

Multiscale Bioelectric Fields

Implications for Neural Dynamics and Sensing

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I applied to work with Dr. John Lewis as a C.V. line item without any academic curiosity. I did not expect to become fascinated with bioelectric fields, “drinking the electric fish kool-aid” as someone once put it.

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$$-\nabla \cdot \nabla_{\sigma} \Phi = J$$

Abstract

Bioelectric fields are produced in many tissues including muscle, heart and brain. These electric fields arise from the transmembrane ionic currents that underlie action potentials. Electric fish use such fields to sense in the dark. A specialized electric organ generates large currents, the electric organ discharge (EOD), resulting in an electric field around the fish body. This self-generated field is perturbed by external heterogeneities and these perturbations modulate the activity of receptor cells on their skin, forming the basis of the electric sense. The EOD is oscillatory with an individual-specific frequency that is extremely stable. Despite this stability, fish modulate their EOD frequency on short time-scales during social interactions. When electric fish with similar frequencies interact, their EODs interfere with one another and compromise sensing. To mitigate this, fish diverge their frequencies through the jamming avoidance response. These fish also communicate via a transient desynchronization of neurons in the brain network that controls EOD timing, the pacemaker network (PN). Subsequent resynchronization occurs in tens of milliseconds, too fast to be explained by the network properties of the PN.

In the first part of this thesis, we consider the hypothesis that the EOD entrains the PN through electric field effects and increases resynchronization rate. We first develop a computational tool (E_LFENN) to explore how neurons are affected by electric fields. We also develop a model of pacemaker cells in the PN and validate it against experimental data. We then combine these developments to show that feedback entrainment between the EOD and PN mediates resynchronization time.

In the second part, we focus on the electric field perturbations that occur during sensing. We first show that the spatial structure of the field is important

for effective frequency separation during the jamming avoidance response. We then develop novel computational models of electric fish that are freely deformable (pyFEM²S); we can thus simulate natural poses and study how fish shape their electric field and the resultant sensory corollaries.

Finally, we consider how insight from studying bioelectric fields for sensing and control can be applied to more general aspects of electric field effects and brain function.

Résumé

Les champs bioélectriques sont produits dans de nombreux tissus, notamment les muscles, le cœur et le cerveau. Ces champs électriques proviennent des courants ioniques transmembranaires qui sous-tendent les potentiels d'action. Les poissons électriques utilisent ces champs pour détecter dans l'obscurité. Un organe électrique spécialisé génère des courants importants, la décharge d'organe électrique (EOD), qui se traduit par un champ électrique autour du corps du poisson. Ce champ auto-généré est perturbé par des hétérogénéités externes et ces perturbations modulent l'activité des cellules réceptrices sur leur peau, formant la base du sens électrique. La décharge est oscillatoire avec une fréquence spécifique à l'individu qui est extrêmement stable. Malgré cette stabilité, les poissons modulent la fréquence de l'EOD sur une petite échelle à courte durée lors de leurs interactions sociales. Lorsque des poissons électriques ayant des fréquences similaires interagissent, leurs EOD interfèrent entre eux et compromettent la perception. Pour atténuer cela, les poissons font diverger leurs fréquences par la réponse d'évitement de brouillage. Ces poissons communiquent également via une désynchronisation transitoire des neurones dans le réseau cérébral qui contrôle la synchronisation des EOD, le réseau de neurones pacemaker (PN). La resynchronisation subséquente se produit en quelques dizaines de millisecondes, trop rapidement pour être expliquée par les propriétés du réseau PN.

Dans la première partie de cette thèse, nous considérons l'hypothèse que l'EOD entraîne le PN par des effets de champ électrique et augmente le taux de resynchronisation. Nous développons d'abord un outil (ELFENN) pour explorer comment les neurones sont affectés par les champs électriques. Nous développons également un modèle de cellules pacemaker dans le PN et le

validons par rapport à des données expérimentales. Nous combinons ensuite ces développements pour démontrer que l’entraînement de rétroaction entre l’EOD et le PN intervient dans le temps de resynchronisation.

Dans la deuxième partie, nous nous concentrons sur les perturbations des champs électriques qui se produisent lors de la détection. Nous montrons d’abord que la structure spatiale du champ est importante pour une séparation efficace des fréquences pendant la réponse d’évitement de brouillage. Nous développons ensuite de nouveaux modèles informatiques de poissons électriques librement déformables (PyFEM2S); nous pouvons ainsi simuler des poses naturelles et étudier comment les poissons façonnent leur champ électrique et les corollaires sensoriels qui en résultent.

Enfin, nous examinons comment les connaissances acquises par l’étude des champs bioélectriques pour la détection et le contrôle peuvent être appliquées à des aspects plus généraux des effets des champs électriques et du fonctionnement du cerveau.

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Chapter 1

Introduction

Electric fields in biology (bioelectric fields) span many spatial scales. At the smallest level, many types of animal cells including muscle and brain generate electric fields. These small cells (on the order of microns to millimeters), generate correspondingly low amplitude ($\mu\text{V}/\mu\text{m}$) and small scale (micron–millimeter) electric fields. On the opposite side, electric eels are quite long (on the order of meters), and create equivalently large amplitude ($100\text{V}/\text{m}$), and large scale (meters) electric fields. These fields share the same electric field physics and similar cellular mechanisms yet are widely different. What role (if any) do these fields play in the day-to-day lives of organisms and cells? And what properties and roles are shared by these widely different fields?

At the small scale, some work has gone into the role of bioelectric fields, yet there is still a lot of controversy and mystery. In this work we will use electric fish as a model of electric field generation at both small and large scales in order to gain insight into general bioelectric fields, and how their roles change as they're scaled from the cellular scale to the body scale.

1.1 Bioelectric Fields

Electrically active tissues (muscles, neurons, and cardiac cells) generate electric fields. This fact has been known for nearly 200 years beginning with Leopold Nobili first measuring current flow in frog muscle in 1827 (McDonald [2004](#)). Richard Caton then in 1877 showed electrical fields originating in exposed rabbit cerebrum (McDonald [2004](#); Stone et al. [2013](#)). Later Hans Berger (arguably the father of human electroencephalography

(Millett 2001)) showed that human brain activity could be recorded from the scalp: the human EEG. Perhaps most interestingly, Berger’s development of the electroencephalogram (EEG) was not motivated out of scientific curiosity, but out of the search for a “Psychic Energy”. After falling from a horse, and later receiving an unmotivated letter of concern from his distant sister, he believed that the fear he felt during his fall was exchanged via psychic energy with his sister (Millett 2001).

Berger’s work (while experimenting on his 15 year old son (Chase 2006)) lead to the discovery of what we understand today as the prominent frequency EEG band (α and β waves). In recent years Berger’s EEG principles have been extended to a veritable zoo of electrophysiological techniques such as electrocorticograms (ECoG), local field potentials (LFP), and magnetoencephalography (MEG) recordings to name a few. These techniques span spatial resolutions from microns to centimeters (Pesaran et al. 2018; Albert 2001; Buzsáki, Anastassiou, and Koch 2012), yet common patterns of oscillations are present across recordings made by all of these techniques. These techniques are of broad interest in studying large scale brain dynamics (Pesaran et al. 2018; Buzsáki, Anastassiou, and Koch 2012; Hagen et al. 2018), and are at the forefront of most modern neuroscience, but what is it about the brain that gives rise to these electric fields? During day-to-day operations, the brain functions on a unit of information (not unlike the “bit” in computers) called the action potential, and it is the creation of the action potential the gives rise to electric fields.

1.2 Neural Dynamics: The Action Potential

The biochemical basis of electric fields arising from excitable tissues is the action potential (Pesaran et al. 2018; Gratiy et al. 2017; Tveito et al. 2017). Without loss of generality we will introduce these concepts in neurons, however the same applies to any excitable tissue. Generally speaking, at rest the cell membrane of neurons is electrically polarized (membrane potential; V_m): this membrane separates electrical charges (ions) between the inside and outside of the cell (intracellular and extracellular spaces respectively). This charge separation is given by virtue of the membrane structure; as the membrane is made up of “fatty” phospholipids it is impermeable to ions.

For the classical neuron the intracellular space has an excess of potassium ions (on the order of 10:1; intracellular : extracellular), and the extracellular space has an excess of sodium ions (again on the order of 10:1 extracellular : intracellular). Since ions

are charged, these ionic gradients are in fact electrochemical gradients, with a potential equaling the Nernst potential (typically $\sim 50\text{mV}$ for sodium, and $\sim -80\text{mV}$ for potassium). If we consider a slightly permeable membrane (see later) we get a weighted average given by the Goldman-Hodgkin-Katz equation setting the resting potential (Purves et al. 2001). This is the model for a neuron at rest; however, when perturbed, changes in the membrane potential affect so-called ion channels which fundamentally underlie the dynamic brain.

Ion channels are proteins which span the cell membrane and form hydrophilic (water-loving) pores across the membrane which ions are able to pass through (Hille 2001). Broadly speaking these channels are selective to a particular ion, e.g. a sodium channel will only pass sodium ions, or a potassium channel with potassium ions. Neural dynamics arise from the fact that these channels open or close for a variety of reasons, here we will consider the case of voltage-sensitive channels: channels that open or close in both a voltage, and time dependent manner (Purves et al. 2001; Hille 2001).

The end goal of this channel opening and closing is the “action potential”: the basis of brain function. For the purposes of explaining its mechanism, we will consider that somehow a perturbation has increased a neuron’s membrane potential (depolarized). In a classical cell when a weak perturbation occurs, the membrane potential will depolarize on the order of a few millivolts (related to the perturbation strength) before returning to its rest state. Interesting dynamics occur however when a sufficiently large perturbation occurs causing the membrane potential to cross some sort of threshold. In this case a regenerative process occurs in the membrane with membrane potential interacting with ion channels causing a large and fast depolarization (on the order of 10s of millivolts in and milliseconds), and a subsequent fast recovery to rest (Purves et al. 2001).

This rapid excursion and recovery of membrane potential is known as the action potential (AP or spike): a temporal process in which the membrane potential rapidly increases and then resets in response to a sufficiently strong perturbation or stimulus. An electrical analogy is the comparator; when an input is above some threshold, the comparator’s output is “high”, otherwise the output is “low”. This notion of threshold while certainly insufficient to cover the breadth of all neuron dynamics is adequate to introduce classical neural behaviour (Dayan and Abbott 2005; Izhikevich 2007).

Action potentials while being a temporal signal are strongly spatial. Neurons are spatially distributed, and composed of three main segments: dendrites, somata, and axons. Neurons receive these above-mentioned perturbations at their dendrites: an integration

accumulating area. These inputs are summed at the soma (information integration), and if some definition of threshold is reached, an action potential is initiated and it then propagates down the axon as a traveling wave (Purves et al. 2001; Johnson, Winlow, and Fraser 2018).

1.3 Action potentials in neural computation

The brain is a massively complex network of neurons, comprised of approximately 10^{11} neurons which form 10^{15} connections (Sporns, Tononi, and Kötter 2005), meaning about 10,000 connections per cell. This coupling is formed by synapses; either chemical, or electrical. A chemical synapse is formed when the (end of an) axon from one cell, meets the dendrite of another cell (pre and post-synaptic cells respectively). When the action potential reaches the end of the pre-synaptic axon it causes the release of neurotransmitters. These neurotransmitters are small chemicals (ligands) that cause the opening or closing of so-called ligand-gated channels on the dendrite of the post-synaptic cell. Much like voltage-gated channels, ligand-gated channels open in response to a specific neurotransmitter causing a similar perturbation (Hille 2001). Alternatively, electrical synapses (also known as gap junctions) are a physical, electrical continuity between two cells. The voltage in one cell physically drives electrical current into the second cell causing another voltage perturbation (Evans and Martin 2002; Jefferys 1995; Faber and Pereda 2018).

Generally, the post-synaptic neuron will receive only a weak perturbation from the pre-synaptic neuron (i.e. no action potential will be created). However if many action potentials are transmitted in rapid succession to a post-synaptic neuron, then the inputs will sum (so-called temporal integration). Alternatively, the post-synaptic neuron may receive many inputs from many pre-synaptic neurons in a short amount of time and sum them (spatial integration). When these integrated inputs become “large-enough”, then an action potential is initiated and this information processing cycle can continue (Purves et al. 2001).

1.4 Neural Dynamics: Modelling

All of the work in this manuscript, along with a large amount of existing work involves treating neurons from a theoretical perspective. Many excellent perspectives and de-

scriptions of this already exist (Dayan and Abbott 2005; Izhikevich 2007; Gerstner et al. 2014). Here we will reproduce the derivation of a class of neural models known as Hodgkin-Huxley models as done previously (Dayan and Abbott 2005) to give context for later chapters. The Hodgkin-Huxley model describes the squid giant axon from a first principles perspective (Hodgkin and Huxley 1952), by breaking down the action potential into a set of processes guided by physical (electrical) laws. Hodgkin and Huxley were the first to understand the mechanism behind action potential generation, this work was so revolutionary that they were awarded the Nobel prize in 1963 (along with John Eccles).

