Bidomain model of action potential propagation, extracellular fields, and cardiac defibrillation

Niels F. Otani
Department of Biomedical Engineering
Case Western Reserve University, Cleveland, OH 44106

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1 Introduction and Motivation

In the past few years, in your pursuit of the biomedical engineering degree, you have learned many different concepts from many different areas: math, physics, electrical engineering, computer science, signals and systems, physiology and biophysics, and biomedical instrumentation, among many others. You may have wondered why you have had to learn these things. One answer is that engineering projects often require knowledge from many of these diverse areas of learning simultaneously. This is particularly true of biomedical engineering, a field which is, by nature, interdisciplinary. Another answer is that, although your current training is in some specialty area within biomedical engineering, this may not be the engineering field you will end up in. You never know where your career journey will take you, and what knowledge will turn out to be critical to your job. To prepare you for these possibilities, we have provided you with a broad spectrum of knowledge, which we believe will hold you in good stead no matter what form of engineering your career requires.

As an example of how knowledge from the many different fields you have learned about can be brought together, for the final project for this course (EBME 309/359), we will be constructing a model of action potential propagation in the heart, which includes the effects of, and the effects on, the surrounding extracellular electrical field. Once constructed, this model should be a lot of fun to play with, allowing you to examine the basics of (1) how EKGs are produced, (2) how certain types of ventricular tachycardia and fibrillation are thought to occur, and (3) how the process of cardiac defibrillation works.

While we will concentrate on *cardiac* bioelectric applications, much of what we discuss here is applicable to the electrical field associated with any excitable tissue, including the nervous system and the brain, and skeletal muscle. The techniques you will be learning in constructing this simulation model enjoy even wider applicability—they appear in the development of all sorts of computer simulation models, from weather prediction models, to air flow over wings, to spacecraft orbital dynamics, to bridge and building structural analysis. The common thread is that all of these topics involve the simulation of sets of nonlinear ordinary or partial differential equations. While specific types of equations have specific

tools, they all share a number of common features, which have, in turn, led to common considerations when designing simulation methods for these equations. These include: how to choose the discretization method (that is, how large a timestep should be used in pushing the simulation forwards in time; how fine a simulation spatial grid should be used? How should the simulation code be structured–what sorts of functions should be defined; how should outputting of the data be handled? And so on.) So, by constructing this cardiac bioelectric model, you will be learning skills that have a multitude of applications, which hopefully will be useful to you whether or not your main interests currently lie bioelectric phenomena.

2 Development of the equations in one spatial dimension

The key to the creation of our model of the electrical heart is the formulation of the equations. This may be scary thought—the develoment of the equations defining a system is thought of by many as being the first step in a journey which ultimately leads to a monstrosity whose behavior is a total mystery not understood by anyone. In fact, with a little care, the equations governing the system under study can be thought of almost as a table of contents for the system, specifying exactly which physical effects are present in the system, and how they interact. Furthermore, not only are the equations important in developing an understanding of the system of interest, but so is the derivation of the equations. It is the derivation that often provides the connection between the individual terms appearing in the equations and the physical effects they represent.

So, let's look a simple representation of the system we would like to model, and see how it can be converted in a set of equations. Along the way, let's see if we can develop an understanding for the behavior of the model that the derivation of the equations is supposed to produce.

We begin by representing our excitable tissue as a series of biological cells. These cells are connected to each other electrically by means of gap junctions (for the case of cardiac cells). Each cell also can communicate with the outside world, which we will call the extracellular space. This can happen in two ways: through the capacitance of the cell membrane, and through ion channels, which are embedded in the cell membrane. A simple drawing of this situation (Figure 1) shows that the description to this point looks like the beginnings of an electrical circuit. In the Figure, we represent the gap junctions as resistors, because, to a good approximation, that is how they behave. In contrast, the behavior of the ion channels is quite complex and nonlinear, so we just represent them as little boxes, with the understanding that something very complicated is going on inside.

Because the extracellular space is also a resistive medium, it too can be represented as a series of resistors. The values of these extracellular resistors are often thought of as being lower than their gap junction counterparts, because generally current has less trouble flowing in the continuous extracellular space than it does through the narrow confines of gap junctions.

Finally, we would like to be able to stimulate our model, both by inserting electrodes

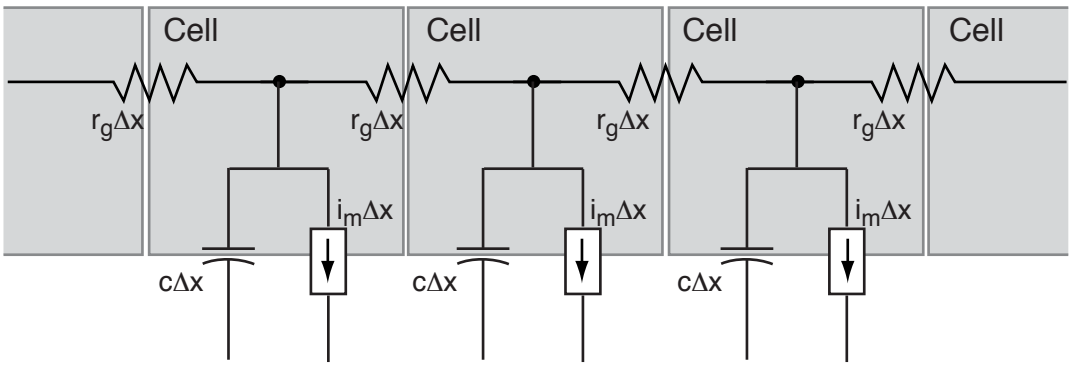

Figure 1: Partial circuit representation of a series of excitable cells.

inside the cells (intracellular stimulation) or by placing the electrodes in the extracellular space (extracellular stimulation). The addition of these components is reflected in the circuit shown in Figure 2.

With the circuit complete, our next task is to assign values to the main components. The main complication here is that we generally do not think about values of individual gap junctions; rather we think of what the resistance of a whole chain of gap junctions is. The natural quantity, given this mode of thinking, is the resistance due to gap junctions *per unit length* along the chain. The units for this quantity would then be, for example, ohms/cm. We can then figure out what the resistance is for any length chain. In particular, we can determine the value of an individual gap junction connection by multiplying this resistance per unit length times the length of an individual cell. Calling this resistance per unit length r_g and the length of a cell in the x-direction Δx, this means the value of each gap junction resistor is $r_g \Delta x$.

Similar arguments can be made for many of the other quantities. The membrane capacitance for an individual cell, for example, is $c\Delta x$, where c is the capacitance of the membrane per unit length. If the current flowing through the ion channels per unit length is i_m, then the ion channel current flowing out of an individual cell is $i_m \Delta x$. Finally, if the extracellular resistance per unit length for current flowing in the x direction is r_e, then the value of the resistors representing this resistive extracellular medium is $r_e \Delta x$.

As long as we are thinking of the various cells as being Δx in length, we may as well establish an entire coordinate system in the x direction, so that we can refer to the center of a given cell as being located at position x, the location of its neighbor as being at $x + \Delta x$, the location of the neighbor on the other side as $x - \Delta x$, etc. We can then refer to the various nodal voltages by where they are located: the potential inside the cell located at position x will be referred to as $\Phi_i(x)$; the corresponding potential outside that cell will be $\Phi_e(x)$, etc. $\Phi_i(x)$ and $\Phi_e(x)$ are then the intracellular and extracellular potentials, respectively as functions of x.

We can even label the resistors and other components this way, if they vary as functions of x. The gap junction resistor between the cells located at x and $x + \Delta x$ would then have resistance $r_g(x + \Delta x/2)\Delta x$, etc.

With our circuit defined and the components labeled, the next step is simply to apply circuit analysis techniques, using methods that you are already familiar with from ENGR

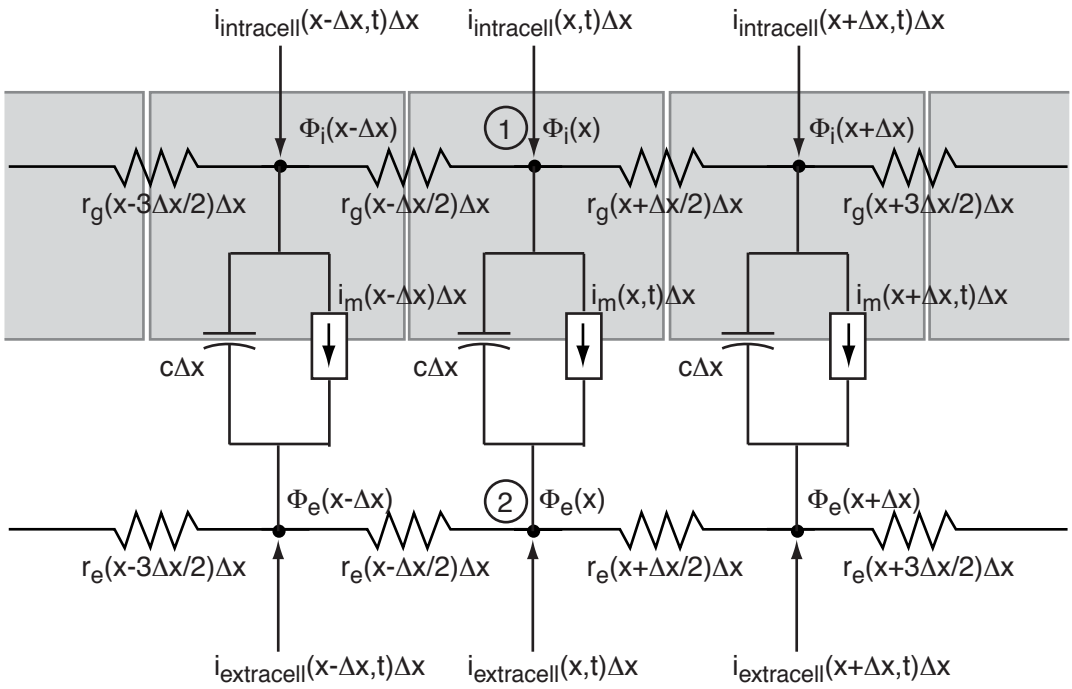

Figure 2: Complete circuit representation of a series of excitable cells, including the extracellular space and intracellular and extracellular stimulation.

210. Let's look at the node labeled "1" in Fig. 2. Kirchhoff's current law (KCL) says that the total current leaving this node, through all branches, must sum to zero. Looking at these currents one by one...

