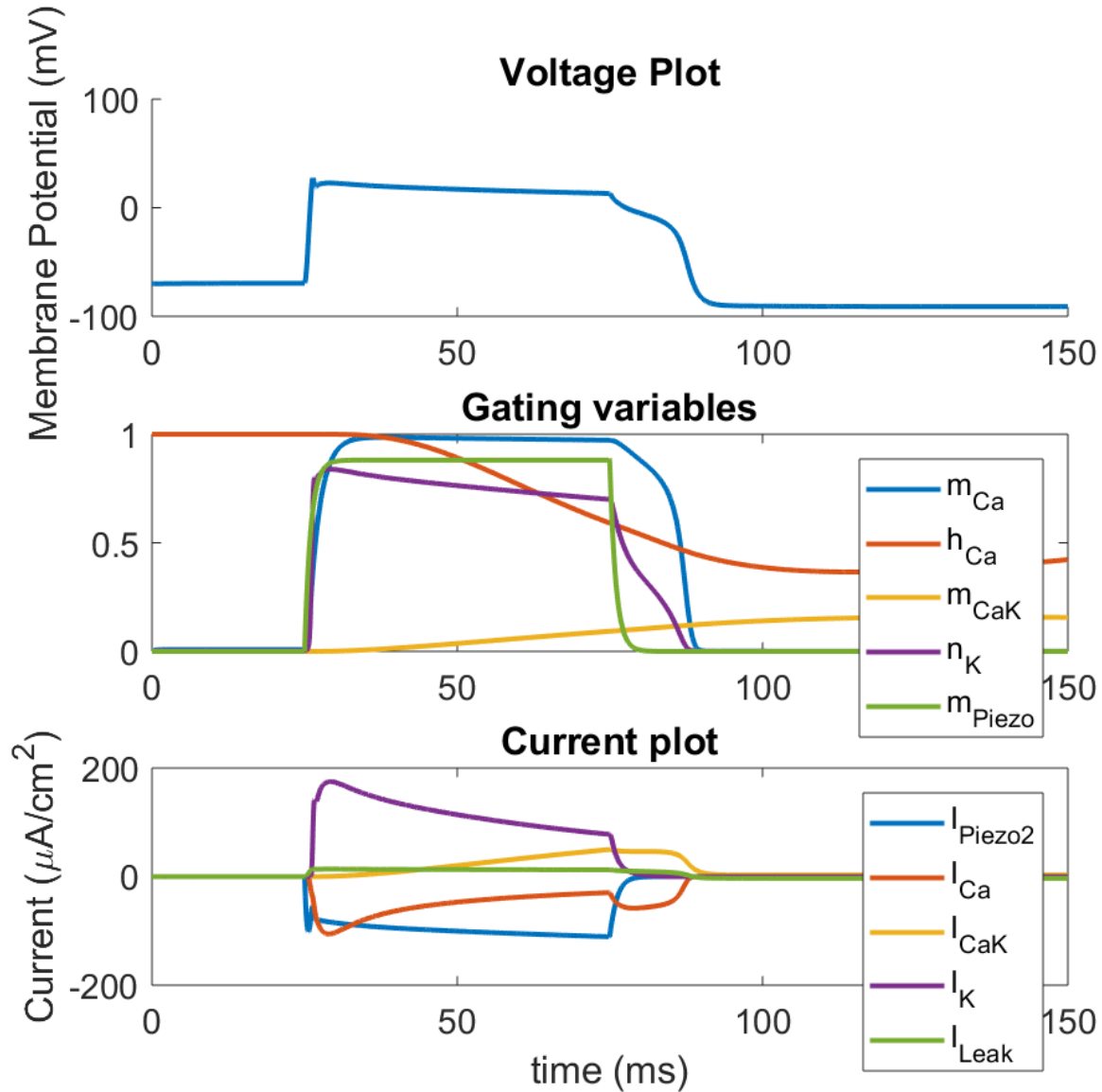
Figure S3: (top) a voltage trace of a Merkel cell from our model. The conductance g_P is chosen to be 3mS/cm^2. An indentation of 4μm is applied at 25 ms, and is constant until 75 ms. The voltage trace after the indentation is removed is convex because an indentation creates a current on an order of magnitude of -100mS/cm^2, which is much higher than any applied current and overloads the cell. Thus when the indentation is removed, the cell's voltage trace follows the given path as the membrane potential is still high. (middle) The gating variables for this plot. The m_{Piezo} variable trace follows the shape of the applied indentation. (bottom) Each ion channel current. The potassium currents are positive, which drives down the voltage (since the membrane potential is a subtraction of currents), and the calcium and Piezo2 currents are negative, indicating a positive effect on the voltage. These currents are investigated to check that they are of the same order of magnitude, or are balanced in the cell.