Considering the ability of the cell membrane to separate charge, analogous to an electrical capacitor, we will begin with its definition where a capacitance C , separates a charge Q , at a voltage (potential) V (Purcel and Morin 2013).

$$C = \frac{Q}{V} \quad (1.1)$$

If we assume a fixed capacitance which is the case for the cell membrane, differentiating and recalling that electrical current (I) is defined as the rate of charge transfer we achieve

$$C \frac{dV}{dt} = I \quad (1.2)$$

which by Ohm's law (substituting conductance $g = 1/r$ for resistance by convention) gives the passive membrane equation

$$C \frac{dV_m}{dt} = -g(V_m - E) \quad (1.3)$$

describing membrane dynamics about an equilibrium (rest) potential (E). Note from now on, we shift from considering an electrical component to the dynamics of the cell membrane therefore we will use V_m in place of V . If we additionally consider that the membrane current is a superposition of several currents, namely those due to the conductance of sodium and potassium ions

$$C \frac{dV_m}{dt} = -g_{Na}(V_m - E_{Na}) - g_K(V_m - E_K) \quad (1.4)$$

with each ion having some equivalent membrane conductance (g) and equilibrium potential (E , based on the Nernst equilibrium).

As mentioned earlier, channels open and close in a time and voltage dependent manner. If we consider that each channel has a gate with an open or closed configuration,

we can describe this by a set of opening (α) rates and closing (β) rates that depend on voltage. For example, we will consider a potassium channel gate, with the fraction open (n) then

$$\frac{dn}{dt} = (1 - n)\alpha_n(V_m) - n\beta_n(V_m) \quad (1.5)$$

which can be reformulated as

$$\frac{1}{\alpha_n(V_m) + \beta_n(V_m)} \frac{dn}{dt} = \frac{\alpha_n(V_m)}{\alpha_n(V_m) + \beta_n(V_m)} - n \quad (1.6)$$

typically denoted

$$\tau_n(V_m) \frac{dn}{dt} = n_\infty(V_m) - n \quad (1.7)$$

describing $n \rightarrow n_\infty$ as $t \rightarrow \infty$ with time constant (τ_n) (for a fixed V_m) (Dayan and Abbott 2005). We do this as it is more convenient to describe n as a voltage dependent process with characteristic timescale τ than to describe the dynamics of n as kinetic opening and closing rates (α and β).

Since this variable n is taken as the fraction of potassium channels that are open, we can imagine that n scales the potassium conductance of the membrane. For this reason currents are typically modeled as a scaled maximum conductance ($\overline{G}$)

$$C \frac{dV_m}{dt} = -m\overline{G_{Na}}(V - E_{Na}) - n\overline{G_K}(V - E_K) \quad (1.8)$$

with new variable m representing sodium channel state in a manner similar to n . It should be noted that generally ion channels can have multiple “gate-copies” (in some cases attributed to protein subunit conformation (Chapman, VanDongen, and VanDongen 1997)) which have an independent probability of opening. Recalling that for independent events A, B

$$P(A \cap B) = P(A)P(B) \quad (1.9)$$

we typically write

$$C \frac{dV_m}{dt} = -m^3 h \overline{G_{Na}}(V - E_{Na}) - n^4 \overline{G_K}(V - E_K) \quad (1.10)$$

where h represents a different type of sodium gate and the exponents represent multiple separate subgates being simultaneously open. Equation 1.10 is a representation

of a Hodgkin-Huxley model, these models describe how transmembrane ionic currents charge the membrane capacitor. It is important to note for the purposes of this work, the first step of this derivation (equation 1.2) showing an electric current is the most important. As we will see in the subsequent section, a time-varying charge density leads to a spatially distributed electric field.

1.5 Physical Origin of Bioelectric Fields

As mentioned, the ionic currents underlying the AP additionally give rise to electric fields (Buzsáki, Anastassiou, and Koch 2012; Hagen et al. 2018; Gratiy et al. 2017) (for distinction with externally applied electric fields we will call these bioelectric fields). The basis for electric fields are the Maxwell Electromagnetic Equations (Purcel and Morin 2013). The goal of this section is to show using standard approximations that in biologically relevant applications, the electromagnetic formulation can be restated as distinct electrical and magnetic laws. This is known as the quasielectrostatic and quasimagnetostatic formalism (Hagen et al. 2018; Gratiy et al. 2017). Ultimately we will show that under this formalism and making some further assumptions about what the extracellular medium can look like, we can recapitulate Maxwell as the Poisson equation as has been done previously (Gratiy et al. 2017; Bédard, Kröger, and Destexhe 2004; Haus and Melcher 1981).

Beginning with the Macroscopic Maxwell Equations (Purcel and Morin 2013) which are a set of 4 equations written here in their differential form (equations 1.11–1.14). Beginning with Gauss’ Law

$$\nabla \cdot E = \frac{\rho}{\epsilon_0} \quad (1.11)$$

describing the relationship between the electric field (E), the free charge density (ρ), and the permittivity of free space (ϵ_0). Additionally, we have the aptly named Gauss’ Law of magnetism

$$\nabla \cdot B = 0 \quad (1.12)$$

which describes the lack of sources (monopoles) in the magnetic field (B). Next are two coupling equations the Maxwell-Faraday law (induction)

$$\nabla \times E = -\frac{\partial B}{\partial t} \quad (1.13)$$

describing how a time varying magnetic field is associated with a spatially varying electric field, and the Maxwell-Ampere law

$$\nabla \times B = \mu_0 J + \mu_0 \epsilon_0 \frac{\partial E}{\partial t} \quad (1.14)$$

describing how the time varying electric field and free current density (J) is associated with a spatially varying magnetic field. It should be noted here that we are omitting bound currents as neuron membranes and extracellular media make poor dielectrics hence magnetization and polarization currents are negligible, therefore we will only consider free charges.

1.5.1 Magnetostatics and Electrostatics

In the case that E , and B fields are truly static then by equation 1.13, and assuming $\frac{\partial B}{\partial t} = 0$ we have

$$\nabla \times E = 0 \quad (1.15)$$

However neural fields are not truly static, but they are “slow” on EM field scales. We will first assume them to be sufficiently slow, and examine the consequences. We will consider a capacitor system with characteristic scale L (radius L and plate separation L). Because of this we will approximate the spatial derivatives as $1/L$. Additionally we will sinusoidally charge it with angular frequency ω , setting a characteristic timescale

$$\tau = \frac{1}{\omega} \quad (1.16)$$

which additionally gives an approximate time derivative $1/\tau$. Under these approximations equation 1.11 becomes

$$\nabla \cdot E \approx \frac{E}{L} = \frac{\rho}{\epsilon_0} \implies E \approx \frac{L\rho}{\epsilon_0} \quad (1.17)$$

Computing the now decoupled magnetic field related to this electric field from equation 1.14 (because there is no dielectric in the capacitor $J = 0$)

$$\nabla \times B \approx \frac{B}{L} = \mu_0 \epsilon_0 \frac{\partial E}{\partial t} \approx \mu_0 \epsilon_0 \frac{E}{\tau} \implies B \approx \frac{\mu_0 \epsilon_0 E L}{\tau} \quad (1.18)$$

Recalling that by equation 1.17 that $E \approx L\rho/\epsilon_0$ we have

$$B \approx \frac{\mu_0 L^2 \rho}{\tau} \quad (1.19)$$

These approximations were derived given the assumption that the magnetic field does not affect the electric field. However since this magnetic field should create a “second order” error electric field (back-EMF) by equation 1.13, what is the magnitude of the error field?

$$\nabla \times E_{error} \approx \frac{E_{error}}{L} = \frac{\mu_0 L^2 \rho}{\tau^2} \implies E_{error} \approx \frac{\mu_0 L^3 \rho}{\tau^2} \quad (1.20)$$

which is a relative error (where E is given by equation 1.17)

$$\frac{E_{error}}{E} \approx \frac{\mu_0 \epsilon_0 L^2}{\tau^2} \quad (1.21)$$

which is valid when the relative error $\ll 1$ or

$$\mu_0 \epsilon_0 L^2 \ll \tau^2 \quad (1.22)$$

Recalling that electromagnetic waves travel at the speed of light ($c = 1/\sqrt{\epsilon_0 \mu_0}$) then we have the distance traveled in characteristic time (τ) given by L/c . Which means the bounds expressed in 1.22 can be restated as

$$\frac{L}{c} \ll \tau \quad (1.23)$$

Interestingly this shows that contrary to what might be expected, semantically it's the length scale of the system that sets the validity of this approximation, not the frequency of the field. To put a number to the error, using a characteristic scale of 1mm in grey matter the relative error is on the order of 10^{-7} . I.e. in physiological systems electrostatic approximations are valid.

By Helmholtz decomposition, since the curl of the electric field is 0 (equation 1.15), we have that E can be expressed as the gradient of a scalar potential (Φ). For convention we negate this term.

$$E = -\nabla \Phi \quad (1.24)$$

Equation 1.24 recovers the properties of an electrostatic field (conservative and solenoidal). Now if we consider the current in the extracellular space this can be broken down into

ohmic (J_o) and diffusion currents (J_d) with diffusion currents for each ion being

$$J_d = F z_{ion} D_{ion} \nabla c_{ion} \quad (1.25)$$

with F being Faraday's constant, z , D , and c , being the valence, diffusion coefficient, and concentration of each ion. If we assume a relatively uniform ion concentration (valid away from the membrane interface layer). We can ignore diffusion currents leaving an ohmic current which is defined as

$$J = \sigma E = -\sigma \nabla \Phi \quad (1.26)$$

which is Ohm's law re-applied to fields instead of 1D currents. As a brief aside: when considering the Lorenz force Ohm's law is actually

$$J = \sigma(E + v \times B) \quad (1.27)$$

for charges traveling at a velocity v . In biology however, the largest velocity is $\sim 1\text{m/s}$ (arterial blood flow) giving a ratio $vB/E < 10^{-12}$ for physiological electric and magnetic field strengths, allowing us to ignore the magnetic component. Combining equation 1.26 with conservation of current (divergence of eq. 1.14, and recalling $\nabla \cdot \nabla \times u = 0$) gives the famous electrostatic Poisson equation.

$$\nabla \cdot J = \nabla \cdot (-\sigma \nabla \Phi) = \frac{\partial \rho}{\partial t} = C_{CSD} \quad (1.28)$$

with neuron sources acting as a current source density (C_{CSD}). In this work, every novel result is based on this Poisson quasielectrostatic formulation, with the exception of Chapter 3.

1.6 Roles of Bioelectric fields

Bioelectric fields have been shown to be useful phenomena for large scale brain recordings and inferring brain state and responses to various stimuli (Pesaran et al. 2018; Buzsáki, Anastassiou, and Koch 2012; Einevoll et al. 2013). However in this context, bioelectric fields are mostly considered epiphenomenal, anecdotally referred to as the “exhaust fumes of neural computation”. But is this true? Neuron activity is based off of voltage sensitive membrane proteins (which respond to voltage fluctuations across the membrane) (Hille 2001), therefore if the extracellular potential changes, then the membrane potential will

change in kind affecting ion channels (Anastassiou 2014; Anastassiou and Koch 2015). But how strongly do they respond? What is the effect of this response?

Philosophically we’re approaching science in a backwards manner, the underpinning of the scientific method is to observe an effect then proceed to understand it mechanistically. However this is the opposite. The existence of a plausible mechanism has been shown and we’re now in search of an effect, if there is any.

The effect of electric fields from one neuron affecting a neighbouring neuron is called ephaptic coupling (Jefferys 1995; Anastassiou 2014; Anastassiou and Koch 2015; Arvanitaki 1942; Anastassiou et al. 2011; Weiss and Faber 2010). In this work we will use the terms electric field effect(s) and ephaptic coupling interchangeably as in the literature there is incoherence with regards to the distinction if any (Jefferys 1995), and certainly for some cases in this work the term “ephaptic” is too restrictive or historically burdened to be sufficient.

This work will address the function of bioelectric fields from two different perspectives. Firstly we will explore the electrosensory system of weakly electric fish, a fish that generates a spatially large electric field for environmental sensing and communication. Subsequently we will study how network oscillations and synchrony are affected by bioelectric fields.

1.6.1 Bioelectric Fields in Weakly Electric Fish

One attractive system in which to study bioelectric fields is the electrosensory system of weakly electric fish. Electric fish are a group of fish which generate electric fields outside their body for the purposes of offense, defense, or communication (Moller 1995; Caputi et al. 2003; Hupe and Lewis 2009). Broadly speaking these fish come in two varieties: weakly and strongly electric (although it should be noted that many strongly electric fish have weak electric fields as well (Catania 2019; Bennett 1971a) However in both cases these fish have an electric organ (EO) which is comprised of modified muscle or motor neurons which create the electric field known as the electric organ discharge (EOD) (Moller 1995; Bennett 1971a). Indeed, the notion of bioelectricity was first explored scientifically in these fish by John Walsh in 1773 (Walsh 1773) and later Michael Cavendish in 1776 (Cavendish 1776). For interest sake we note that the (strongly) electric fish Torpedo was used as a headache and gout treatment in ancient Rome (Wu 1984). Additionally, the development of the modern day battery (first created by Alessandro Volta) was modeled after the EO of electric fish (Wu 1984; Assad 1997).

Strongly Electric Fish (Discharges)

Strongly electric fish were the first fish known (Wu 1984) and are what most people think about when imagining electric fish (Catania 2019). These include electric eels, rays, skates, and the like, with electrical discharges on the order of 600V (not millivolt), at up to an ampere (Moller 1995). These fish generate high-power electrical discharges in order to interact with prey or predators. Interestingly the highest potential discharge was recently discovered in a species of electric eel with a discharge of up to 860 volts (Santana et al. 2019) (on the order of $\sim 400\text{V/m}$) in contrast typical neuron field strengths are on the order of 1V/m (Anastassiou et al. 2010).