(1) The current leaving through the gap junction resistor on the left of node "1" is, from Ohm's law,

$$\frac{\Phi_i(x) - \Phi_i(x - \Delta x)}{r_g(x - \Delta x/2)\Delta x}$$

(2) Similarly, the current leaving through the gap junction on the right is,

$$\frac{\Phi_i(x) - \Phi_i(x + \Delta x)}{r_g(x + \Delta x/2)\Delta x}$$

(3) The current flowing away through the capacitor is given by $C(dV/dt)$, where C is the capacitance, and V is the voltage drop across the capacitor. Filling in our values, the current through the capacitor is,

$$c\Delta x \frac{\partial}{\partial t}\left(\Phi_i(x) - \Phi_e(x)\right)$$

(4) With the polarity for i_m shown in Fig. 2, the current flowing away from node "1" is $i_m(x)\Delta x$.

(5) Similarly, for the polarity of the intracellular stimulation current shown in Fig. 2, the stimulus current is, $-i_{intracell}(x)\Delta x$.

In these expressions, Φ_i, Φ_e, i_m, $i_{intracell}$ and $i_{extracell}$ all depend on the time t as well as on x; I've left out the dependence on t for the sake of brevity.

We can simplify the derivation by assuming the gap junction resistances are all the same, so that $r_g(x - \Delta x/2) = r_g(x + \Delta x/2) = r_g$, a constant. (Allowing r_g to be dependent on x was a homework problem.) Putting it all together, we have,

$$c\frac{\partial}{\partial t}\left(\Phi_i(x) - \Phi_e(x)\right) + i_{m(x)} + \frac{\Phi_i(x) - \Phi_i(x - \Delta x)}{r_g \Delta x^2} + \frac{\Phi_i(x) - \Phi_i(x + \Delta x)}{r_g \Delta x^2} - i_{intracell}(x) = 0$$

where we have divided through by one factor of Δx.

Let's look at the two gap junction terms for a moment. If the cell size Δx is small, we can use a Taylor expansion to simplify the expression:

$$\begin{aligned}\frac{\Phi_i(x) - \Phi_i(x - \Delta x)}{r_g \Delta x^2} + \frac{\Phi_i(x) - \Phi_i(x + \Delta x)}{r_g \Delta x^2} = \\ \frac{\Phi_i(x) - \Phi_i(x) + \frac{\partial \Phi_i}{\partial x}(x)\Delta x - \frac{\partial^2 \Phi_i}{\partial x^2}(x)\frac{\Delta x^2}{2} + \frac{\partial^3 \Phi_i}{\partial x^3}(x)\frac{\Delta x^3}{6} + O(\Delta x^4)}{r_g \Delta x^2} \\ + \frac{\Phi_i(x) - \Phi_i(x) - \frac{\partial \Phi_i}{\partial x}(x)\Delta x - \frac{\partial^2 \Phi_i}{\partial x^2}(x)\frac{\Delta x^2}{2} - \frac{\partial^3 \Phi_i}{\partial x^3}(x)\frac{\Delta x^3}{6} + O(\Delta x^4)}{r_g \Delta x^2} \\ = -\frac{1}{r_g}\frac{\partial^2 \Phi_i}{\partial x^2}(x) + O(\Delta x^4)\end{aligned}$$

Thus, for small cell size Δx, the two gap junction terms reduce down to a second derivative of Φ_i with respect to x.

We also notice that the quantity $\Phi_i(x) - \Phi_e(x)$ is just the membrane potential $V_m(x)$—the difference in potential between the inside and outside of the cell, the potential drop across the cell membrane. Making these two substitutions,

$$c\frac{\partial V_m}{\partial t}(x,t) + i_m(x,t) - \frac{1}{r_g}\frac{\partial^2 \Phi_i}{\partial x^2}(x,t) - i_{intracell}(x,t) = 0 \tag{1}$$

A derivation of the equation for node "2" is almost identical to the calculation just performed. In fact, if you just flip Figure 2 upside down, then you get that node "2" is where node "1" used to be, $r_e \to r_g$, $i_{extracell} \to i_{intracell}$, $\Phi_e \to \Phi_i$, and the sense of flow of i_m is up instead of down. It follows that, if we make these same substitutions into the equation for node "1", it will give the equation for node "2". So, making these substitutions into Eq. (1), we have,

$$c\frac{\partial(-V_m)}{\partial t}(x,t) - i_m(x,t) - \frac{1}{r_e}\frac{\partial^2 \Phi_e}{\partial x^2}(x,t) - i_{extracell}(x,t) = 0 \tag{2}$$

Or, if you don't believe this little sleight of hand, you can simply apply Kirchhoff's current law to node "2", just as we just did for node "1.".

A useful form of Eq. (1) can be produced by substituting $\Phi_i = V_m + \Phi_e$:

$$\frac{\partial V_m}{\partial t} = -\frac{i_m}{c} + D_g \frac{\partial^2 V_m}{\partial x^2} + D_g \frac{\partial^2 \Phi_e}{\partial x^2} + \frac{i_{intracell}}{c} \tag{3}$$

Here, we define $D_g = 1/(r_g c)$. Similarly, a useful form for Eq. (2) can be constructed by substituting for $c(\partial V_m/\partial t) + i_m$ from Eq. (1) to obtain,

$$(D_e + D_g)\frac{\partial^2 \Phi_e}{\partial x^2} = -D_g \frac{\partial^2 V_m}{\partial x^2} - \frac{i_{intracell}}{c} - \frac{i_{extracell}}{c} \tag{4}$$

where $D_e = 1/(r_e c)$. Another useful form of Eq. (2) comes from simply defining $j_m = c(\partial V_m/\partial t) + i_m$ and substituting it...

$$D_e \frac{\partial^2 \Phi_e}{\partial x^2} = -\frac{j_m}{c} - \frac{i_{extracell}}{c} \tag{5}$$

Notice that j_m, defined as it is, is just the current per unit length flowing through the ion channels and the membrane capacitance from the inside of cells to the extracellular space.

Equations (3) and (4) are often referred to as the *cable equations*. They are essentially a one-dimensional description of action potential propagation and the surrounding extracellular fields.

3 Interpretation of the cable equations

Now let's discuss why Eqs. (3–5) are useful expressions. They are useful because of what they tell us about how the system operates. These equations are a perfect example of a fundamental principle of physics and engineering—that "mathematics is a language." These equations are trying to *tell* us something. This, in fact, is one of the main uses of system equations. It is a myth that the only reason system equations are derived is so that they can be solved. Quite to the contrary, you can extract a lot of useful information from the system equations *without* solving them. Once we have discovered as much as we can from the equations through this approach, only then do we conduct simulations of the equations. Even here, the purpose of simulations is often misstated. We run simulations mainly to provide us with additional clues helpful for the further interpretation of the equations; in other words, we run computer simulations to aid us in trying to understand how the system works. So again, the main purpose for running simulations is generally not simply to find the solution to the equations. Running a simulation without interpreting the results gives you a solution for only the one set of parameters for which the simulation was run—not generally very useful. Interpretation of the results in the context of what the equations are trying to tell us allows us to understand how the observed behavior of the system depends on the parameters, which in turn allows us to predict how the system behavior changes as the parameters are changed, a much more useful outcome.

Let's see if we can see this technique in action. It is often the case that each of the terms in the system equations corresponds one-to-one to the various effects possible in the system.

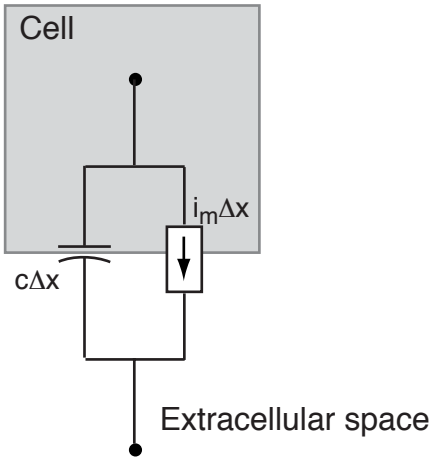

Figure 3: Circuit corresponding to the equation, $c(\partial V_m/\partial t) = -i_m$

Because of this, it is often useful to look at only a few of the terms present in a equation at a time. In Eq. (3), for example, let's first just consider this subset of the full equation:

$$\frac{\partial V_m}{\partial t} = -\frac{i_m}{c} \tag{6}$$

This portion of the equation is simply telling us that the membrane, thought of as a capacitor, can be charged through the action of current i_m flowing through the ion channels. If you look back to where these two terms come from, they originated from the two components of the circuit shown in Fig. 3.

We have already seen a simple example of Eq. (6). If we choose for the definition of the ion channel current the following:

$$-\frac{i_m}{c} = \frac{1}{\epsilon}\left(V_m - \frac{V_m^3}{3} - W\right) \tag{7}$$

where W is governed by the equation,

$$\frac{\partial W}{\partial t} = \epsilon(V_m - \gamma W + \beta) \tag{8}$$

we have that Eq. (6), together with Eqs. (7) and (8), is none other than the Fitzhugh-Nagumo equations, which we have already studied previously.

More generally, the two terms in Eq. (6) are expressing the excitability of each cell. Once one of the other terms in Eq. (3) raises the membrane potential above a threshold value, we know that the term i_m (that is, the excitability of the ion channels), will kick into action, firing the cell. The mechanism by which this happens is described Eq. (6). Once the membrane potential is raised above the threshold defined by the internal workings of i_m (that is, the ion channels, Eqs. (7) and (8)), a large negative current i_m is generated which, as we see from Eq. (3) or (6) will contribute positively to $\partial V_m/\partial t$, thus rapidly raising the membrane potential V_m, firing the cell.