These electric eels (for convenience we will use the name “eel” but these are in fact a species of knifefish (Albert 2001)) are not included in this work, but they are interesting in their own right and warrant some discussion. Electrically, eels are fascinating, they’ve recently been shown to instinctually understand voltage dividers (Catania 2017). Eels will jump out of the water towards large predators increasing the current passed through the predator as opposed to dissipating in the water. Eels have additionally developed unique prey-capture techniques. Most smaller fish exhibit a c-start response, a rapid turn-around-and-flee behaviour in response to a predator. This behaviour has evolved to be extremely quick (as fast as 10ms to turn around, and 30ms to flee) (Korn and Faber 2005). This can pose a problem for large conspicuous predators such as eels (Catania 2015). Eels use their high-power electric field to arrest movement in prey causing a whole-body tetanus; not unlike the mechanism of a “Taser”. However in the eels’ case it actually works on prey motor neurons instead of muscle, an effect which has been described as “remote-control” (Catania 2015). Eels have even taken this one step further: instead of only causing tetanus they can additionally use their electric field to induce muscle twitches, creating motion in the water. This provides an additional mechanosensory cue (lateral line) which can aid in prey localization (Catania 2014).

Weakly Electric Fish (Discharges)

In contrast to strongly electric fish, weakly electric fish generate an electric discharge (electric organ discharge; EOD) on the order of 10s of millivolts (Moller 1995; Bennett 1971a; Bennett 1971b). The electrosensory system of these fish is the basis for most of this work. In brief the EOD is created by electric current generated by a large current source: the electric organ (EO). As this current flows through the skin it creates a voltage across the skin which is measured by electroreceptors embedded in the skin (Moller 1995;

Pereira and Caputi 2010; von der Emde G 1999), in a process not unlike ionic currents in a neuron membrane. When a heterogeneity is present in the environment, conductive objects will locally increase the current density whereas insulators will locally decrease the current density (here conductive and insulative is defined relative to the conductivity of water) (Crampton 2019; Assad, Rasnow, and Stoddard 1999). Therefore more, or less current will be driven through the skin and therefore induce a weak (order of microvolt) change to the induced potential measured by the receptors (Crampton 2019; Bullock et al. 2005). In electric fish the EOD can take many forms, the focus herein are the wave-type electric fish. The EOD of wave-type fish is periodic with a frequency which varies across both species and individuals. Low frequency fish can have EOD frequencies as low as 100Hz (Tricas and Carlson 2012), and high-frequency fish can have discharge frequencies in the 1.8kHz-2kHz range (Turner et al. 2007; Tagliacollo et al. 2016). While transient high frequency spiking in the mid 500 Hz is seen in many systems (Hu, Gan, and Jonas 2014; Mager et al. 2018), multi kilohertz spiking is generally not seen, and certainly not tonic spiking as is seen in the electric fish EOD.

This oscillatory EOD is controlled by the pacemaker nucleus (PN) in the fish’s hind-brain (Moortgat et al. 1998; Moortgat, Bullock, and Sejnowski 2000a; Elekes and Szabo 1985; Dye and Heiligenberg 1987). The PN is a collection of ~ 150 oscillatory pacemaker cells and ~ 30 relay cells (Lucas et al. 2019; Moortgat, Bullock, and Sejnowski 2000b; Ellis and Szabo 1980) which drive the EOD in a 1-to-1 fashion: for every spike in the PN, there is a corresponding cycle of the EOD (Lucas et al. 2019). The PN has two particularly interesting clock-like features. The timing precision, or variability in interspike interval (ISI) of cells in the PN (taken as coefficient of variation: CV) is $\sim 2 \times 10^{-4}$: more than an order of magnitude better than any other biological oscillator (Moortgat et al. 1998). In fact this clock is so precise that it corresponds to just over 100 minutes per year. Additionally the PN of the fish has near-zero-phase-lag synchrony across all cells ($\sim 2\%$ phase distribution cell-to-cell), in spite of incredibly weak coupling (Moortgat, Bullock, and Sejnowski 2000a; Lucas et al. 2019). The mechanism for this synchrony and precision is currently unknown, and in this work we will explore some of these problems.

1.6.2 Electrosense and Communication

To explain how fish sense their environment we will consider a fish slowly moving past an object in the water around them. At rest each electroreceptor will see a unique periodic waveform. However as the electroreceptor moves past the object, the current passing

through the receptor will grow and decay as the fish approaches and passes the object (for the conductive case), weakly modulating the amplitude of the receptor potential (Bastian 1981; Budelli and Caputi 2000; Stamper, Fortune, and Chacron 2013). This temporally changing amplitude is an amplitude modulation (AM), and electric fish electroreceptors can efficiently extract the amplitude modulation from this signal (Stamper, Fortune, and Chacron 2013; Metzen and Chacron 2014; Wessel, Koch, and Gabbiani 1996).

Despite the emphasis on electric sense, weakly electric fish additionally use their electric fields for communication between conspecifics (within their own species). One communication signal created by fish are called chirps, and are the focus of Chapter 4. In brief, chirping manifests as an increase in EOD frequency accompanied by a brief decrease in amplitude. Despite first being identified in 1968 (Hupe and Lewis 2009; Larimer and MacDonald 1968), the role of chirps is believed to be an aggression signal (Dunlap, DiBenedictis, and Banever 2010; Dunlap and Larkins-Ford 2003; Walz et al. 2013), associated with differences in frequencies between fish. One could argue that this is a specific manifestation of a more general behaviour; the jamming avoidance response (JAR).

When two fish of similar frequencies (with $\sim 5\text{Hz}$) approach each other, their electric fields interact with one another creating a beat frequency (or amplitude modulation) which is within the range of electro sensory AMs, creating a “virtual object” (Heiligenberg, Baker, and Matsubara 1978; Heiligenberg 1991). The JAR involves both fish adjusting their frequencies to maximize the bandwidth between them (higher frequency fish increases its frequency and *vice versa* for the other fish). This shifts the beat frequency into a non electrosensory-regime eliminating the virtual object created.

1.7 Interplay Between Bioelectric Fields and Neural Dynamics

The case for bioelectric fields affecting neural dynamics has a long, if sparse history spanning ~ 80 years (Jefferys 1995; Arvanitaki 1942; Weiss and Faber 2010; Furukawa and Furshpan 1963; Blot and Barbour 2014; Korn and Axelrad 1980) (for historical reviews see (Jefferys 1995; Anastassiou 2014; Anastassiou and Koch 2015; Weiss and Faber 2010)). Generally electric field effects are considered too weak to have any functional effect or role (Anastassiou and Koch 2015), and have been ignored. As a measure of “interest” as of 14/05/20 there are under 8000 Google Scholar matches for “ephaptic”

from 1939-present). Conversely there are 950,000 results for “hippocampus” in the same time period. Despite this lack of interest, there have been several landmark studies showing functional roles for electric field effects. The first role for electric field effects may have been the work of Furukawa and Furshpan (Furukawa and Furshpan 1963) where they showed that in the Mauthner cell (a neurocomputational mechanism for initiating the c-start response in fish), inhibitory interneurons come very close to the soma of the Mauthner cell in a region of very low extracellular conductance (large electric field). By virtue of the conductance, and cell geometry spiking in these inhibitory neurons strongly hyperpolarizes the Mauthner cell. The net effect being an incredibly fast (as soon as the spike reaches the end of the inhibitory axon) inhibitory mechanism which is involved in the c-start initiation (recalling that the c-start response is extremely quick $\sim 30\text{ms}$). This mechanism of cells very close together, particularly at synapses has been shown or predicted to have feed forward excitatory effects in electric fish (Matsushita and Kawasaki 2004; Carr 2004), and feedback inhibitory effects in clearing the synaptic cleft (Voronin 2000).

Arguably the second landmark ephaptic demonstration was in its role in epilepsy and epileptiform activity in 1982 by Jefferys and Haas (Jefferys and Haas 1982). They showed that by depriving hippocampal slices (CA1 region) of calcium, depolarizing the cells, that synchronous spiking emerged even in the absence of synaptic activity. This was later tied more directly to epilepsy in later computational (Traub et al. 1985b; Traub et al. 1985a), and experimental work (Dudek, Yasumura, and Rash 1998) showing similar effects of self-entrained network spiking. Some have argued that this does not constitute an “ephaptic mechanism” due to its pathological requirement (Weiss and Faber 2010), however, we will not make this distinction here.

What are the reasons that ephaptic coupling is dismissed as too weak? This question is particularly interesting considering that there are studies showing a clear and pronounced effect. Generally electric field effects are ignored for three main reasons. Firstly, its accepted that conductivity is too low. Secondly, since effects decay with distance, we are constrained by locality. Lastly, neurons often have the wrong geometry to facilitate electric field effects.

Firstly, we have the conductivity argument. From the electrostatic Poisson equation (1.28) we can see the electric field size scales with the conductivity of the extracellular medium; this scaling is reciprocal (doubling the conductivity halves the electric field strength). Several works have shown that in general, cortical tissue has a relatively

high conductivity (Miceli et al. 2017; Gabriel, Lau, and Gabriel 1996) meaning that the generated fields will be small (Tveito et al. 2017; Weiss and Faber 2010; Lindén et al. 2014; Shifman and Lewis 2019). Additionally the magnitude of the ephaptic effect is again related to the conductivity (Holt and Koch 1999), suggesting that the so-called ephaptic current will be small.

The second argument relies on the fact that electric fields decay with distance (Hagen et al. 2018; Buzsáki, Anastassiou, and Koch 2012; Holt and Koch 1999), as such any effect would be very spatially localized (Jefferys 1995). Spatial scales in the brain vary by several orders of magnitude. Synaptic clefts are approximately 30nm across (Kandel et al. 2012), and in white matter axons can have sub micron distances (Mingasson et al. 2017). In cortex dendritic assemblies (minicolumns), and microcolumns are on the order of 100 μ m (Innocenti and Vercelli 2010; DeFelipe, Markram, and Rockland 2012), and 200 μ m respectively (Markram et al. 2015). While it is true that given the $1/r^2$ spatial scaling of electric fields, a single spike may only be relevant a few microns away, limiting these sorts of field effects to very local patches of membrane. It is important to recall that LFPs arising from synchronous activity can span 100s of microns to millimeters (Lindén et al. 2011; Herreras 2016), weakening locality constraints.

The last argument against electric field effects is the geometric or “open-field/closed-field” argument. When describing field potentials, cells are often classed into open-field geometries or closed-field geometries (Buzsáki, Anastassiou, and Koch 2012). Pyramidal cells are typical examples of open-field geometries, being axially dispersed (apical vs. basal dendrite) and leading to a well defined dipole via current conservation. Conversely, for example, stellate cells are more spatially compact, and uniform. The activity on the various dendrites occur quasi randomly in time and amplitude, implying that there will be little to no net electric fields. The argument is therefore that for electric field effects, only open-field cells are of interest eliminating anything other than neurons with spatially-heterogeneous branching. In conflict to this however see the body of work showing ephaptic interaction in Purkinje cells (Blot and Barbour 2014; Han et al. 2018; Korn and Axelrad 1980)).

One, or a combination of these reasons is traditionally used to justify the omission of electric field effects from models of brain networks. However recently there have been several examples showing an uptake in field effect considerations. This may be in part due to particular interest in the similarity to external neuromodulation (Weiss and Faber 2010). In the hippocampus, traveling waves of activity have been shown to have

an ephaptic underpinning (Chiang et al. 2019) where the activity of many CA1 cells have summed to create a specially coherent field, eliminating concerns of locality. As a last ephaptic example with a particularly elegant similarity to work presented in Chapter 4 is work done in the medial-superior olivary nucleus (Goldwyn and Rinzel 2016). This system generates a large, coherent LFP in response to auditory stimuli, where it performs sub-microsecond timing computations for sound localization. The LFP modulates excitability of axons priming it for input in a similar frequency band. The relation to electric fish is in the pacemaker where synchronous cells are entrained to a large self-generated field modulating (or entraining) neuron timing. These weak comparisons will be a feature across most of this work creating a “poor man’s homeomorphism” between systems. This is a key technique from comparative physiology that we’ve adapted to neuroscience and the study of electric field effects in order to better understand them.

1.8 Thesis Overview

Examples of functional electric field effects in the literature are patchwork, with little commonality or overlap in system, effect, or mechanism between experiments. We have picked an organism to study, the electric fish, which create large spatially distributed electric field. We show how they’ve either adapted to or co-opted this field into their day-to-day life. We show common features between electric field effects acting over microns: the micro-scale involving their EOD control circuitry, and 10s of centimetres: the macro-scale involving their electrosense and electrocommunication.

1.8.1 Part One: the Micro-Scale

In part one we will study how electric fields interact with neurons. We will first develop a tooling and infrastructure platform called E_LFENN which provides a common interface for modeling electric field effects which is not possible in modern neuron solvers (Chapter 2). With this we are able to couple neuron models to each other through ephaptic coupling or to external electric fields. This work was published in Frontiers in Neuroinformatics (Shifman and Lewis 2019). We then develop a model of pacemaker cells in the PN (Chapter 3). We create this model by fitting a Hodgkin-Huxley style model to experimental waveforms. We then validate this model against experimental manipulations and compare our model in kind. Lastly we used E_LFENN in concert with our new cellular model to create an *in silico* PN in order to study how it resynchronizes in the

presence of electric field effects (Chapter 4). Ultimately we show that electric field effects from the EOD greatly improve synchronization time in the PN.

1.8.2 Part Two: the Macro-Scale

In part two we study fish behavior. We first study how EODs interact when similar EOD frequencies come in proximity (the proximate cause of the JAR) (Chapter 5). We show that the complexity in the spatio-temporal field of *Apteronotus* impairs its ability to effectively discriminate between fish higher or lower in frequency, leading to an impaired JAR response. We take a comparative physiological standpoint to explain JAR differences across species, we are then able to gain enough insight from this viewpoint to infer details about the evolution of these species. This was published in Royal Society Interface (Shifman and Lewis 2018). We subsequently develop new advanced modeling tools in order to extend electrosensory modeling to address more complex and physiologically relevant questions (Chapter 6). Current models are limited to stationary, and flat fish. Our new tooling allows fish to move freely allowing use to study how fish take advantage of their (non-stationary) EOD geometry in order to explore their environment.

1.9 References

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Part I

Micro-scale Bioelectric Fields

Chapter 2

E_LFENN: A Generalized Platform for Modeling Ephaptic Coupling in Spiking Neuron Models¹

Abstract

The transmembrane ionic currents that underlie changes in a cell’s membrane potential give rise to electric fields in the extracellular space. In the context of brain activity, these electric fields form the basis for extracellularly recorded signals, such as multiunit activity, local field potentials and electroencephalograms. Understanding the underlying neuronal dynamics and localizing current sources using these signals is often challenging, and therefore effective computational modeling approaches are critical. Typically, the electric fields from neural activity are modeled in a post-hoc form, i.e., a traditional neuronal model is used to first generate the membrane currents, which in turn are then

¹A. R. Shifman and J. E. Lewis (2019). “ELFENN: A Generalized Platform for Modeling Ephaptic Coupling in Spiking Neuron Models”. In: *Front. Neuroinform.* 13.May, pp. 1–11

used to calculate the electric fields. When the conductivity of the extracellular space is high, the electric fields are weak, and therefore treating membrane currents and electric fields separately is justified. However, in brain regions of lower conductivity, extracellular fields can feed back and significantly influence the underlying transmembrane currents and dynamics of nearby neurons—this is often referred to as ephaptic coupling. The closed-loop nature of ephaptic coupling cannot be modeled using the post-hoc approaches implemented by existing software tools; instead, electric fields and neuronal dynamics must be solved simultaneously. To this end, we have developed a generalized modeling toolbox for studying ephaptic coupling in compartmental neuron models: E_LFENN (E_LElectric Field Effects in Neural Networks). In open loop conditions, we validate the separate components of E_LFENN for modeling membrane dynamics and associated field potentials against standard approaches (NEURON and LFPy). Unlike standard approaches however, E_LFENN enables the closed-loop condition to be modeled as well, in that the field potentials can feed back and influence membrane dynamics. As an example closed-loop case, we use E_LFENN to study phase-locking of action potentials generated by a population of axons running parallel in a bundle. Being able to efficiently explore ephaptic coupling from a computational perspective using tools, such as E_LFENN will allow us to better understand the physical basis of electric fields in the brain, as well as the conditions in which these fields may influence neuronal dynamics in general.

2.1 Introduction

Electrical signaling in nervous systems involves large transmembrane ionic currents that lead to the formation of electric fields. These electric fields can be recorded in a variety of ways at different spatiotemporal resolution, from single unit activity to local field potentials (LFPs) and electroencephalograms (EEG) (Buzsáki, Anastassiou, and Koch 2012; Einevoll et al. 2013; Pesaran et al. 2018). In recent years, interest in the biophysical basis of these signals has increased, in part because of their importance in many brain-machine interface applications (Flint et al. 2013; Moran 2010; Waldert 2016). LFPs are generally characterized by the low-frequency (below ~ 100 Hz) components of extracellular signals thought to be dominated by synaptic processes (Buzsáki, Anastassiou, and Koch 2012; Einevoll et al. 2013). To better understand these signals, many modeling approaches have been developed, often in the form of software packages such as LFPy (Lindén et al. 2014), LFPsim (Parasuram et al. 2016), or VERTEX (Tomsett et al. 2014). Many of these packages are based on the NEURON simulation environment (Carnevale and Hines 2006), but regardless of the underlying equation solver, the membrane potential and ionic currents are calculated first, and then subsequently (post-hoc), the extracellular potentials are calculated. Because the underlying neural dynamics are considered independent of the extracellular fields in this case, we refer to this post-hoc LFP computation as the open-loop condition (Fig. 2.1A,C). In other words, the neural dynamics generate the LFP but the associated fields do not influence the neural dynamics. This scheme will be valid when the resulting fields are sufficiently weak, and the relevant timescales are short (Tveito et al. 2017).

However, when extracellular fields are sufficiently strong, they can affect membrane potentials, and in a sense, “feed back” and influence neuronal dynamics (Fig. 2.1B,D); in such cases, the open-loop assumption is no longer valid. This closed-loop condition of the LFP is commonly referred to as ephaptic coupling (Anastassiou et al. 2010; Anas-

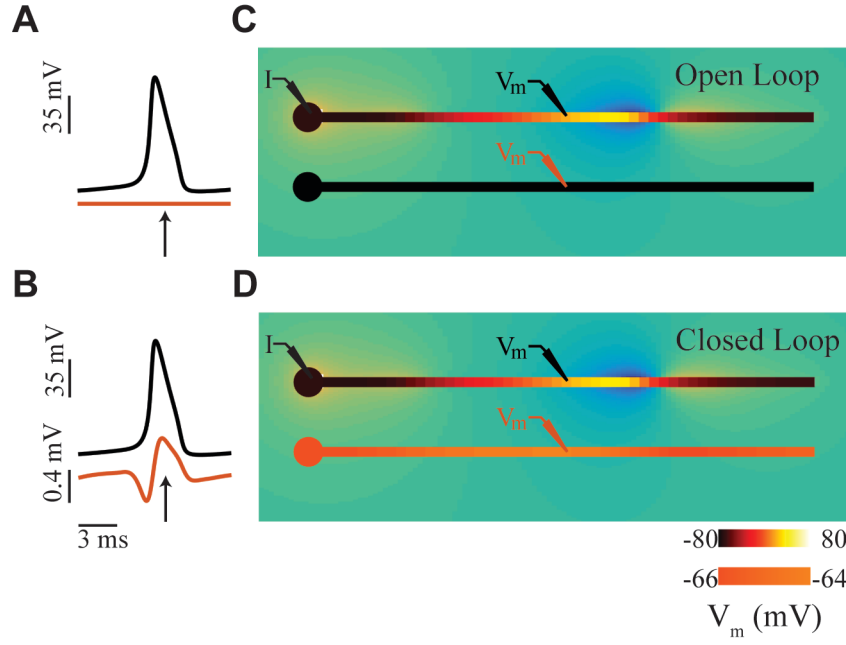


Figure 2.1: Intuition for ephaptic coupling. (A) Time series of membrane potentials in two adjacent neurons (comprising soma and axon compartments; see panel C) in an open-loop condition. (B) Similar to panel A, except in closed-loop condition involving ephaptic coupling (see panel D). The electric field generated by an action potential in the upper axon depolarizes the membrane potential of its neighbour. (C) Snap shots in time of open-loop condition representing a typical LFP simulation; time of snap shot is indicated by an arrow in panel A. (D) Similar to panel C, except in closed-loop condition involving ephaptic coupling; time of snap shot is indicated by an arrow in panel B. In all panels, a constant DC current is injected in the soma of the upper neuron (I) to produce propagating action potentials. In panels C and D, neuron color indicates membrane potential: in upper neuron, black denotes the resting potential (-80mV), and yellow is the spike peak ($+40\text{ mV}$); the color scale for lower neuron is inflated by a factor of 16 for illustrative purposes. The transmembrane currents involved generate an electric field in the extracellular space (blue negative, orange positive); low extracellular conductivities were used for illustrative purposes, resulting in extracellular potentials ranging from -15mV to 8mV .

tassiou and Koch 2015; Arvanitaki 1942; Holt and Koch 1999; Jefferys 1995). While the existence of ephaptic coupling is often acknowledged, it is not usually included in neuronal models. Indeed, this has been the subject of much debate (Anastassiou and Koch 2015; Weiss and Faber 2010). The common justification for omitting ephaptic coupling is that its influence is weak and insignificant. Recently however, weak ephaptic effects due to low-frequency oscillations (producing changes in membrane potential $<0.5\text{mV}$) have been shown to strongly entrain neuronal activity (Anastassiou et al. 2011; Fröhlich and McCormick 2010). And given that spiking probability can be dependent on the LFP phase (Gupta, Singh, and Stopfer 2016) and greatly influenced by noise transients (Destexhe and Contreras 2006; Kuhn, Aertsen, and Rotter 2004), the extracellular effects of local and population-level spiking activity could have a significant impact on neural computation.

In some contexts, weak electric field effects have been shown to play significant functional roles. For example, ephaptic coupling can modulate cardiac conduction velocity with respect to gap junctional connections, increasing conduction velocity when connectivity is weak and *vice versa*. (Lin and Keener 2010). Ephaptic coupling has also been implicated in the Mauthner cell system involved in the c-start escape response in fish, to enhance selectivity in response direction (Furukawa and Furshpan 1963; Korn and Axelrad 1980). Another interesting example has been described in some motor units, where ephaptic effects from muscle activity feeds back onto motor neuron axons, resulting in reverberating loops that enhance repetitive firing (Roth 1994) (Ephaptic coupling may also play a role in neuropathic pain through crosstalk between damaged nerves and adjacent fibers (Bridges, Thompson, and Rice 2001; Cohen and Mao 2014)). And most recently, ephaptic coupling was shown to synchronize firing of cerebellar Purkinje cells (Han et al. 2018). In other systems, ephaptic coupling may be difficult to avoid. Weakly electric fish generate an oscillating field for electric sensing that permeates their entire body. The potential ephaptic effects which this relatively strong electric field has on

neuronal processing is not known.

Although it is clear that ephaptic effects can be important in at least some conditions, the added complexity of extracellular influences on neurons in this closed-loop condition can lead to challenges from a modeling perspective; indeed, the tools required to compute ephaptic effects have not yet been packaged in any easy-to-use format. To this end, we have developed a general-purpose modeling toolbox to study ephaptic coupling that includes documentation and tutorials for various use cases.

2.2 Existing modeling tools

From a neural dynamics perspective, there are a multitude of feature-rich compartmental model solvers: for example NEURON (Carnevale and Hines 2006), GENESIS (Bower and Beeman 1998), and BRIAN (Goodman and Brette 2009). These solvers, as well as more specialized solvers (Tomsett et al. 2014), typically form the basis for post-hoc calculation of the LFP (or other bioelectric field measures). For example, LFPy (Lindén et al. 2014) is a popular tool that calculates LFPs (and now ECoG, EEG, and MEG signals (Hagen et al. 2018)) for neurons with geometries that can be as complex as the underlying NEURON environment can handle. In addition, BioNet is a recently developed tool which on top of enabling large simulations is also able to compute LFPs during NEURON simulations (Gratiy et al. 2018). None of these tools however are currently capable of easily integrating ephaptic coupling.

For ephaptic coupling (and extracellular stimulation in general), there are no software packages *per se*, but common methods involve the use of a resistive grid to describe the coupling of neurons in the extracellular space (Park et al. 2005; Traub et al. 1985), or in some cases the extracellular potentials are computed during the simulation and coupled directly to the neural dynamics (Goldwyn and Rinzel 2016; Holt and Koch 1999; Stacey, Hilbert, and Quail 2015). In the context of extracellular stimulation, finite element mod-

els implemented using COMSOL or equivalent tools are common (Elia and Lamberti 2013; Joucla, Glière, and Yvert 2014; McIntyre and Grill 2002; Pelot, Thio, and Grill 2018). This set of techniques spans a broad spectrum of biological realism. On one side of this spectrum are one dimensional linear cable models (Goldwyn and Rinzel 2016), which are the easiest to evaluate computationally. On the other side of the spectrum are finite element models (Joucla and Yvert 2012), which even after standard approximations (Elia and Lamberti 2013; Pelot, Thio, and Grill 2018) are computationally expensive, often making a detailed exploration of parameter spaces prohibitive. In addition, these model implementations are not always freely available and accessible to the general user; and in cases where models are published, they are often application specific. To this end, we have developed E_LFENN (E_LElectric Field Effects in Neural Networks), a MATLAB (Mathworks.com) toolbox which provides an accessible interface to the (Holt and Koch 1999) method of modeling ephaptic coupling. By using standard compartmental methods, notation and terminology (i.e. similar to that used in the NEURON environment), our goal is to make modeling ephaptic coupling accessible to the community at large.

2.3 Modeling ephaptic coupling: theory

In recent years both, ephaptic coupling (Goldwyn and Rinzel 2016; Holt and Koch 1999; Stacey, Hilbert, and Quail 2015), and extracellular stimulation (Joucla and Yvert 2012; McIntyre and Grill 2002) have been modeled computationally. Depending on the particular question, the methods vary from highly abstracted, but simple-to-evaluate linear cable models (Goldwyn and Rinzel 2016) to highly detailed realistic neuronal morphologies implemented using computationally expensive finite element models (McIntyre and Grill 2002). It is clear that neuron morphology plays a strong role in shaping the LFP (Lindén, Pettersen, and Einevoll 2010) and thus will influence ephaptic coupling dynamics. Here, we strike a balance between anatomical realism and computational expense

and provide, based on previous work (Holt and Koch 1999), a simple modeling interface to directly couple neuronal membrane potential dynamics and the LFP.