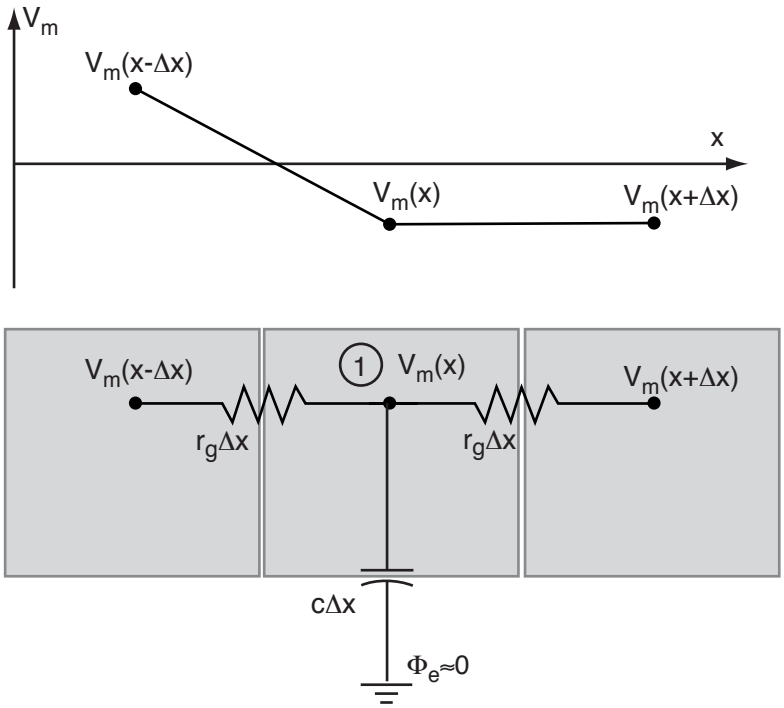

Figure 4: Circuit corresponding to the equation, $\partial V_m/\partial t = D_g(\partial^2 V_m/\partial x^2)$

Let's next try looking at these two terms from Eq. (3):

$$\frac{\partial V_m}{\partial t} = D_g \frac{\partial^2 V_m}{\partial x^2} \tag{9}$$

Looking back at where these two terms came from, we find that the two resistors and the membrane capacitance are responsible. We therefore obtain the equivalent circuit shown in Fig. 4. One complication is that, strictly speaking, the potentials on the intracellular nodes should be $\Phi_i(x-\Delta x)$, $\Phi_i(x)$ and $\Phi_i(x+\Delta x)$ (see Fig. 2), not $V_m(x-\Delta x)$, $V_m(x)$ and $V_m(x+\Delta x)$ as shown in Fig. 4. This complication is produced by our desire to express this equation in terms of the variables we are interested in, Φ_e and V_m (rather than Φ_e and Φ_i). A convenient way to look at this situation is to think of Φ_e as being small, which is often the case. The reason is that the extracellular resistance is often small, so, by Ohm's law, the potential differences are bound to be small also. So here's what we can do. We can first assume that the extracellular potential Φ_e is so small we can think of it as being zero. If this is the case, then V_m, which is defined to be the difference in potentials $\Phi_i - \Phi_e$ is now simply Φ_i, so the potentials shown on the intracellular nodes in Fig. 4 are now correct. Similarly, if the extracellular potential is zero, then the entire extracellular space is at electrical ground, as shown in the Figure. Of course, Φ_e is not actually zero, so this explanation is not strictly correct. We need to add correction terms to fix things. That correction term is the $D_g(\partial^2\Phi_e/\partial x^2)$ in Eq. (3).

Now back to Eq. (9). What Eq. (9) is telling us is that the membrane potential V_m will increase as function of time when the V_m is a concave up function (second derivative is positive) as a function of space. Let's see if this makes sense. Suppose that some particular

time, the membrane potentials on three adjacent cells are arranged as in the graph in Fig. 4. What will happen? Well, current will want to flow from the node located at $x - \Delta x$ to the node located at x, because the potential is higher at the former than it is at the latter. In contrast, very little current will want to flow out of the node located at x to the node on its right, because the potentials at these two nodes are nearly equal. So current is flowing into node "1" from the left, but little is leaving to the right. So where must that excess current flow? Down into the capacitor, of course, which will result in charging of the capacitor, which raises the potential $V_m(x)$ across it. Notice now that the profile of the membrane potential in the graph in Fig. (4) is concave up. And further, notice that this upward concavity immediately implies that more current must be flowing in from the left than is leaving from the right. In fact, you can see pretty easily that the capacitor connected to node "1" will continue to charge until the potential $V_m(x)$ forms a straight line with $V_m(x - \Delta x)$ and $V_m(x + \Delta x)$. Only then will the current flowing from the left equal the current flowing to the right.

Equation (9) is actually pretty common. Suppose, for example that the cells in Fig. 4 are townhouses instead, and the graph represents the temperatures in the houses. If you're living in the middle house, the temperature in the house to your left is higher than your temperature, but temperature in the neighbor's house on the right is about the same. What is going to happen to your temperature? Of course, your temperature will go up, since heat will be flowing down the temperature gradient from your neighbor on your left, there will be no heat exchange with your right-hand neighbor, since your temperatures are the same. As another example assume that we are talking about the concentration of some chemical instead of temperatures or potentials. If the concentration on one side is higher, while the concentration on the other side is about the same, then what is going to happen to your concentration?... So not surprisingly, Eq. (9) is used for both of these situations. It is called the "heat equation" when describing temperature and D_g is called the thermal conductivity. It is called the "diffusion equation" when describing concentrations, and then D_g is called the diffusion coefficient. In fact, the "D" in D_g stands for diffusion. In our system, it is the membrane potential that "diffuses."

Now let's look at all three of these terms together:

$$\frac{\partial V_m}{\partial t} = -\frac{i_m}{c} + D_g \frac{\partial^2 V_m}{\partial x^2} \tag{10}$$

These three terms are enough to describe action potential propagation. In fact, when we are only concerned with the membrane potential V_m and are willing to ignore the effects of the extracelluar potential Φ_e, we often just model Eq. (10) and dump the other equations. Equation (10) is sometimes called the *monodomain* equation, since it involves principally the intracellular domain only.

So let's see how these equations produce action potential propagation. Suppose that, in the graph in Fig. 4, the membrane potential $V_m(x - \Delta x)$ is the top of the leading edge of an action potential, approaching from the left. What happens at node "1"? At first, diffusion is the dominant mechanism. Current flowing from the action potential on the left flows into the node "1" cell, charging its membrane. However, when the threshold potential is reached through this charging process, the cell fires through the action of its ion channels (the i_m component). The peak potential is reached very quickly through this process. Node "1" is

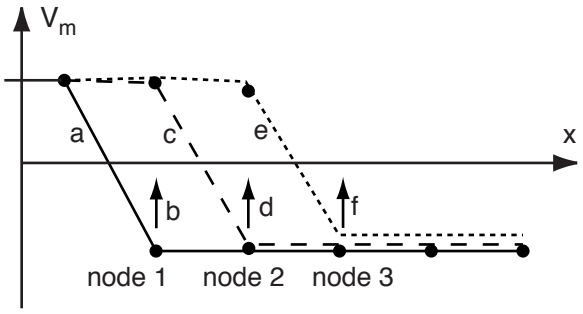

Figure 5: Membrane potential V_m at three different times on several consecutive nodes.

now the new location of the leading edge of the action potential. Current would then begin flowing from node "1" to the node on its right, eventually firing it, etc.

We can see this action more clearly by looking at several adjacent nodes, as in Figure 5. Initially, the action potential leading edge is located just to the left of node 1, as depicted by the trace "a" in the Figure. The membrane potential profile is thus concave up at node 1, causing the current to flow into node 1 from the left, raising its potential, as depicted by arrow "b". Node 1 eventually fires, resulting in trace "c". The leading edge of the action potential is now located between nodes 1 and 2. The concave up portion of the membrane potential profile is now located at node 2, causing its membrane potential to rise as suggested by arrow "d". Node 2 eventually reaches threshold, whereupon its ion channel component i_m fires the cell, resulting in the membrane potential profile shown as trace "e". The leading edge of the action potential is now located between nodes 2 and 3. This process continues (node 3 is now the site of upward concavity of V_m, etc.). This is how action potentials propagate! Notice that this is all deduced by careful examination of (but not the outright solving of) the system equation. It is often more productive to do this kind of analysis on systems equations, than it is to solve them!

Equation (3) also shows two other ways the membrane potential can be increased, corresponding to the two remaining terms. The $D_g(\partial^2\Phi_e/\partial x^2)$ term shows that the presence of a substantial extracellular potential Φ_e can change the membrane potential. We can think of this term as the "defibrillation" term; that is, defibrillation of the heart acts through the effect of this term. When a large electrical jolt is applied to the heart in an effort to terminate life-threatening arrhythmias like ventricular fibrillation, the current from this jolt flows primarily in the extracellular medium. A large potential field Φ_e is established as a result. This field then can modify the action potentials involved in fibrillation through the action of the $D_g(\partial^2\Phi_e/\partial x^2)$ term. If the electrical jolt is formed properly, the resulting extracellular field can annihilate all the action potentials present, essentially resetting the heart. With some luck, normal functioning of the heart's rhythm system, as orchestrated by the SA node, can then take hold.

Finally, the presence of the $i_{intracell}$ term in Eq. (3) shows that injection of current directly into the cell interior can raise its membrane potential. This term is useful both experimentally and in the computer simulation as a means of initiating an action potential at the point in space and time we desire.

Now let's briefly examine the two forms of the extracellular equation, Eqs. (4) and (5).

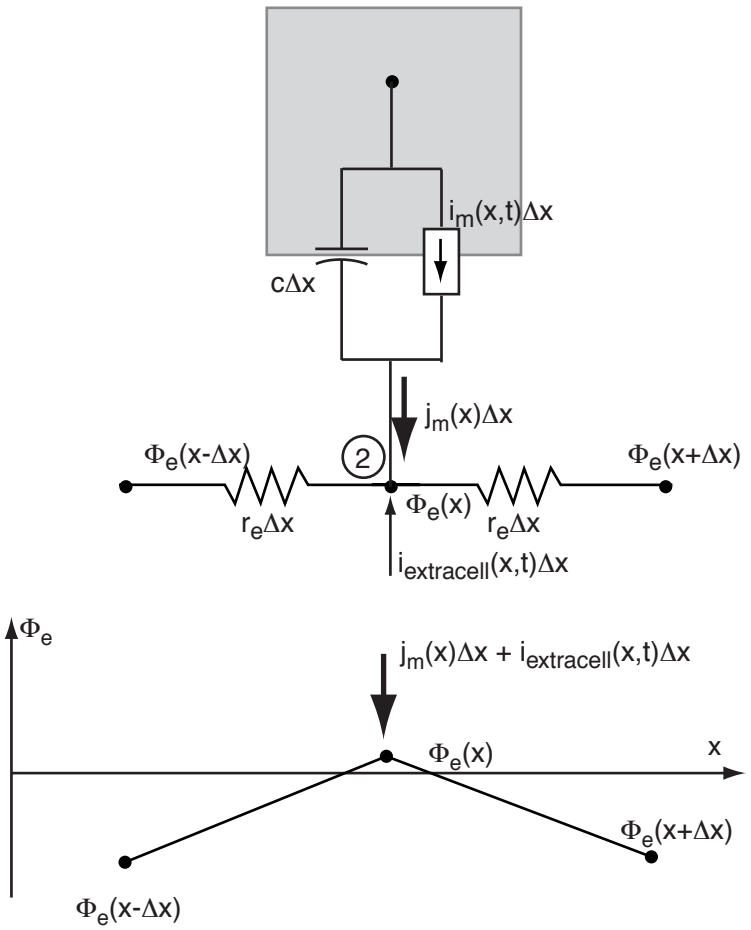

Figure 6: Portion of the circuit corresponding to the equation, $D_e(\partial^2\Phi_e/\partial x^2) = -j_m/c - i_{extracell}/c$. Also shown: a possible profile for Φ_e when current from either a stimulus or the interior of a cell is injected into an extracellular node.