We begin with the Hodgkin-Huxley formalism for the transmembrane potential of a spatially-extended neuron (Dayan and Abbott 2005; Hodgkin and Huxley 1952). For a given neuronal compartment i , there is a membrane potential (V_m^i), a set of voltage-dependent ion channel conductances (g_{ion}^i , determined by their respective dynamical gating variables e.g. m, h , and n , not shown here) and equilibrium potentials (E_{ion}); in addition, there is a current between any adjacent compartment j , through an intracellular resistance $R^{i,j}$. The membrane dynamics for compartment i coupled to an adjacent compartment j are summarized in equation 2.1. While it is true in general that a typical compartment would have at least two neighbours, we omit the second compartment here for simplicity:

$$C_m \frac{dV_m^i}{dt} + \sum_{ion} g_{ion}^i (V_m^i - E_{ion}) = \frac{1}{R^{i,j}} (V_m^j - V_m^i) \quad (2.1)$$

For any given compartment, the transmembrane potential (V_m), can be expressed as the difference between the intracellular potential (V_{in}), and the extracellular potential (V_{out}) (equation 2.2):

$$V_m \equiv V_{in} - V_{out} \quad (2.2)$$

If the extracellular potential V_{out} is 0 (more accurately, if the gradient in the extracellular potential is 0), then equation 2.1 holds. In this situation, the axial current term is more appropriately described by the intracellular potential, leading to a modification of equation 2.1:

$$C_m \frac{dV_m^i}{dt} + \sum_{ion} g_{ion}^i (V_m^i - E_{ion}) = \frac{1}{R^{i,j}} (V_{in}^j - V_{in}^i) \quad (2.3)$$

Following previous methods (Goldwyn and Rinzel 2016; Holt and Koch 1999), we can

rewrite equations 2.2 and 2.3 to incorporate non-zero extracellular potentials (equation 2.4):

$$C_m \frac{dV_m^i}{dt} + \sum_{ion} g_{ion}^i (V_m^i - E_{ion}) = \frac{1}{R_{i,j}} (V_m^j - V_m^i) + \frac{1}{R_{i,j}} (V_{out}^j - V_{out}^i) \quad (2.4)$$

This extra term is referred to as the ephaptic current (equation 2.5; (Holt and Koch 1999)):

$$i_{eph} = \frac{1}{R_{i,j}} (V_{out}^j - V_{out}^i) \quad (2.5)$$

Finally, we use a common formalism in both ephaptic and LFP literature to define V_{out} (Holt and Koch 1999; Lindén et al. 2014). Under a quasi-electrostatic approximation, the extracellular potential will be the solution to the Poisson equation (eq 2.6) where V is the potential over the extracellular domain, σ is the conductivity of the medium and C_{CSD} is the current source density arising from neural sources (Gratiy et al. 2017; Tveito et al. 2017).

$$\nabla \cdot \sigma \nabla V = -C_{CSD} \quad (2.6)$$

While this equation can be solved using a finite element approach, as previously noted, this can be computationally expensive in practice. However, for certain boundary conditions these equations have explicit solutions. This is the case for standard compartmental neuronal geometries that use combinations of spherical and cylindrical compartments to model somata, axons, and dendrites. The solution for a cylindrical current source (eq 2.7) comes from the line source approximation (Holt and Koch 1999), and that for a spherical current source (eq 2.8) comes from the point (spherical) source (see figure 2.2 and legend for definitions).

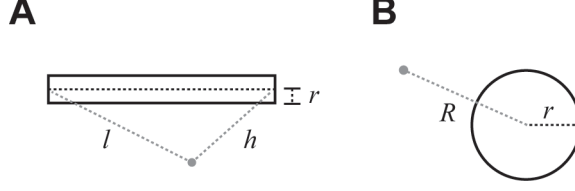


Figure 2.2: Illustration of variables for electric field calculations (see equations 2.7 and 2.8). A) cylindrical current source: r is the radius of the cylinder, l is the distance from the beginning of the cylinder, h is the distance from the end. B) spherical current source: R is the distance from the center of the sphere, and r is the radius of the sphere.

$$V_{out} = \frac{I_m r}{2\sigma} \log \left(\left| \frac{\sqrt{h^2 + r^2} - h}{\sqrt{l^2 + r^2} - l} \right| \right) \quad (2.7)$$

$$V_{out} = \frac{I_m r}{\sigma R} \quad (2.8)$$

2.4 Modeling ephaptic coupling: implementation using E_LFENN

We have implemented the approach described in the previous section as a software toolbox called E_LFENN (**E**Lectric **F**ield **E**ffects in **N**eural **N**etworks). E_LFENN can be downloaded (see availability section) and installed from within MATLAB. E_LFENN comprises two parts, a geometry toolchain and a solver toolchain.

To construct neuronal geometries, we use standard compartmental neuron modeling approaches, and for ease of use and comparison, standard terminology has been adopted where possible. As in the NEURON environment, model neurons are defined by a combination of spherical (somata) and cylindrical (axons and dendrites) geometries called Sections, which are then discretized into nodes (where the equations are solved) called Segments.

To solve models with ephaptic coupling, we provide a wrapping solver which wraps commonly-used neural dynamics models with the extracellular dynamics. The resulting

dynamics, as described above (eq 2.3–2.8), form a system of differential algebraic equations (DAE). Extracellular potentials for each segment are given by equations 2.7 or 2.8 (for cylindrical and spherical sections respectively). Because the Poisson equation (eq 2.6) is a linear PDE, linear superposition holds, i.e. the solution to the sum of several compartments (i.e. Segments) can be calculated as the sum of contributions from each individual compartment (Lindén et al. 2014; Parasuram et al. 2016). To calculate a single extracellular potential for each compartment, V_{out} is averaged over the boundary of the segment, which will be valid when the radius and length of the segment is small relative to the characteristic length of the field (at that point). Note that in some previous work, the cable equation is not discretized, leaving a partial DAE (PDAE), which is solved as a boundary value problem (Goldwyn and Rinzel 2016).

The membrane dynamics depend on the extracellular potential (V_{out}) (eqs. 2.7 and 2.8), which in turn depend on the membrane current defined (eq 2.4). Unlike traditional ODEs which when solved explicitly take the form of a function applied to the previous time step to compute the future time step, the circularity in this system requires the future time step to be solved self-consistently (similar to implicit methods). The DAE solver used here (MATLAB’s ode15s) solves systems of the form:

$$M\dot{x} = f(x, t) \tag{2.9}$$

where M is the identity matrix of equal dimension to that of the DAE with the exception that 0’s on the diagonal specify the algebraic components. Given that all equations in the DAE are solved simultaneously, the time step is adjusted (shortened) until the numerical approximation of the DAE is satisfied to within tolerance, i.e. a self-consistent solution. The solver we have implemented here allows ephaptic dynamics to be included automatically without any extra work from the end user.

2.5 Validating the components of E_LFENN

Given that E_LFENN implements a combination of common algorithms, we can validate each component separately in open-loop conditions (i.e. no ephaptic coupling) against existing LFP and compartmental neuron model solvers. In the interest of brevity, we present only two comparisons here: action potential propagation using NEURON (to validate the membrane potential dynamics in open loop) and LFPy (to validate the LFP in open-loop); additional examples are included with E_LFENN.

2.5.1 Validating neural dynamics

In our first example (figure 2.3), we consider action potential propagation in the classic Hodgkin-Huxley model included in NEURON (Carnevale and Hines 2006). To validate the cable equation solver used in E_LFENN, we implemented these dynamics using four basic neuronal morphologies with both E_LFENN and NEURON (CVODE) solvers (in the E_LFENN solver ephaptic coupling is turned off). Figure 2.3 (A-D) shows a 30 ms simulation for each geometry, with membrane potential recordings at three representative locations (color-coded as green, orange, purple by location). A schematic of each neuron is presented on the right of each panel showing the recording locations along with the site of a constant current injection (I) used to initiate the repetitive action potentials. The solutions from E_LFENN are color-coded by location, and the solutions from NEURON are overlaid as a dashed black line in each case. The different solutions essentially overlap, with average RMS errors well below 0.5mV, and the majority of error arising from slight discrepancies in spike timing (10-20 μ s).

2.5.2 Validating generated LFPs

In our second example (figure 2.4), we consider the same Hodgkin-Huxley model but limited to a single axon and calculate the LFP using LFPy (Lindén et al. 2014) to

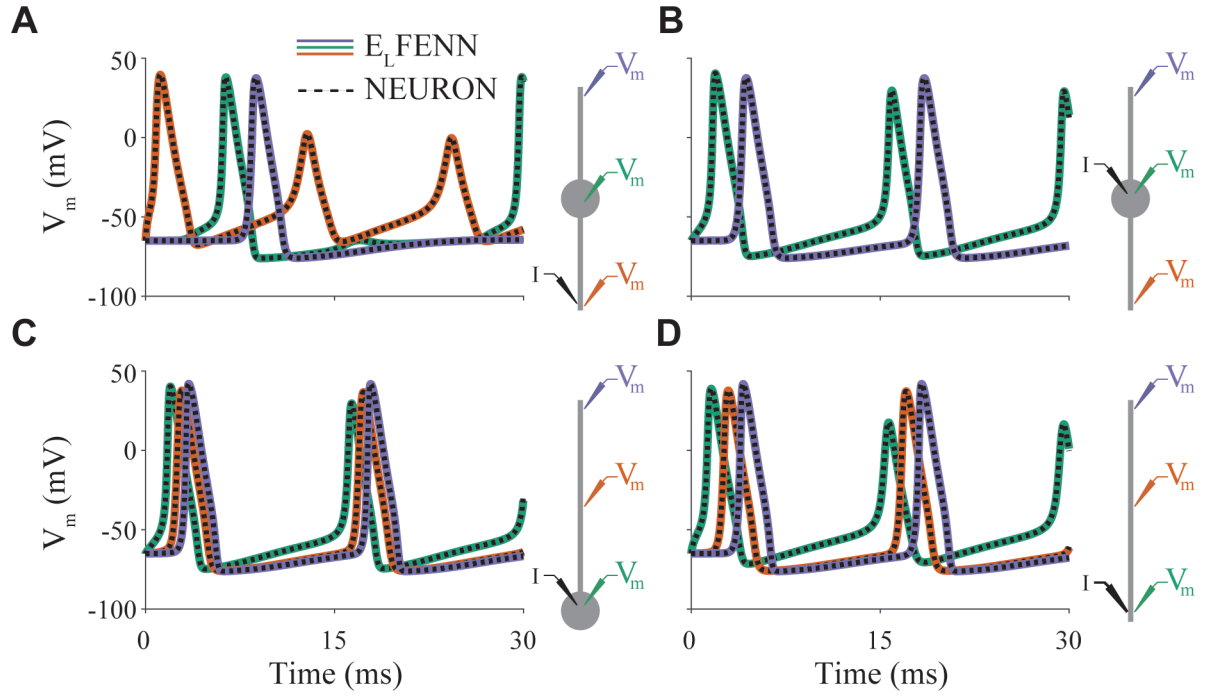


Figure 2.3: Validation of neural dynamics. Each panel shows membrane potential over time for a different neuron morphology (indicated by schematics on right). Colored traces are E_LFENN simulations at the recording locations denoted in schematic with appropriate color. Dashed traces are the corresponding NEURON solutions in each case. Current is injected at location denoted by “I”. Orange trace in panel B is occluded by purple trace; the solutions are identical due to symmetry.

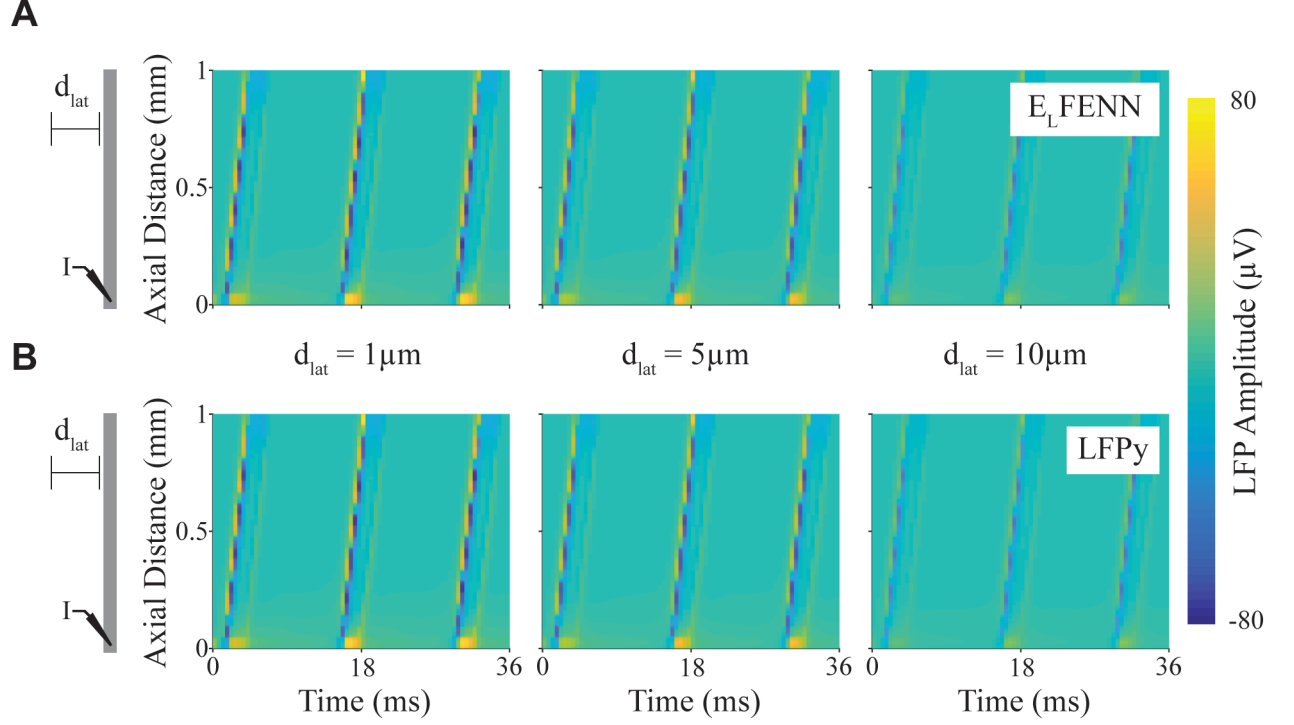


Figure 2.4: Validation of LFP calculation. Spatiotemporal LFPs from an axon firing repetitive action potentials calculated using LFPy or E_LFENN (schematic shows DC current injection at “I”, and length of axon is scaled to plot). (A) LFP computed using E_LFENN at lateral distances, d_{lat} , of $1 \mu\text{m}$, $5 \mu\text{m}$ and $10 \mu\text{m}$ respectively, from the axon. (B) LFP computed using LFPy at lateral distances, d_{lat} , of $1 \mu\text{m}$, $5 \mu\text{m}$ and $10 \mu\text{m}$ respectively, from the axon.

validate the LFP computed by E_LFENN (in open loop). While only one geometry is presented here, all of the geometries considered in figure 2.3 show similar results, and are included as additional comparisons with E_LFENN software.