Both of these equations will be studied in more detail later, when we extend the equations to three spatial dimensions. Equation (4) shows us that the membrane potential V_m, or more specifically, the second spatial derivative of the membrane potential $\partial^2 V_m/\partial x^2$, which we now think of as a source, generates an extracellular field. This field, in fact, is the field measured in an electrocardiogram (ECG). Measurable extracellular fields are generated by other excitable tissue as well, for example, by the brain and nerves. The extracellular field can also be manipulated through the injection of current from the outside, both into the intracellular space ($i_{intracell}$) and the extracellular space ($i_{extracell}$).

The other form of the extracellular equation, Eq. (5),

$$D_e \frac{\partial^2 \Phi_e}{\partial x^2} = -\frac{j_m}{c} - \frac{i_{extracell}}{c} \tag{5}$$

shows explicitly the effect of the current flowing through the membrane (either through the membrane capacitance or through the ion channels) on the extracellular potential. In some sense, this effect is the reverse of the effect described earlier for Fig. 4 and Eq. (9). As shown

in Fig. 6, the current flowing out of the cell (together with the extracellular stimulus current $i_{extracell}$) flow into node "2" and then must flow out through the two resistors. Using the same reasoning as before, we see this means that the profile of Φ_e must be concave down. This is the only way for there to be net current flow away from node "2" out through the resistors. Notice that positive j_m and $i_{extracell}$ leads to downward concavity and therefore a negative second spatial derivative $-\partial^2\Phi_e/\partial x^2$. This explains the minus signs in Eq. (5).

4 Generalization to three spatial dimensions: the bidomain model

You may have noticed that we made a number of simplifications in constructing the cable equation model described in the previous section. For one thing, real structures like the cardiac tissue and its accompanying extracellular space are not one-dimensional in space—they're three dimensional. Other simplifications we made were to assume that the resistance per unit length is the same in any direction (a property known as *isotropy*), and that the tissue, and in particular the gap junction and extracellular resistances, were the same at every point in space (*homogeneity*). Generalizing the model to three dimensions is potentially a daunting task—specifically, are we really going to have to include all the anatomical details of membrane folds and invaginations (for example, the T-tubules, etc.) so that we know where the extracellular and intracellular regions are everywhere? Fortunately, there is a simple way out of this, called the *bidomain* model. In this model, there are two co-existing, interpenetrating "universes." One universe represents all the spaces inside the cells. The other universe consists of all the space outside the cells. Of course, our bodies aren't really made up of parallel universes. Actually, at any point in the body, you are either in one of these "universes" or the other. The network of fibers in the heart is so intricate and fine, though, that it really is almost the case that the two regions do exist everywhere. In other words, it is very nearly true that the two universes both occupy the same space at the same time, just like on Star Trek. Parallel universes in the real world, right in your own body! Furthermore, it turns out that this model is a good approximation; that is, the electric fields in our body behave as if these two overlapping universes really did co-exist. These two universes are electrically connected to one another through the presence of ion channels in the membranes of the excitable fibers, just as they do in our bodies. Current can flow from the universe outside the fibers, the "extracellular" universe into the "intracellular" universe through these ion channels. When current exits one these universes at point (x, y, z), it enters the other universe at the same point (x, y, z). Science fiction often makes a big deal about these "doors" which connect the parallel universes—in our case the door are just the ion channels (and also the membrane capacitances). Developing models such as this, which some way idealizes and simplifies reality in an effort to study it, is what modeling is all about.

Let's first look at the three-dimensional extracellular universe by itself. Let's assume that the extracellular universe is a homogeneous, resistive medium. (You've done the heterogenous case for homework.) Suppose, however, that the medium is anisotropic. We can therefore model the extracellular universe as a three-dimensional grid of resistors, as shown

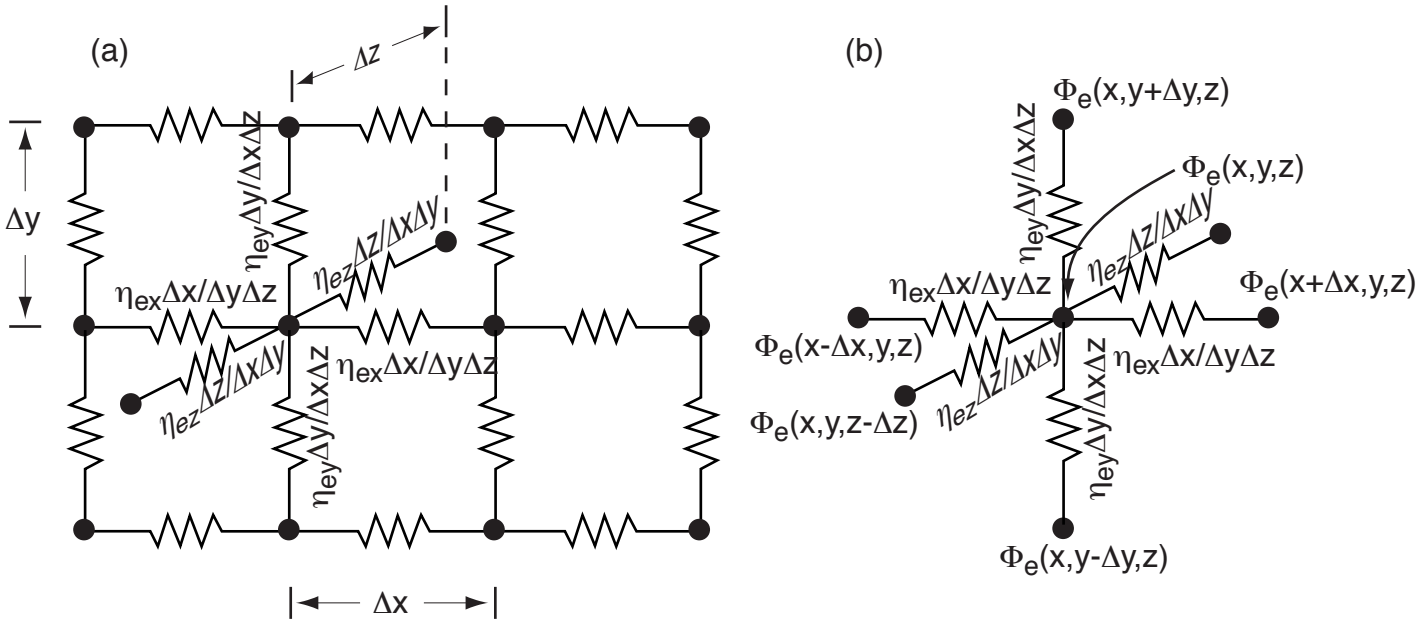

Figure 7: (a) A portion of the extracellular network of resistors. The pattern continues indefinitely in all three dimensions as a rectangular lattice of resistors. (b) Resistors and nodal voltages used to compute Kirchhoff's current law at the point (x, y, z).

in Fig. 7(a).

The spacings between the nodes in the x, y and z directions are Δx, Δy and Δz, respectively. We let Δx, Δy and Δz each go to zero to obtain a continuous, resistive medium. In a uniform medium, the value of each resistor must be proportional to its length and inversely proportional to its cross-sectional area. If the medium is anisotropic, the proportionality constant is different in the different directions. These proportionality constants, called the intrinsic resistivities, of the medium, will be designated as η_{ex}, η_{ey} and η_{ez}. Thus, each of the resistors oriented in the x direction must be proportional to Δx (the length of the resistor) and inversely proportional to $\Delta y \Delta z$ (its cross-sectional area). The value of each of these resistors is therefore $\eta_{ex}\Delta x/\Delta y\Delta z$, as illustrated in Fig. 7. Similar reasoning leads to the values of the resistors oriented in the other two directions.

We can now derive the equations governing the voltages in the extracellular medium by applying the Kirchhoff current law. Referring to Fig. 7(b), which shows a typical node in the extracellular universe, we find that the sum of the six currents leaving the node located at point (x, y, z) is given by (using Ohm's law):

$$\begin{aligned}
&\frac{\Phi_e(x,y,z) - \Phi_e(x+\Delta x,y,z)}{\eta_{ex}\Delta x/\Delta y\Delta z} + \frac{\Phi_e(x,y,z) - \Phi_e(x-\Delta x,y,z)}{\eta_{ex}\Delta x/\Delta y\Delta z} \\
&+\frac{\Phi_e(x,y,z) - \Phi_e(x,y+\Delta y,z)}{\eta_{ey}\Delta y/\Delta x\Delta z} + \frac{\Phi_e(x,y,z) - \Phi_e(x,y-\Delta y,z)}{\eta_{ey}\Delta y/\Delta x\Delta z} \\
&+\frac{\Phi_e(x,y,z) - \Phi_e(x,y,z+\Delta z)}{\eta_{ez}\Delta z/\Delta x\Delta y} + \frac{\Phi_e(x,y,z) - \Phi_e(x,y,z-\Delta z)}{\eta_{ez}\Delta z/\Delta x\Delta y} = 0
\end{aligned} \tag{11}$$

Dividing the entire equation by $-\Delta x \Delta y \Delta z$, we obtain,

$$\begin{aligned}
&\frac{1}{\eta_{ex}} \frac{\Phi_e(x+\Delta x, y, z) - 2\Phi_e(x, y, z) + \Phi_e(x-\Delta x, y, z)}{\Delta x^2} \\
&\frac{1}{\eta_{ey}} \frac{\Phi_e(x, y+\Delta y, z) - 2\Phi_e(x, y, z) + \Phi_e(x, y-\Delta y, z)}{\Delta y^2} \\
&\frac{1}{\eta_{ez}} \frac{\Phi_e(x, y, z+\Delta z) - 2\Phi_e(x, y, z) + \Phi_e(x, y, z-\Delta z)}{\Delta z^2} = 0
\end{aligned} \tag{12}$$

As before, we can expand each term as a Taylor series. For example, the expression in the first term expands as,

$$\begin{aligned}
&\frac{\Phi_e(x+\Delta x, y, z) - 2\Phi_e(x, y, z) + \Phi_e(x-\Delta x, y, z)}{\Delta x^2} \\
&\approx \frac{\Phi_e(\mathbf{x}) + \frac{\partial \Phi_e}{\partial x}(\mathbf{x})\Delta x + \frac{1}{2}\frac{\partial^2 \Phi_e}{\partial x^2}(\mathbf{x})\Delta x^2 - 2\Phi_e(\mathbf{x}) + \Phi_e(\mathbf{x}) - \frac{\partial \Phi_e}{\partial x}(\mathbf{x})\Delta x + \frac{1}{2}\frac{\partial^2 \Phi_e}{\partial x^2}(\mathbf{x})\Delta x^2}{\Delta x^2} \\
&= \frac{\partial^2 \Phi_e}{\partial x^2}(x, y, z)
\end{aligned} \tag{13}$$

where $\mathbf{x}$ is shorthand for (x, y, z). Similar expressions hold for the other two terms on the left-hand side of Eq. (12). Thus, we have that

$$\frac{1}{\eta_{ex}} \frac{\partial^2 \Phi_e}{\partial x^2} + \frac{1}{\eta_{ey}} \frac{\partial^2 \Phi_e}{\partial y^2} + \frac{1}{\eta_{ez}} \frac{\partial^2 \Phi_e}{\partial z^2} = 0 \tag{14}$$

As you showed in the homework, if the resistivities (and therefore the resistances) depend on (x, y, z) (the *heterogeneous* case), then these second derivatives change into the following expressions,

$$\frac{\partial}{\partial x}\left(\frac{1}{\eta_{ex}} \frac{\partial \Phi_e}{\partial x}\right) + \frac{\partial}{\partial y}\left(\frac{1}{\eta_{ey}} \frac{\partial \Phi_e}{\partial y}\right) + \frac{\partial}{\partial z}\left(\frac{1}{\eta_{ez}} \frac{\partial \Phi_e}{\partial z}\right) = 0 \tag{15}$$

Now let's try connecting this extracellular universe to the intracellular universe at a single node. As Fig. 8 shows, the connection appears as a current source, apparently coming from nowhere, but actually coming from the intracellular space, through the cell membrane, via the membrane capacitance and the ion channels. If the amount of current coming from the other universe is j_m per unit volume, then the current flowing into any one node will be j_m times the volume associated with that node, which is $\Delta x \Delta y \Delta z$. Thus, the current coming from the intracellular universe is $j_m \Delta x \Delta y \Delta z$.

When $j_m \Delta x \Delta y \Delta z$ is added as a new current flowing into the node located at (x, y, z) and Kirchhoff's current law is applied, and we again divide by $-\Delta x \Delta y \Delta z$ and perform the Taylor expansions, we now obtain,

$$\frac{\partial}{\partial x}\left(\frac{1}{\eta_{ex}} \frac{\partial \Phi_e}{\partial x}\right) + \frac{\partial}{\partial y}\left(\frac{1}{\eta_{ey}} \frac{\partial \Phi_e}{\partial y}\right) + \frac{\partial}{\partial z}\left(\frac{1}{\eta_{ez}} \frac{\partial \Phi_e}{\partial z}\right) = -j_m \tag{16}$$

While we're at it, we may as well also include the possibility of a stimulus being applied in the extracellular space at this point, of magnitude $i_{extracell}$ per unit volume. Not surprisingly,

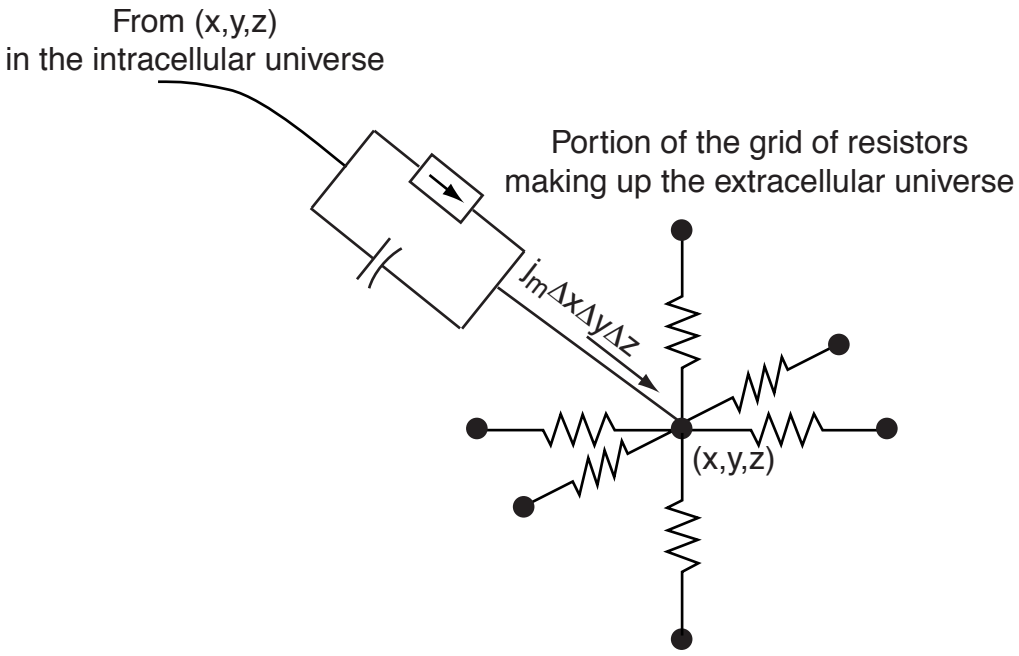

Figure 8: Relevant portion of the circuit needed to apply Kirchhoff's current law to the point (x, y, z) when connected to the intracellular universe.

this results in the expression,

$$\frac{\partial}{\partial x}\left(\frac{1}{\eta_{ex}}\frac{\partial \Phi_e}{\partial x}\right) + \frac{\partial}{\partial y}\left(\frac{1}{\eta_{ey}}\frac{\partial \Phi_e}{\partial y}\right) + \frac{\partial}{\partial z}\left(\frac{1}{\eta_{ez}}\frac{\partial \Phi_e}{\partial z}\right) = -j_m - i_{extracell} \tag{17}$$

Now let's try to relate j_m explicitly to currents flowing the membrane capacitance and ion channels. Suppose that the membrane capacitance per unit volume is c, and the ion channel current per unit volume is i_m. The total current flowing out from the intracellular universe in volume $\Delta x\Delta y\Delta z$ center at location (x, y, z) would then be,

$$j_m\Delta x\Delta y\Delta z = (c\Delta x\Delta y\Delta z)\frac{\partial V_m}{\partial t} + i_m\Delta x\Delta y\Delta z \tag{18}$$

yielding the same expression as in the one-dimensional case,

$$j_m = c\frac{\partial V_m}{\partial t} + i_m \tag{19}$$

Actually, this equation is different from the 1-d case, because the definitions are different. Now j_m, c and i_m are the total current through the membrane, the capacitance of the membrane, and the ion channel current *per unit volume* of tissue, not per unit length. Substituting this into Eq. (17) and dividing by c,

$$\frac{\partial}{\partial x}\left(D_{ex}\frac{\partial \Phi_e}{\partial x}\right) + \frac{\partial}{\partial y}\left(D_{ey}\frac{\partial \Phi_e}{\partial y}\right) + \frac{\partial}{\partial z}\left(D_{ez}\frac{\partial \Phi_e}{\partial z}\right) = -\frac{\partial V_m}{\partial t} - \frac{i_m}{c} - \frac{i_{extracell}}{c} \tag{20}$$

where $D_{ex} = 1/(\eta_{ex}c)$, $D_{ey} = 1/(\eta_{ey}c)$, and $D_{ez} = 1/(\eta_{ez}c)$.

The differential expression appearing on the right-hand side of Eq. (20) is quite common—so much so that there is a standard symbol for it:

$$\nabla \cdot \mathbf{D_e} \cdot \nabla \Phi_e = \frac{\partial}{\partial x}\left(D_{ex}\frac{\partial \Phi_e}{\partial x}\right) + \frac{\partial}{\partial y}\left(D_{ey}\frac{\partial \Phi_e}{\partial y}\right) + \frac{\partial}{\partial z}\left(D_{ez}\frac{\partial \Phi_e}{\partial z}\right) \tag{21}$$

Notice that the quantity $\mathbf{D_e}$ is defined to contain the scalar quantities D_{ex}, D_{ey} and D_{ez} as part of its definition. (In fact, $\mathbf{D_e}$ turns out to be the 3x3 matrix,

$$\begin{bmatrix} D_{ex} & 0 & 0 \\ 0 & D_{ey} & 0 \\ 0 & 0 & D_{ez} \end{bmatrix}$$

for reasons that need not concern us here.) Using this definition, Eq. (20) may be written more succinctly as,

$$\nabla \cdot \mathbf{D_e} \cdot \nabla \Phi_e = -\frac{\partial V_m}{\partial t} - \frac{i_m}{c} - \frac{i_{extracell}}{c} \tag{22}$$

This is the three-dimensional, anisotropic, heterogeneous version of Eq. (2). In a similar manner, the following equations, the 3-d, anisotropic, heterogeneous versions of Eqs. (3–5), are easily derived:

$$\frac{\partial V_m}{\partial t} = -\frac{i_m}{c} + \nabla \cdot \mathbf{D_g} \cdot \nabla V_m + \nabla \cdot \mathbf{D_g} \cdot \nabla \Phi_e + \frac{i_{intracell}}{c} \tag{23}$$

$$\nabla \cdot (\mathbf{D_e} + \mathbf{D_g}) \cdot \nabla \Phi_e = -\nabla \cdot \mathbf{D_g} \cdot \nabla V_m - \frac{i_{intracell}}{c} - \frac{i_{extracell}}{c} \tag{24}$$

$$\nabla \cdot \mathbf{D_e} \cdot \nabla \Phi_e = -\frac{j_m}{c} - \frac{i_{extracell}}{c} \tag{25}$$

Much of what we said about Eqs. (3–5) and the various simplification we discussed remain true for these three-dimensional versions. For example, the first three terms in Eq. (23),

$$\frac{\partial V_m}{\partial t} = -\frac{i_m}{c} + \nabla \cdot \mathbf{D_g} \cdot \nabla V_m \tag{26}$$

still describe the ability for action potentials to propagate, as did Eq. (10). The main difference is that, now that there are second derivatives in all three directions in the definition of $\nabla \cdot \mathbf{D_g} \cdot \nabla V_m$, this means that propagation of action potentials is now possible in any direction within the three dimensional space.