In figure 2.4, a schematic of the setup shows a straight axon with DC current injected (I) at one end. LFPs are measured along a line parallel to the axon at lateral distances (d_{lat}) of $1 \mu\text{m}$, $5 \mu\text{m}$ and $10 \mu\text{m}$ (note that we focus on the accuracy close to the axon boundary where V_{out} is determined). The upper (A) and lower plots (B) show the spatiotemporal LFP at these three locations, for E_LFENN and LFPy respectively. Contrary to many LFP plots which are in two spatial dimensions, only the vertical axis here represents space, with time represented on the horizontal axis. Wave-like behaviour is apparent due to the periodicity of action potential firing caused by the DC current

injection. Overall, the results of the two methods are quite similar with the RMS error of all results less than $1.7\mu\text{V}$ (1.1%), and again the majority of the error arises from slight spike timing differences ($\sim 10\mu\text{s}$).

2.6 Scope, Capabilities and Limitations

In this section we will describe the main components of the E_LFENN toolbox. Further explanation and examples can be found in our documentation which can be accessed by running the MATLAB ‘doc’ command and clicking the E_LFENN toolbox link once E_LFENN has been installed.

2.6.1 Using E_LFENN: Geometry

The first step in the modeling process is to create a cell geometry. Using NEURON-like terminology, cells are composed of sections: cylindrical chunks for axons and dendrites, and spheres for somata. Cells in E_LFENN are created section by section as seen in the following code snippet, where a spherical soma and a cylindrical axon are connected together to create a cell named *ball_and_stick*. Several additional functions for setting angles, orientations, and other morphological properties are explained in our documentation with examples.

```

1 soma = ELFENN.Section('soma', 'radius', 15,...
2     'sectionLength', 30, 'sectionGeometry', 'S');
3 axon = ELFENN.Section('axon', 'radius', 2, 'sectionLength', 1000);
4 cell = ELFENN.Cell('ball_and_stick');
5 cell.connectsection(soma, axon);

```

Alternatively, E_LFENN is also able to import SWC files, of which a large database can be accessed from neuromorpho.org (Ascoli 2006; Ascoli, Donohue, and Halavi 2007). The parser outputs an E_LFENN compatible cell object (see section on realistic neuron example) which can then be tied to dynamics and simulated.

Once a cell, or multiple cells have been created they can be added to a network; for our purposes the word “network” refers to the whole system, i.e. whether the network is a single compartment or ten cells, the network label applies. In the following code, cell1 is added to the origin and a copy is added with a 100 μ m offset in the z-dimension.

```
1 network = ELFENN.Network();
2 network.addcell(cell1);
3 network.addcell(cell1, [0, 0, 100]);
```

Much like cells, there are tools for setting orientation and position of networks that are described in our documentation.

2.6.2 Using E_LFENN: Dynamics

Action potential dynamics are typically modeled using two classes of models: continuous models, i.e. Hodgkin-Huxley-like where the dynamics are described by a set of differential equations and so-called hybrid models such as the Izhikevich model (Izhikevich 2003) or leaky integrate-and fire (LIF) models (Gerstner et al. 2014) which rely on discontinuities to generate spikes. E_LFENN can only solve models of the continuous type. Any specific continuous model can be solved, as long as the dynamics can be set up as a function involving time, state, and parameters as inputs, and the right-hand side of the differential equations as a column vector of outputs. As an example, the source code for the Hodgkin-Huxley model is presented below.

```
1 function dY = ode(t, y, p)
2
3 am = @(v) 0.1 * (v + 40) ./ (1 - exp(-0.1*(v + 40)));
4 bm = @(v) 4 * exp(-0.0555556*(v + 65));
5
6 ah = @(v) 0.07 * exp(-0.05*(v + 65));
7 bh = @(v) 1 ./ (1 + exp(0.1*(-v - 35)));
8
9 an = @(v) 0.01 * (v + 55) ./ (1 - exp(-0.1*(v + 55)));
10 bn = @(v) 0.125 * exp(-0.0125*(v + 65));
11
12 dY = zeros(size(y));
```

```

13 Vm = y(1:4:end);
14 m = y(2:4:end);
15 h = y(3:4:end);
16 n = y(4:4:end);
17
18 membraneCurrent = (-m.^3 .* h .* p.gNa .* (Vm - p.ENa) - ...
19                    n.^4 .* p.gK .* (Vm - p.EK) - p.gL .* (Vm - p.EL));
20
21 dY(1:4:end) = membraneCurrent / p.C;
22 dY(2:4:end) = (am(Vm) .* (1 - m) - bm(Vm) .* m);
23 dY(3:4:end) = (ah(Vm) .* (1 - h) - bh(Vm) .* h);
24 dY(4:4:end) = (an(Vm) .* (1 - n) - bn(Vm) .* n);
25 end

```

E_LFENN includes three example dynamics with accompanying parameters: Hodgkin-Huxley, fast-spiking interneurons (Mancilla et al. 2007), and passive dynamics which require no custom code. However, any dynamics following the format of the above code snippet can be implemented.

E_LFENN also includes a variety of features that allow synaptic interactions between neurons as well as external inputs (both synaptic and electrode-based, which can be applied to both the intracellular and extracellular space). For intracellular and extracellular stimuli, we include DC, and sinusoidal functions, however arbitrary stimulus functions can also be used, both autonomous (state dependent) and non-autonomous (time dependent). Extracellular stimuli can be either point current sources or parallel plate electric fields. Synaptic coupling between cells can involve gap junctions (electrical synapses) and/or chemical synapses. Lastly, E_LFENN also provides functionality for external synaptic inputs with pre-set spike times (e.g. from a Poisson spike train).

2.6.3 Using E_LFENN: Limitations and Cost

Traditional compartmental models have an associated computational cost, and this will be true for any solver, including NEURON. Solving these models in the absence of ephaptic coupling will be primarily an order n operation ($\mathcal{O}(n)$) since the axial current

can be represented by a dot product of a sparse (almost) tridiagonal matrix (Hines 1984). However, when incorporating ephaptic coupling, all currents will affect all compartments, and thus all pairwise interactions must be evaluated, i.e. an $\mathcal{O}(n^2)$ operation. While any LFP solver (for example LFPy, LFPsim, or BioNet) will have the same $\mathcal{O}(n^2)$ complexity they are not tied to the dynamical solution and therefore only need to be computed for successful time steps and can be down-sampled if required. These advantages are not available to ELFENN as the extracellular potentials are intrinsic to the dynamical system. Additionally, solving stiff DAEs (implicit methods), for which the Jacobian must be frequently estimated, and Newton iterations must be run to compute self-consistent values, can lead to high computational costs not typically seen when solving models without ephaptic coupling.

In terms of scalability, the aforementioned $\mathcal{O}(n^2)$ complexity limits the size of the network (in terms of number of compartments) to whatever speed the user is willing to accept given their processor. Furthermore, because these algorithms in MATLAB are locked to a single processor, memory limitations are also a factor (e.g. with 8GB of RAM, 2000-3000 compartments might cause MATLAB to run out of memory). That said, much can still be learned about ephaptic coupling through the investigation of relatively small networks, for which the cost will be comparable to that of a standard model without ephaptic coupling solved using NEURON.

2.7 Ephaptic coupling in realistic Geometries

As a simple example case, we present a model of two neurons with previously described stellate-like geometry (neuromorpho.org NMO_66468) (Ascoli 2006; Ascoli, Donohue, and Halavi 2007; Morelli et al. 2017) and neural dynamics (Mancilla et al. 2007). The two cells are positioned in close-proximity, in an extracellular space with conductivity 0.01 S/m. The left (active) neuron has its soma at the origin ($[0,0,0]$), and the right

neuron is mirror image and offset 140 μ m to the right (figure 2.5A). The soma of the left neuron receives a supra-threshold external synaptic input at 5ms (location denoted by red marker). The red, purple and blue markers indicate compartments where membrane potential is recorded and displayed in figure 2.5B.

In figure 2.5B, the red traces are from the active (left) neuron (with synaptic conductance: upper trace) showing a full action potential; the blue and magenta traces are from the inactive (right) neuron and show the ephaptic coupling potentials ($\sim 500\mu$ V deviation in membrane potential). To show the spatial heterogeneity of the extracellular potential (LFP), snapshots of the LFP (figure 2.5C) are taken at 10ms (vertical arrow in figure 2.5B) and displayed as slices taken at $z=20, 0$, and -20μ m.

The source code below highlights the simplicity of implementing this model using ELFENN:

```

1  cell = ELFENN.Geometry.load_swc('P7i_WT3.CNG.swc');
2  cell.name = 'cell1';
3  network = ELFENN.Network();
4  network.addcell(cell);
5  cell.name = 'cell2';
6  cell.rotatecell([0, pi, 0], [0, 0, 0])
7  network.addcell(cell, [140, 0, 0]);
8  network.complete();
9  network.assignsolutionindex("Vm","m","h","n","q");
10
11 synapse_params = ELFENN.Mechanisms.Synapse.Alpha.default_parameters;
12 synapse_params.tau = 3;
13 synapse_params.gSyn = 5;
14 synapse_params.t0 = 5;
15 network.addexternalsynapse(network.getcellbyname('cell1').soma,...
16                             @ELFENN.Mechanisms.Synapse.Alpha.s, synapse_params, 'unscaled');
17
18 sigma = 0.01;
19 IC = [-69.7548 0.05, 0.59 0.31 0.0002];
20 network.setdynamics(ELFENN.Mechanisms.Cellular.FS.default_parameters());
21 solver = ELFENN.Supervisor(@ELFENN.Mechanisms.Cellular.FS.ode, network, IC, sigma);
22
23 solver.ephapticStatus = 'on';

```

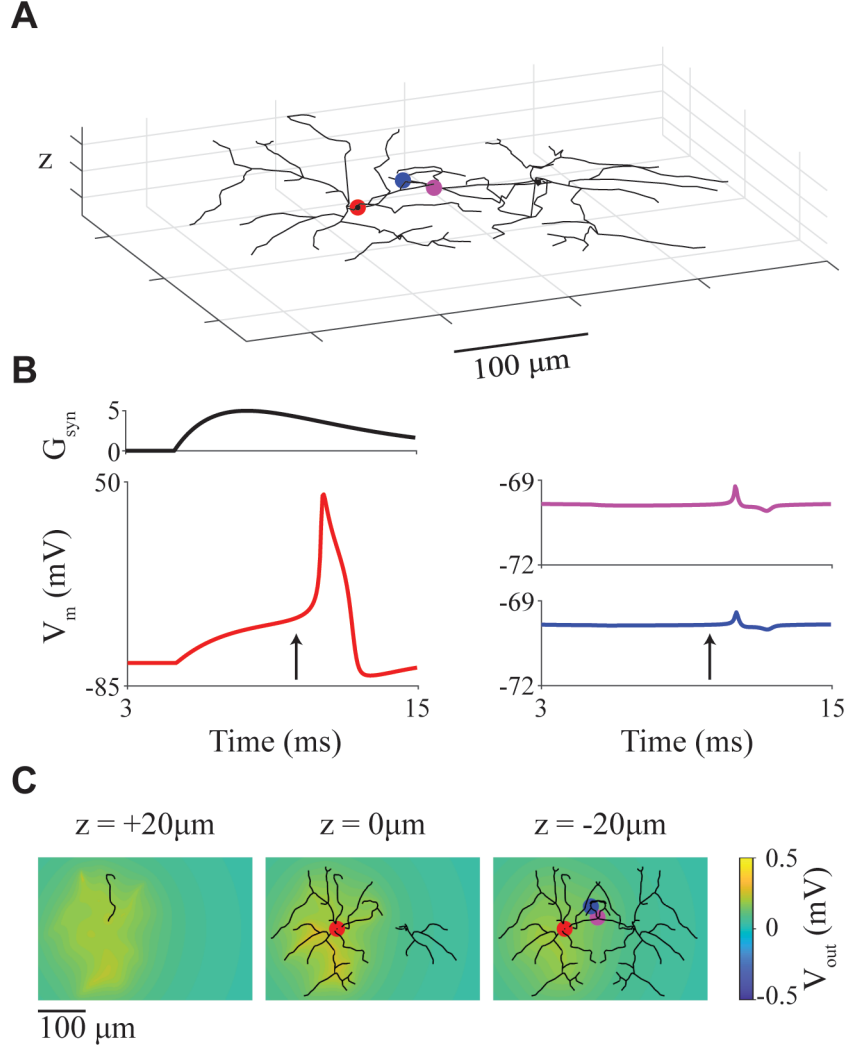


Figure 2.5: Ephaptic coupling between model neurons with realistic geometries. A) Representation of two cortical interneuron models placed with somata 140 μm apart. Markers represent recording locations (red: active neuron, magenta and blue: inactive neuron). Red marker also represents location of a suprathreshold chemical synapse. B) Synaptic conductance of synapse (G_{syn}) at red point in panel A as well as membrane potential at red, blue, magenta points in panel A. C) LFP at slices at $z=20$, 0, -20 μm through the network at the time indicated by arrows in panel B.

```

24 solver.tmax = 15;
25 solver.rtol = 1e-3;
26 solver.transientLength = 2;
27 [t,y] = solver.run();
28
29 %% Plots
30 [~, soma] = network.segmentclosestto([0, 0, 0]);
31 [~, bottom_seg] = network.segmentclosestto([69, 23.7, -2]);
32 [~, edge_seg] = network.segmentclosestto([55, 47, -2]);
33
34 make_fig_1(soma, bottom_seg, edge_seg, network)
35 make_fig_2(soma, bottom_seg, edge_seg, t, y, synapse_params)
36 make_fig_3(soma, bottom_seg, edge_seg, t,y, network, solver, sigma)

```

Note that the code for the plots do not relate to E_LFENN specifically and as such are not displayed other than as function calls (see E_LFENN documentation for full implementation).