Now let's go back and take a careful look at Eq. (25). We can get an idea about the mechanism that Eq. (25) is trying to tell us about by first consideriing the homogeneous, isotropic case. For this situation, $\mathbf{D_e}$ is the same everywhere (homogenous) and therefore does not depend on $\mathbf{x}$. Furthermore, the three quantities used to define $\mathbf{D_e}$, D_{ex}, D_{ey} and D_{ez}, are equal ($D_{ex} = D_{ey} = D_{ez} \equiv D_e$, isotropic). The definition of $\nabla \cdot \mathbf{D_e} \cdot \nabla \Phi_e$ given by Eq. (21) then simplifies to:

$$\nabla \cdot \mathbf{D_e} \cdot \nabla \Phi_e = \frac{\partial}{\partial x}\left(D_{ex}\frac{\partial \Phi_e}{\partial x}\right) + \frac{\partial}{\partial y}\left(D_{ey}\frac{\partial \Phi_e}{\partial y}\right) + \frac{\partial}{\partial z}\left(D_{ez}\frac{\partial \Phi_e}{\partial z}\right)$$

$$= D_e \left(\frac{\partial^2 \Phi_e}{\partial x^2} + \frac{\partial^2 \Phi_e}{\partial y^2} + \frac{\partial^2 \Phi_e}{\partial z^2} \right)$$
$$= D_e \nabla^2 \Phi_e \tag{27}$$

Here we use another commonly defined symbol:

$$\nabla^2 \Phi = \frac{\partial^2 \Phi}{\partial x^2} + \frac{\partial^2 \Phi}{\partial y^2} + \frac{\partial^2 \Phi}{\partial z^2} \tag{28}$$

for any function $\Phi(x, y, z)$. Also, $\nabla^2 \Phi$ is often called the *Laplacian* of Φ.

What we find, then, is when the extracellular medium is homogeneous and isotropic, the extracellular potential is given by,

$$D_e \nabla^2 \Phi_e = -\frac{j_m}{c} - \frac{i_{extracell}}{c} \tag{29}$$

This also implies that the resistivities η_{ex}, η_{ey}, and η_{ez} are all equal to each other and are the same everywhere in space, since $D_{ex} = 1/(\eta_{ex} c)$ and c is a constant. If we also choose $\Delta x = \Delta y = \Delta z$ so that the network of resistors in Fig. 7 is a cubic lattice, then it should be clear that all the resistors shown in that Figure are equal, with value $\eta \Delta x / \Delta x^2 = \eta_e / \Delta x$, where $\eta_e \equiv \eta_{ex} = \eta_{ey} = \eta_{ez}$.

Now let's look at this homogeneous, isotropic, extracellular resistive medium from a slightly different perspective. Suppose we want to know how the current flows in this medium when current is injected at a point. More importantly, we would like to know what the extracellular potential $\Phi_e(x, y, z)$ is in this medium when current is injected at a point. To determine this, we look at a different model of the medium. This one consists of an infinite set concentric, thin, spherical shells, one inside another, like layers of an onion, centered around the point at which the current is being injected. A diagram of this model appears in Fig. 9.

From the symmetry of the situation, it is easy to see that the current must flow radially outward in all directions from the point of injection. From Kirchhoff's current law (that is, current in equals current out), we also know that the current passing through each successive shell must be exactly the same, and equal to the injected current, which we will call I_m.

There is therefore a simple equivalent circuit for this situation, shown in Fig. 10. Each of the resistors shown represents the resistance of one of the shells in Fig. 9, while each of the nodes in Fig. 10 corresponds to one of the spherical boundaries between shells. The resistances are determined using the same method we used for the rectangular network of resistors. We take the resistivity of the medium η_e and multiply by the length of the resistor in the direction of current flow and divide by the cross-sectional area. The rationale for this is that the longer the resistor the current must flow through, the higher the resistance, while the larger the cross-sectional area, the lower the resistance. The present case involves some weird-looking resistors (spherical shells), but the same principle still applies. For the highlighted spherical shell shown in Fig. 9, the length of the resistor in the direction of current flow is simply the width of the spherical shell Δr, since current flows radially outward through the shell. The cross-sectional area presented by the shell to current flow is the surface area of the shell. The highlighted shell has radius $r + \Delta r/2$, so using the standard formula for the surface area of a sphere, we have that the cross-sectional area is $4\pi(r + \Delta r)^2$. Thus, the

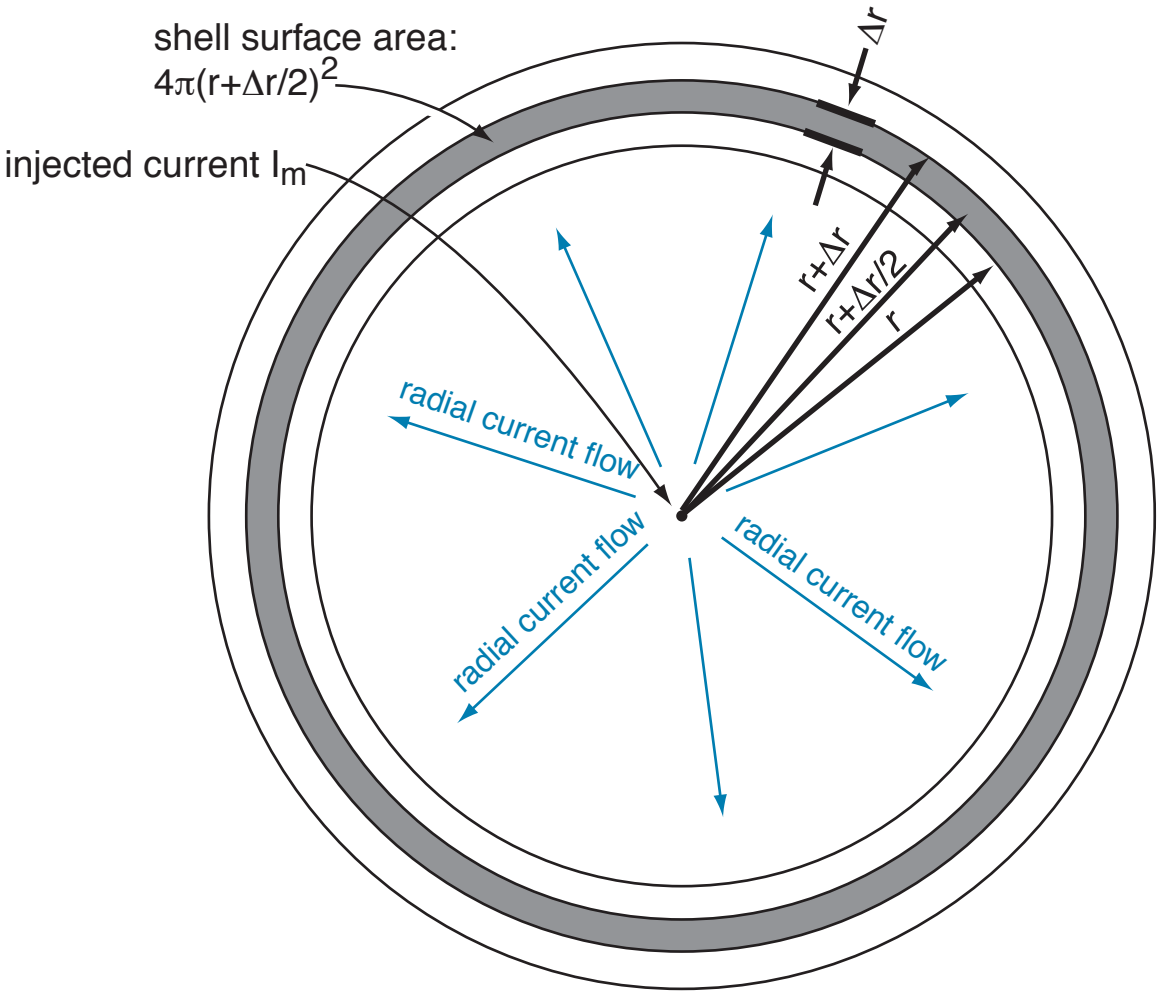

Figure 9: Representation of a homogeneous, isotraopic resistive medium appropriate for the diagnosis of the case of an injected current into the medium at a single point.