2.8 Ephaptic coupling between adjacent axons

We now present a simple use case for the novel closed-loop functionality of E_LFENN: the ephaptic coupling among axons aligned in parallel (Bokil et al. 2001; Goldwyn and Rinzel 2016; Jefferys 1995; Ramón and Moore 1978). In particular, we describe how the phase-locking effects of ephaptic coupling are influenced by extracellular conductivity in this situation. Although the range of conductivities we consider may exceed physiological values, we are interested in identifying the conditions for which ephaptic coupling could be functionally relevant. Conductivities can vary across brain region (Gabriel, Lau, and Gabriel 1996; Miceli et al. 2017) and may even be regulated, for example through the control of extracellular potassium by oligodendrocytes (Larson et al. 2018)

We consider a simplified scenario involving an axon bundle, in which a central axon is surrounded by six others, hexagonally tiled (see figure 2.6A). All axons have standard Hodgkin-Huxley dynamics (figures 2.3 and 2.4) and are set in an oscillatory firing regime,

each with different baseline frequencies, by slightly different levels of DC current injection in the first segment (frequencies are annotated in figure 2.6A). The initial condition for each axon is a random point on its own limit cycle to minimize effects of individual transients; the simulation time was 2 seconds. We use the spike train cross correlation function to characterize phase locking. In open-loop conditions (no ephaptic coupling), or when conductivity (σ) is very high, one would expect the spike trains to precess and thus cross-correlation functions would have a low uniform value on average across all phase lags. On the other hand, when firing is tightly coupled, there would be structure in the cross correlation e.g. dominant peaks at multiples of the locking period, potentially shifted by a phase lag. To measure the cross correlation, spikes in the last second of the simulation were binned into 1ms windows (average oscillator period is 12.5ms) and the cross correlation was computed and presented for ± 1 oscillator period. We vary conductivities (σ) from 10 S/m (well above typical CNS conductivities) to 0.05 S/m which is the lowest estimate of conductivity in the CNS across multiple studies (Gabriel, Lau, and Gabriel 1996; Miceli et al. 2017). We then extend the analysis to a value of 5×10^{-4} S/m as an upper bound on the effect size.

Figure 2.6B shows cross correlation functions for open-loop (ephaptic off; grey), intermediate conductivity ($\sigma = 0.0025$ S/m; blue) and low conductivity ($\sigma = 5 \times 10^{-4}$ S/m; red). Cross correlations are computed for each neuron pair (7 neurons yielding 21 unique pairs) over 15 sets of initial conditions; the data are presented as the mean correlation with shaded region showing standard deviation. For increasing ephaptic effect (decreasing conductivity), we see larger peaks at 0 and 6ms (synchronous and anti-synchronous locking). To summarize these effects, the peak cross-correlation is presented in figure 2.6C as mean and standard deviation across initial conditions and axon pair (all conductivities used the same sets of initial conditions). The red and blue symbols in figure 2.6C show peak measures for the same data shown by the red and blue traces in figure 2.6B, and horizontal line represents the mean cross-correlation value where ephaptic coupling

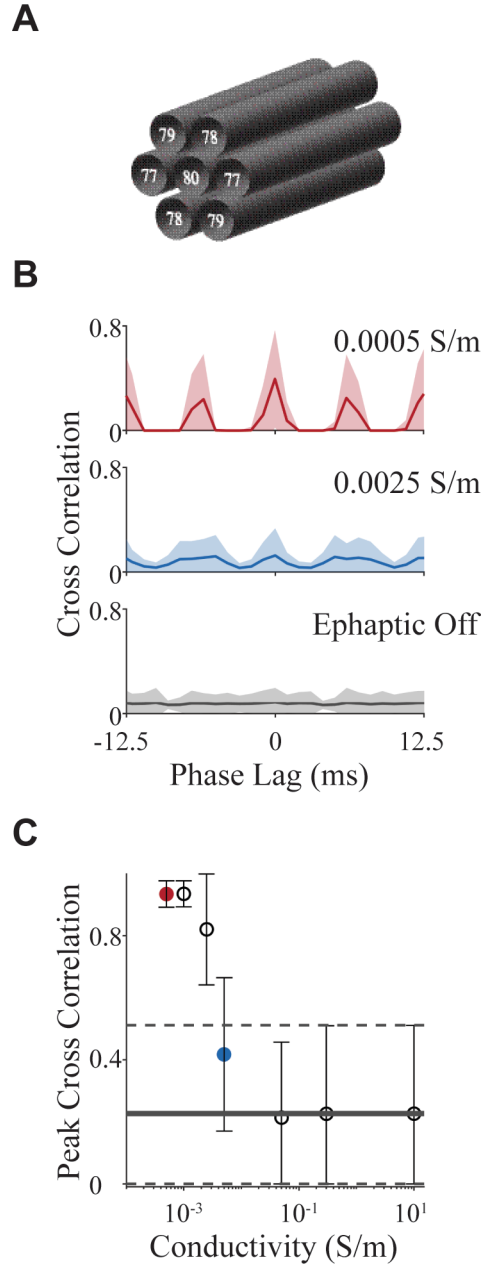


Figure 2.6: Action potential phase locking in an axon bundle through ephaptic coupling. A) schematic of 7 axons aligned in a bundle; base frequency for each is indicated in white text. All parameter values for all examples are provided with E_LFENN software. B) Cross correlation functions for strong ephaptic (red), weak ephaptic (blue) and no ephaptic conditions (grey). Data is presented as mean (solid line) $\pm$ standard deviation (shaded) over axon pair and initial conditions. C) Effect of conductivity on phase locking. Peak cross correlation value (mean $\pm$ standard deviation) is plotted as a function of conductivity; red and blue symbols correspond to red and blue conditions in panel B; horizontal lines (solid and dashed) represent the “ephaptic off” case (mean and standard deviation, respectively).

is removed (standard deviation indicated by dashed lines); note that the peaks of the mean cross-correlations shown in figure 2.6B will generally be much smaller than the peak correlations (figure 2.6C) as they are averaged over different locking regimes for which peaks occur at different phase lags.

Overall, these results show that with increasing ephaptic strength (decreasing conductivity) there is an emergence of phase locking over the time scales tested (within 2s). As in previous studies (Han et al. 2018; Jefferys et al. 2012), this demonstrates the potential for crosstalk between neurons that can lead to phase-locking. It is interesting to note that in some cases, cells can actually inhibit each other through electric field effects (Blot and Barbour 2014); this tendency may be related to the anti-synchronous locking we observe here. More generally, this example demonstrates the relative simplicity by which a simulation can be conceived, implemented and analyzed using ELFENN while avoiding the technical challenges involved in implementing a cable equation solver along with electric field effects.

2.9 Discussion

Here, we have presented E_L FENN, a MATLAB toolbox for modeling ephaptic coupling. We have modeled ephaptic coupling in a standard way: by modeling the membrane potential and LFP and then closing the loop by feeding the extracellular potential back to the membrane potential dynamics through an ephaptic current (Holt and Koch 1999). We have validated each component of our implementation against NEURON (Carnevale and Hines 2006) and LFPy (Lindén et al. 2014). Finally, we have presented two simple use cases from the literature (Goldwyn and Rinzel 2016; Jefferys 1995; Ramón and Moore 1978) to illustrate how ephaptic coupling can be modelled in realistic neuron models and how it can lead to phase-locked firing between adjacent axons.

There is of course room for improvement. Currently ELFENN is restricted to an

isotropic (conductivity is as scalar) and homogeneous (at every point in space the conductivity is the same) extracellular space. There already exist formalisms for removing these simplifications (Ness et al. 2015; Nicholson and Freeman 1975), which are planned for future development. Already without these features, E_LFENN can be used to study a wide range of problems involving ephaptic coupling and explore the conditions in which electric field effects can influence on-going brain dynamics. In addition, E_LFENN can also be used to model extracellular stimulation (where the electrode is another current source), as long as electrodes obey simple geometries.

Furthermore, the primary limitation of E_LFENN is being locked to a single processor in MATLAB. Moving to compiled code with standard numerical libraries (e.g. SUNDIALs) may have a large developmental cost but would have large payouts as code parallelization would be possible and thus high-performance computing resources could greatly reduce the present limitations of E_LFENN.

2.10 Competing Interests

We have no competing interests

2.11 Contributions

ARS and JEL conceived and designed the E_LFENN platform. ARS wrote E_LFENN software with input from JEL. ARS and JEL wrote the manuscript. All authors read and approved the final manuscript.

2.12 Acknowledgement

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2.13 Data Availability

E_LFENN will be available on Github at <https://github.com/E_LFENN> after publication.

2.14 References

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Chapter 3

A Biophysical Model of a Pacemaker Neuron in the Weakly Electric Fish *Apteronotus*

Abstract

The precise timing of neuronal activity is critical for normal brain function. In weakly electric fish, the medullary pacemaker network (PN) sets the timing for an oscillating electric organ discharge (EOD) used for electric sensing. This network is the most precise biological oscillator known, with sub-microsecond variation in oscillator period. The PN consists of two principle sets of neurons, pacemaker and relay cells, that are connected by gap junctions and normally fire in synchrony, one-to-one with each EOD cycle. However, the degree of gap junctional connectivity between these cells appears insufficient to provide the population averaging required for the observed temporal precision of the EOD. This has led to the hypothesis that individual cells themselves fire with high precision, but little is known about the oscillatory dynamics of these pacemaker cells. To this end, we have developed a biophysical model of a pacemaker neuron action potential based on experimental recordings. We validated the model by comparing the changes in oscillatory dynamics produced by different experimental manipulations. Our results suggest that a relatively simple model captures the complex

dynamics exhibited by pacemaker cells, and that these dynamics may enhance network synchrony and precision.

n.b. The experimental work in this chapter was performed by Yiren Sun in the case of the experimental bifurcation data, and the recordings for model fitting were provided by Chloé Benoit.

3.1 Introduction

Timing of neuronal spikes is critical to many brain processes, including sound localization (Carr and Konishi 1988; Grothe and Pecka 2014; Singheiser, Gutfreund, and Wagner 2012), escape responses (Von Reyn et al. 2014; Shimazaki et al. 2019; Evans et al. 2019), and learning and memory (Dan and Poo 2004; Paton and Buonomano 2018). When neural processes are periodic, they can form the basis for biological clocks which span a range of precision (variability in oscillation period), with a higher variability leading to a less reliable clock.

Variability in the period of neuronal oscillators (reported as a coefficient of variation: $CV = \text{s.d.}/\text{mean}$) can be relatively high, as in the bullfrog sciatic nerve with a $CV=0.37$ (Hagiwara 1954; Moortgat, Bullock, and Sejnowski 2000a). For reference, a random Poisson process has a $CV=1$, while neurons in the visual system can have a $CV > 1$ (Orbán et al. 2016; Gabbiani and Cox 2010). In contrast, the neural oscillators underlying the electric organ discharge (EOD) of the weakly electric fish *Apteronotus* have a CV as low as $\sim 10^{-4}$ (corresponding to a raw standard deviation of $\sim 100\text{ns}$), making it the most precise biological oscillator known (Moortgat, Bullock, and Sejnowski 2000a; Moortgat et al. 1998). The high precision of the EOD of *Apteronotus* therefore makes it a particularly attractive model for the study of neural circuit timing (Moortgat, Bullock, and Sejnowski 2000a; Moortgat et al. 1998; Lucas et al. 2019).