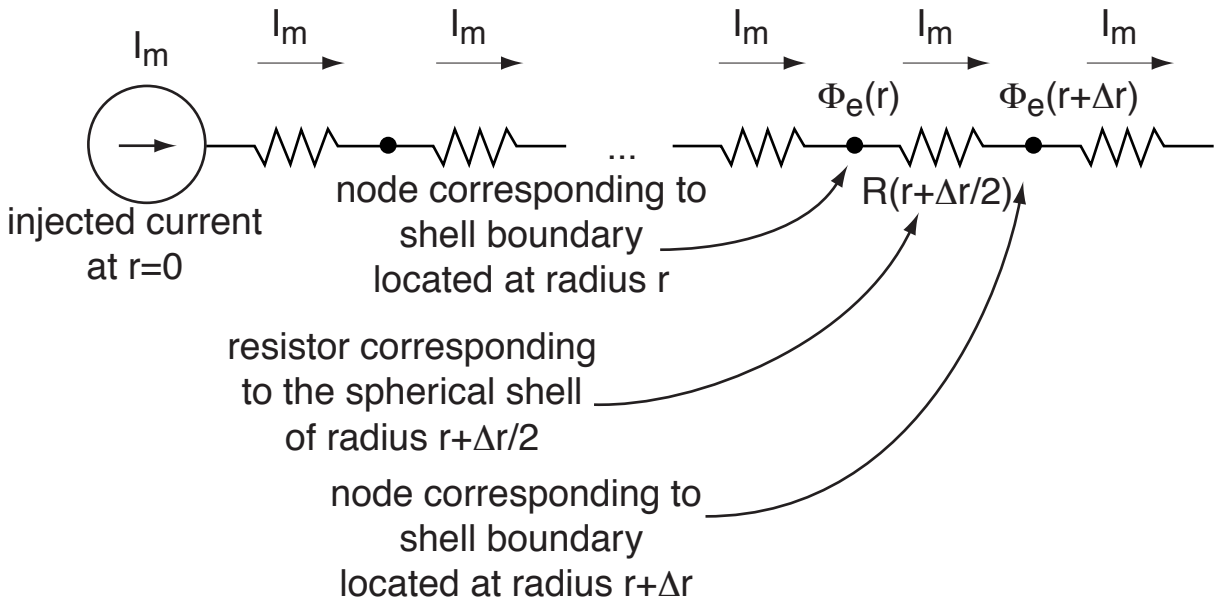

Figure 10: Electrical circuit equivalent to the situation shown in Fig. 9. The injected current may be represented as the current source on the left. The entire current from this source, I_m, then flows through each of the spherical shells in succession, each represented by a resistor.

resistance for the resistor labeled $R(r + \Delta r/2)$ in Fig. 10, corresponding to the highlighted shell Fig. 9, is

$$R(r + \Delta r/2) = \frac{\eta_e \Delta r}{4\pi \left(r + \frac{\Delta r}{2}\right)^2}$$

From Ohm's law, we find that the potential drop across the shell is,

$$\Phi_e(r) - \Phi_e(r + \Delta r) = \frac{I_m \eta_e \Delta r}{4\pi \left(r + \frac{\Delta r}{2}\right)^2} \tag{30}$$

Dividing by Δr, and letting $\Delta r \to 0$ we have,

$$-\frac{\partial \Phi_e}{\partial r} = \frac{\eta_e I_m}{4\pi r^2} \tag{31}$$

Notice that this is just the extracellular radial electric field (since it is the negative derivative of the potential). The extracellular electric field due to a point current injection therefore falls of with distance as $1/r^2$. Integrating from infinitely far away to radius r, we have,

$$\int_\infty^r \frac{\partial \Phi_e}{\partial r} dr = -\frac{\eta_e I_m}{4\pi} \int_\infty^r \frac{dr}{r^2} = \left. \frac{\eta_e I_m}{4\pi r} \right|_\infty^r \tag{32}$$

which yields,

$$\Phi_e(r) - \Phi_e(\infty) = \frac{\eta_e I_m}{4\pi r} \tag{33}$$

or, defining the potential infinitely far away to be 0,

$$\Phi_e(r) = \frac{\eta_e I_m}{4\pi r} \tag{34}$$

The potential due to current injection at a point in a homogeneous, isotropic medium, thus falls off like $1/r$, where r is the distance away from the point of injection. Now that we have been through the derivation using the spherical shell model, we see that the reason for the $1/r$ dependence of the potential on distance is actually pretty simple: the shell resistances go like $1/r^2$ since they are inversely proportional to their surface areas, which go like $4\pi r^2$; the potential difference across each of these shells must therefore also go like $1/r^2$ in order to keep the current constant (remember the current goes like the potential drop divided by the resistance—Ohm's law), and then if the potential drop across a small distance, a.k.a. the electric field, goes like $1/r^2$, then the potential itself, being the integral of the electric field, must go like $1/r$.

This whole situation might remind you of something: the potential due to a point charge also falls off like $1/r$. Not only that, but the electric field from a point charge points radially outward, just as the current does for our case, and scales like $1/r^2$ just as our electric field does. These similarities are not an accident. Depending on how much electricity and magnetism you have had, you may already know that one way of writing Poisson's equation, the equation governing electrostatics, is

$$\nabla^2\Phi = -4\pi\rho \qquad \text{(CGS units)}$$

or

$$\nabla^2\Phi = -\rho/\epsilon_0 \qquad \text{(MKS units)}$$

where ρ is the charge density. It's the same as our equation! Except that, charges are replaced by injected currents. Because of this, the electric field and potential in the extracellular medium behaves as if there were a point charge located at every point at which the current is being injected. Injected current *into* the extracellular medium results in the field of a positive point charge.

We will see later that the pattern of injected current into the extracellular space produced by a propagating action potential often consists of injected currents of opposite signs in physical juxtaposition to one another. It is therefore of relevance to find the extracellular potential due to two injected currents of equal and opposite signs separated from one another by a small distance ϵ. Suppose, for example, that the two injected currents are located on the z-axis, at coordinates $(0, 0, \epsilon/2)$ and $(0, 0, -\epsilon/2)$. We can then ask, what is the potential at some observation point (x, y, z)? The situation is shown in Fig. 11.

To gain some insight into the problem, let's briefly consider what potentials we would expect to see from various observation sites situated on the z axis. Figure 12 shows the fields we would obtain from each of the two current sources individually. Each of these fields has a $1/r$ shape. The total potential on the z-axis would then just be the sum of these two potentials. Note that this sum yields almost complete cancellation of the two potential fields. In fact, you can see that the two fields would completely cancel if the separation between the two currents injected were zero.

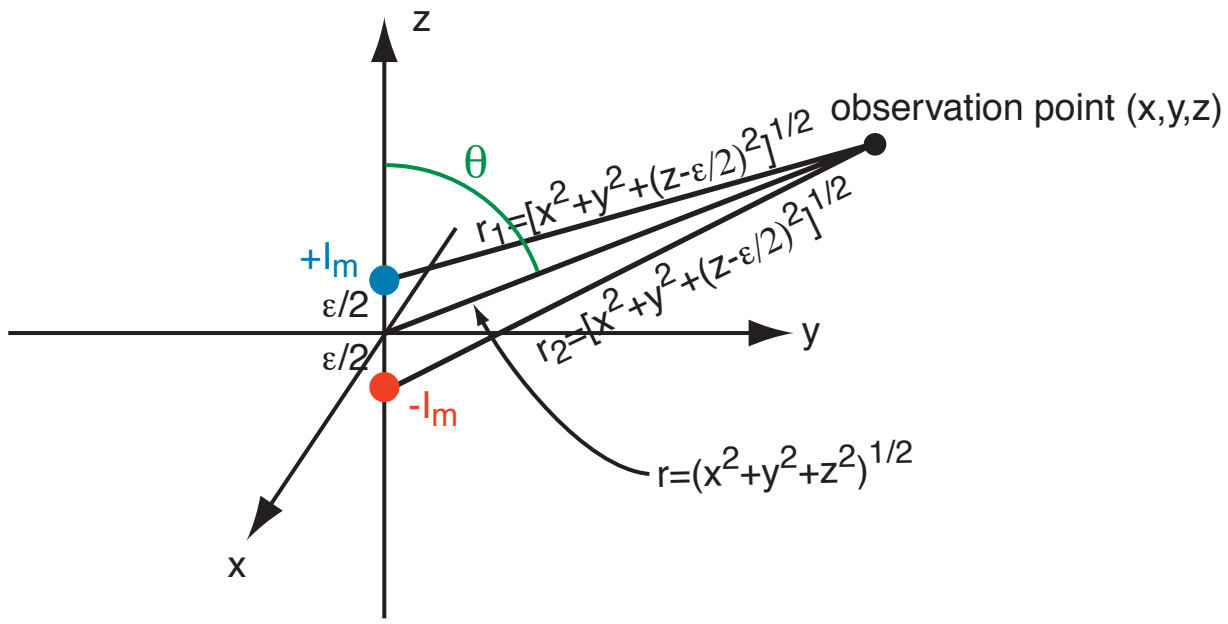

Figure 11: Distances and angles relevant to the calculation of the potential at some distant location (x, y, z) due to two injected currents close to the origin.

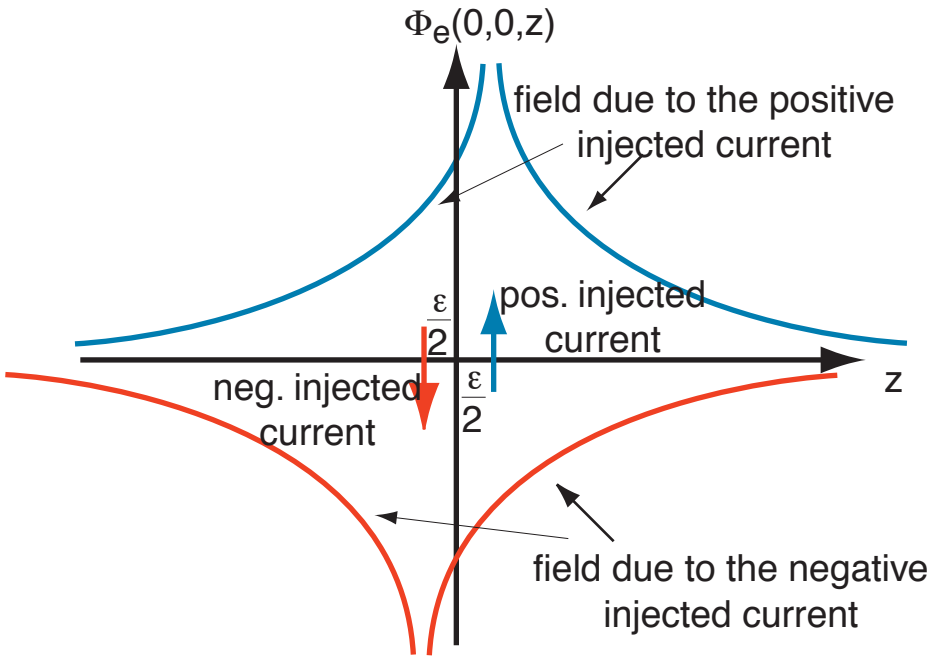

Figure 12: Individual fields of two injected currents as they would be measured on the z axis.

More generally, for arbitrary distant observation points (x, y, z), the potential will just be the sum of two terms each obtained by applying Eq. (34) to each of the current sources:

$$\Phi_e(x, y, z) = \frac{\eta_e I_m}{4\pi r_1} + \frac{\eta_e(-I_m)}{4\pi r_2} \tag{35}$$

where r_1 and r_2 are the distances of the observation point (x, y, z) from the current injection sites $(0, 0, \epsilon/2)$ and $(0, 0, -\epsilon/2)$, respectively, as shown in Fig. 11. Using the Pythagorean theorem, we have that,

$$r_1 = \sqrt{x^2 + y^2 + (z - \epsilon/2)^2}$$
$$r_2 = \sqrt{x^2 + y^2 + (z + \epsilon/2)^2}$$

Substituing these, we find that,

$$\Phi_e(x, y, z) = \frac{\eta_e I_m}{4\pi}\left[\frac{1}{\sqrt{x^2 + y^2 + (z - \epsilon/2)^2}} - \frac{1}{\sqrt{x^2 + y^2 + (z + \epsilon/2)^2}}\right] \tag{36}$$

If ϵ is small (that is, if the two points of injection are close to each other), then we can obtain a simple approximation for the field by Taylor expanding in the small parameter ϵ, the separation between the injected current sources.

The first step in constructing this Taylor expansion is to make each term look like,

$$(\text{const})(1 + \text{something small})^{\text{some power}} \tag{37}$$

We can do this by first expanding the argument of each square root:

$$\Phi_e(x, y, z) = \frac{\eta_e I_m}{4\pi}\left[\frac{1}{\sqrt{x^2 + y^2 + z^2 - \epsilon z + \epsilon^2/4}} - \frac{1}{\sqrt{x^2 + y^2 + z^2 + \epsilon z + \epsilon^2/4}}\right] \tag{38}$$

Ignoring the $\epsilon^2/4$ as being too small, and then factoring out $\sqrt{x^2 + y^2 + z^z}$ out of each denominator, we have:

$$\Phi_e(x, y, z) = \frac{\eta_e I_m}{4\pi}\left[\frac{1}{\sqrt{x^2 + y^2 + z^2}\sqrt{1 - \dfrac{\epsilon z}{x^2 + y^2 + z^2}}} - \frac{1}{\sqrt{x^2 + y^2 + z^2}\sqrt{1 + \dfrac{\epsilon z}{x^2 + y^2 + z^2}}}\right] \tag{39}$$

Defining $r \equiv \sqrt{x^2 + y^2 + z^2}$ (which also happens to be the distance of the observation point from the origin), we have,

$$\Phi_e(x, y, z) = \frac{\eta_e I_m}{4\pi r}\left[\frac{1}{\sqrt{1 - \dfrac{\epsilon z}{r^2}}} - \frac{1}{\sqrt{1 + \dfrac{\epsilon z}{r^2}}}\right] \tag{40}$$

Now each of the terms has the form shown in Eq. (37). Using the Taylor series for Eq. (37):

$$(1 + \text{something small})^{\text{power}} = 1 + (\text{power})(\text{something small}) + O(\text{something small})^2 \tag{41}$$

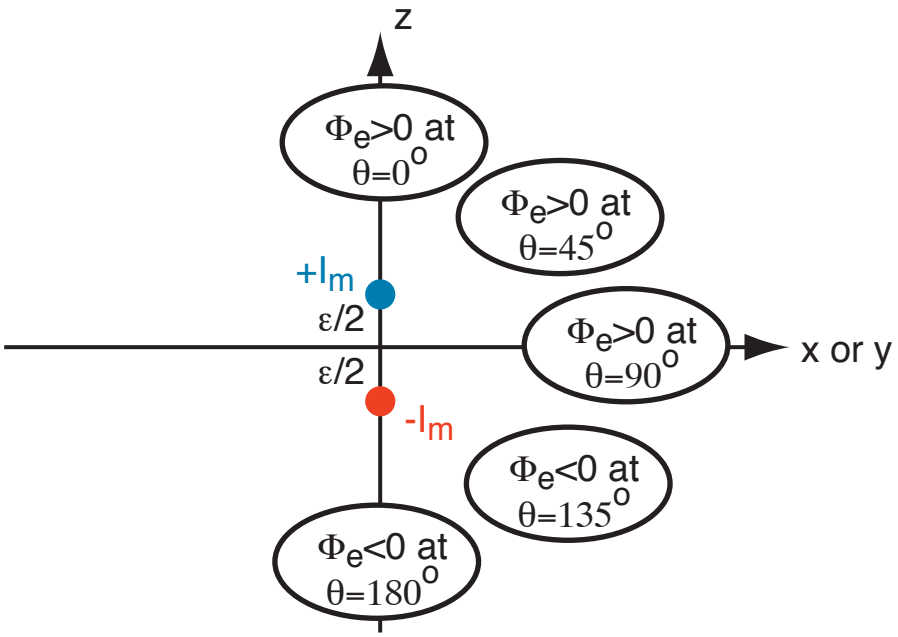

Figure 13: Polar angle for five different observation directions, and the sign of the dipole field for each.

we have,

$$\frac{1}{\sqrt{1-\frac{\epsilon z}{r^2}}} = \left(1-\frac{\epsilon z}{r^2}\right)^{-1/2} = 1+\frac{1}{2}\frac{\epsilon z}{r^2}+O(\epsilon^2) \tag{42}$$

$$\frac{1}{\sqrt{1+\frac{\epsilon z}{r^2}}} = \left(1+\frac{\epsilon z}{r^2}\right)^{-1/2} = 1-\frac{1}{2}\frac{\epsilon z}{r^2}+O(\epsilon^2) \tag{43}$$

Thus,

$$\begin{aligned}\Phi_e(x,y,z) &= \frac{\eta_e I_m}{4\pi r}\left[\left(1+\frac{1}{2}\frac{\epsilon z}{r^2}\right)-\left(1-\frac{1}{2}\frac{\epsilon z}{r^2}\right)\right]+O(\epsilon^2)\\ &= \frac{\eta_e I_m \epsilon}{4\pi r^2}\frac{z}{r}+O(\epsilon^2)\end{aligned} \tag{44}$$

Notice that the 1's cancel in this expression. This corresponds to the fact that the fields due to two equal and opposite currents, injected at nearly the same location, nearly cancel. We have already noticed this in Fig. 12, along with the observation that if the currents had been laid exactly on top of each other (i.e., if $\epsilon = 0$) then their fields would have cancelled everywhere. Analogously, if ϵ is set to zero in Eq. (44), we also get $\Phi_e = 0$ everywhere.

Also notice that it was ok to throw away the $\epsilon^2/4$ terms in Eq. (38)—if we had kept them, after much painful math, they would have ended up in the $O(\epsilon^2)$ term in Eq. (44). (You can take my word for this, or try keeping them in the calculation yourself—a useful, but difficult and messy exercise.) Finally notice that Φ_e is proportional to the separation ϵ between the injected currents. The larger the separation, the larger the fields.

A common way to write Eq. (44) is in terms of the angle θ the observation point vector $\mathbf{r}$ makes with the z axis, as illustrated in Fig. 11. With this definition, $z/r = \cos\theta$. We can now write the extracellular potential as,

$$\Phi_e(x, y, z) = \frac{\eta_e I_m \epsilon}{4\pi r^2} \cos\theta \tag{45}$$

When the observation point is situated along the same line that separates the currents; that is, when $\theta = 0^\circ$ or 180°, as shown in Fig. 13, this is when $\cos\theta$ takes on its largest possible values in absolute terms: $\cos 0^\circ = 1$; $\cos 180^\circ = -1$. Thus the fields produced by a pair of equal and opposite injected currents tend to be largest along the extension of the line that connects the two currents.

Physically, the reason for this is that one of the injected currents is closer to the observation point than the other. This is made more clear by using the analogy to point charges described earlier. We know we can substitute a positive point charge for the injected current located at $(0, 0, \epsilon/2)$, and a negative point charge for the current located at $(0, 0, -\epsilon/2)$. Once we think in terms of point charges, it is clear that the potential will be positive on the entire positive z-axis, since the positive charge is closer than the negative charge for every point on the positive z axis. Similarly, the potential will take on its most negative values for observation points along the negative z axis.

In contrast, when the obsevation point is located broadside relative to the line connecting the two current injections, there is no potential field. Mathematically, this is because $\cos 90^\circ = 0$; physically, it's because the two injected currents are equidistant from the observation point for this case, as should be clear from Fig. 13.

Another feature of the potential field of these two injected currents is that it falls off like $1/r^2$, a more rapid fall-off than is produced by either injected current alone. Again, the rapid fall-off is due to the near cancellation of the two fields.

The whole potential profile is shown in Fig. 14. This field is called a *dipole field*, and the configuration of currents producing it—equal and opposite in amplitude, and separated by a small distance—is called a *dipole source*.

It is fairly easy to construct slightly more complicated injected current configurations in which not only the currents are equal and opposite, but so are the dipole sources. In this case, the potential falls off even more rapidly, like $1/r^3$. The field itself is called a *quadrapole field*. We will see in later discussions that both dipole and quadrapole fields often accompany action potentials under diffeerent circumstances, and therefore can be valuable in characterizing and diagnosing the properties of these action potentials.

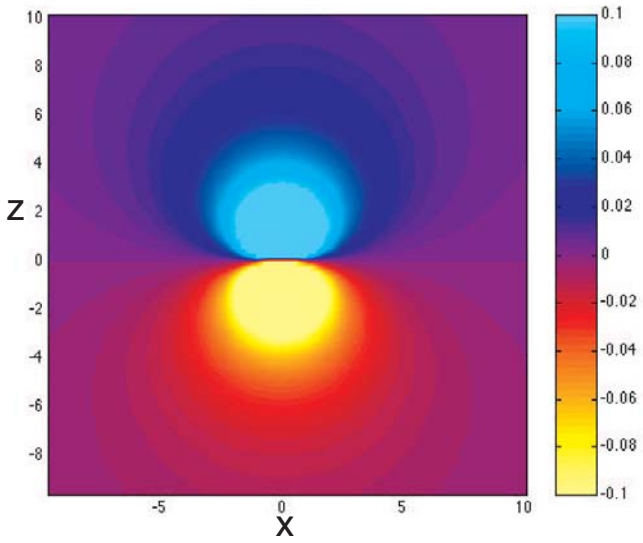

Figure 14: Colormap of a dipole field. Field shown is due to two injected currents at (0,0,1) and (0,0,-1).