Apteronotus generates an oscillating electric field (EOD) to sense their environment in the dark (Moller 1995). Heterogeneities in the environment perturb the EOD, and these perturbations are sensed by electroreceptors on the skin. The timing of the oscillations underlying the EOD are set by the medullary pacemaker network (PN) (Moortgat et al. 1998; Moortgat, Bullock, and Sejnowski 2000b; Zupanc 2017; Elekes and Szabo 1985; Dye and Heiligenberg 1987). This nucleus is a collection of two principle cell types: pacemaker cells, which are oscillatory cells and relay cells which project down the spinal cord to drive

the EOD (Lucas et al. 2019; Moortgat, Bullock, and Sejnowski 2000b; Ellis and Szabo 1980). Additionally, there are parvalbumin positive cells (parvocells) whose function is currently unknown, but are not thought to contribute to the oscillatory function of the PN (Smith, Lu, and Zakon 2000).

Within the PN, the pacemakers cells are highly synchronized with one another, with relative phases across cells close to 2% of the oscillator period (Moortgat, Bullock, and Sejnowski 2000a; Lucas et al. 2019). In general, networks are thought to achieve high-precision and high-synchrony through the population-averaged activity of a large number of strongly-connected cells (Lucas et al. 2019; Moortgat, Bullock, and Sejnowski 2000b; Herzog et al. 2004). However, pacemaker and relay cells are connected only sparsely, with weak gap junctions (Lucas et al. 2019; Moortgat, Bullock, and Sejnowski 2000b; Zupanc 2017; Elekes and Szabo 1985). Although network connectivity may be functionally enhanced through the electric feedback from the EOD itself (Lucas et al. 2019; Shifman and Lewis 2019), the apparent disconnect between high synchrony and low connectivity in the PN may also be explained by the high precision of individual cells (Moortgat, Bullock, and Sejnowski 2000b), with synchrony emerging from weak interactions between precise cells with stereotyped dynamics. Indeed, some underlying oscillatory dynamics are thought to be more amenable to synchronization than others (Izhikevich 2007; Fink, Booth, and Zochowski 2011; Mofakham et al. 2016).

Previous studies have used a Hodgkin-Huxley based model to explore PN synchrony and precision (Lucas et al. 2019; Moortgat, Bullock, and Sejnowski 2000b), but this model was not intended to accurately represent the action potential waveform of pacemaker neurons. While these studies provided insight into pacemaker network interactions, a more accurate biophysical model is required to determine how transmembrane currents, intrinsic oscillatory dynamics and gap junctional coupling impact single cell precision and network synchrony. To this end, we present a biophysically based pacemaker cell model which accurately captures the waveform of pacemaker cells as well as their dynamical responses to experimental manipulations.

3.2 Methods

3.2.1 Model Developement

Previous pharmacological experiments have suggested that pacemaker cells express the following suite of ionic currents: inactivating sodium (I_{Na}) and/or persistent sodium

(I_{NaP}), inactivating potassium (I_K), T/R type calcium (I_{Ca}), and leak (I_L) (Smith and Zakon 2000).

Using the standard Hodgkin-Huxley-style biophysical approach (Dayan and Abbott 2005), these currents underlie the dynamics of our model (see supplemental equations for details). Model parameters were fit to intracellular recordings from previously published experiments on *Apteronotus leptorhynchus* pacemaker cells (Lucas et al. 2019). A standard waveform from a representative pacemaker cell comprising two successive action potentials, averaged over 30 sweeps, was used to fit the primary model. Fitting two successive action potentials (oscillator cycles), rather than one, minimizes frequency drift between model and target waveforms. We also show that the primary model can be generalized by fitting it to waveforms from other pacemaker cells in both *Apteronotus leptorhynchus* and the related species *Apteronotus albifrons* (see figure 3.1). Note that Smith and Zakon (2000) also suggested a role for a persistent sodium current (I_{NaP}), but our initial studies showed that including this current resulted in many solutions that would not spike (not shown), so we did not include I_{NaP} in our final model. This current may provide a means of modulating frequency but it is not necessary to explain variations in pacemaker cell waveform across individuals and species.

We implemented a generic, parameterized model in the Brian2 simulation engine (version 2.3) (Stimberg, Brette, and Goodman 2019), and fit our model using a differential evolutionary algorithm (DEA) provided in the brian2modelfitting package (version 0.3). A DEA (similar to a genetic algorithm) starts with a large set of parameters drawn randomly within set bounds. Based on the fitting performance (i.e. “fitness”; see later discussion on fitting error), some parameter values will have a higher or lower probability of being used in the next iteration. Stochastic perturbations within the parameters allow for an efficient sampling of large parameter spaces (Svensson, Coombes, and Peirce 2012; Van Geit, De Schutter, and Achard 2008). Our DEA was initialized with 5000 initial samples of each parameter, and the algorithm was run for 3 iterations. Each parameter was sampled uniformly between upper and lower bounds, based roughly on known biophysical principles (see table S3.1).

Fitting error was quantified using the root mean squared (RMS eq. 3.1) error when the two waveforms (experimentally measured: V^e , and model: V^m) were aligned by first spike time (defined as the action potential peak).

$$\text{RMS} = \sqrt{\frac{\sum (V^e - V^m)^2}{n}} \quad (3.1)$$

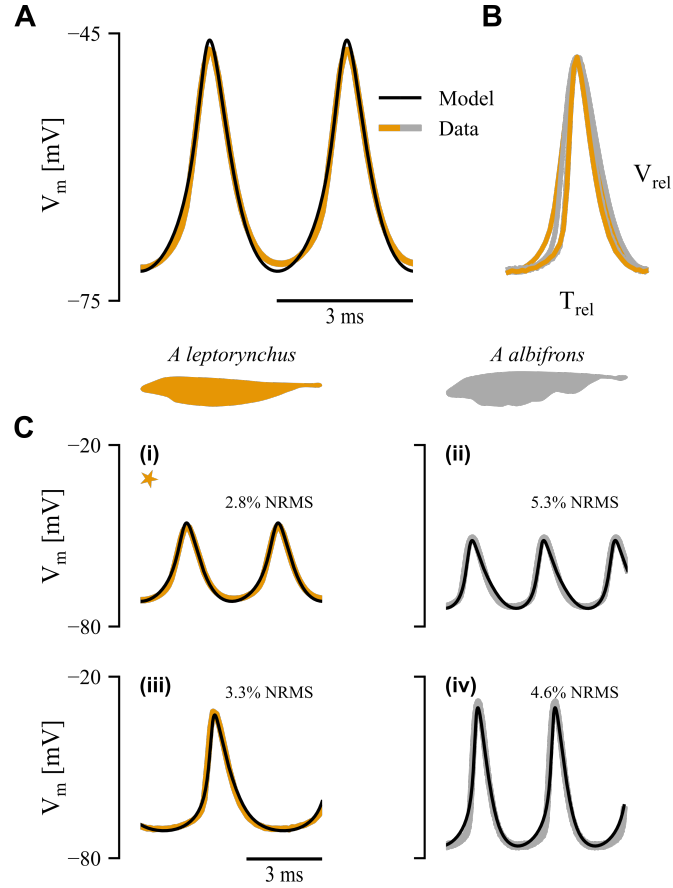


Figure 3.1: Model fit results for *A. leptorhynchus* (orange) and *A. albifrons* (grey). (A) Canonical model fit (black line) to *A. leptorhynchus* action potential waveform (orange). (B) Dimensionless waveform (action potential normalized by period in time and peak-peak amplitude) from two individuals from each species. (C) Data fits showing model flexibility over a range of frequencies, amplitudes and means for *A. leptorhynchus* (left) and *A. albifrons* (right). Orange star indicates model fit in panel A.

3.2.2 Experimental methods

To validate the model, brain slices of the pacemaker nucleus were prepared as described previously (Moortgat, Bullock, and Sejnowski 2000a; Lucas et al. 2019). Briefly, adult black ghost knifefish (*A. albifrons*) were obtained from commercial fish suppliers and housed on a 12/12 light-dark cycle in flow-through tanks at water temperature 27-28°C and conductivity 150-250µS. All housing and experimental protocols were in accordance with guidelines approved by the Animal Care Committee of the University of Ottawa (BL-1773).

Fish (N=5) were deeply anaesthetized using 0.1% Tricaine methanesulfate (TMS, Syndel International Inc, Nanaimo, BC, Canada) before being transferred to a bath of ice-cold artificial cerebrospinal fluid (ACSF; in mM: 124 NaCl, 24 NaHCO₃, 10 D-Glucose, 1.25 KH₂PO₄, 2 KCl, 2.5 MgSO₄, 2.5 CaCl₂; bubbled with 95% O₂ /5% CO₂). The brain was quickly removed and the pacemaker nucleus cut away using fine scissors (~1mm rostral, 2mm caudal, 1mm dorsal) and transferred to a 35mm petri dish perfused with oxygenated room-temperature (22 °C) ACSF. After a minimum of 30 minutes, pacemaker recordings (intracellular and extracellular) were performed with borosilicate glass sharp electrodes (30-90MΩ, P-2000 electrode puller, Sutter Instrument Company, Novato, CA, USA) using an Axoclamp 2B amplifier (Molecular Devices, Sunnyvale, CA, USA). Data was acquired using a Digidata 1440a digitizer (Molecular Devices) at a sampling frequency of 100kHz using pClamp 10 (Molecular Devices). Low Na⁺ ACSF was prepared in a similar fashion as ACSF, only substituting NaCl for equimolar amounts of sucrose (Fisher Chemical, Fair Lawn, NJ, USA). The perfusion system involved a transfer time of approximately 4 minutes when switching between Na⁺ and low-Na⁺ ACSF solutions.

Action potential frequency in the PN was measured from one-second recordings taken at 20s intervals using Fourier analysis (as the highest power, dominant frequency). Cessation of spiking was determined when the power at the dominant frequency was less than 1.5 times the power at 60 Hz (signal-to-noise ratio, SNR<1.5) This criterion, along with the dominant frequency being within 5Hz of a power line harmonic was additionally used to identify overly noisy recordings prior to cessation which were removed from analysis.

3.3 Results

3.3.1 Model Fit

We developed a biophysical Hodgkin-Huxley-based model of a pacemaker neuron in the PN of a weakly electric fish. Motivated by previous studies (Smith and Zakon 2000), our model included voltage-dependent sodium, potassium, and calcium channels, along with leak channels (I_{Na} , I_K , I_{Ca} , I_L). We used a differential evolutionary algorithm (DEA) to survey a 44-dimensional parameter space (see Methods and Appendix). After optimization, the RMS error between model and data waveform was 0.7mV; when normalized by action potential amplitude, this corresponds to a 2.8% error. Note that small differences in action potential timing can lead to relatively large errors due to the fast rise and fall times that are typical of action potentials, so the model matches the data even better than the RMS error would suggest over most of the action potential cycle (figure 3.1A).

At this point, our model describes an action potential of a single cell from an individual *A. leptorhynchus*. It is also of interest to determine how well this model will generalize across individuals and the related species *A. albifrons*. In figure 3.1B, we show action potential waveforms (dimensionless, normalized in both time and amplitude) from pacemaker cells from two individuals of each species (figure 3.1B); the similarity across waveforms suggests that the underlying dynamics are also similar. To demonstrate this and to show the flexibility of the model, we refit the model to each of these four action potential waveforms with the same parameter bounds (figure 3.1C; data from figure 3.1A is indicated by gold star). Over a range of amplitudes and frequencies, the model fits involved a worst-case error of 5.3%. And importantly, there were no systematic differences in the voltage dependence of the gating variables across all models (Supplemental figure 3.A.1).

Previous results suggest that while calcium can contribute to action potential waveform shape, it does not fundamentally underlie pacemaker cell oscillation (Smith and Zakon 2000). We tested this in our model by setting g_{Ca} to 0 (I_{Ca} -Block) and found that changes to the waveform were subtle and the model continues to oscillate (figure 3.2A). In figure 3.2B, we show the contributions of each current to the action potential waveform. As expected, the depolarization of the action potential is driven by the sodium current, and the repolarization/hyperpolarization is driven by potassium current, but I_{Ca} has little effect (compare the full model with the I_{Ca} -Block model, Figure 3.2B). Overall, our modeling results confirm previous experimental results suggesting a minimal role of

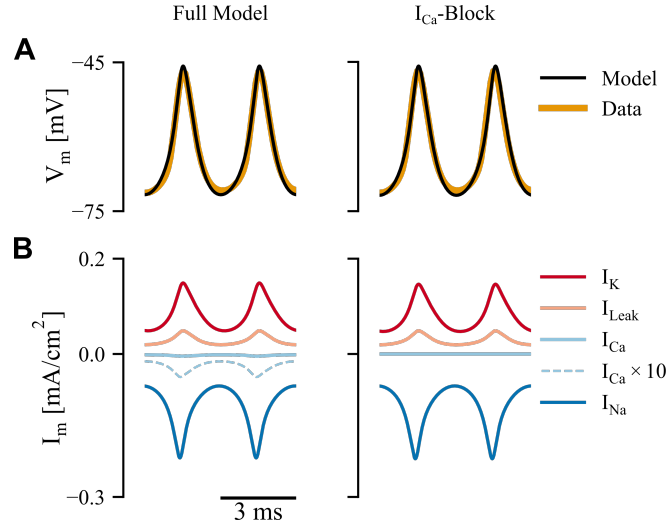


Figure 3.2: Analysis of currents in canonical model (figure 3.1A) and in model with I_{Ca} -block. (A) Model fits for both full model (left) and blocked model (right) showing no systematic differences. (B) Current breakdown with $I_{Ca} \times 10$ (dashed light blue line) showing a 10 $\times$ magnified calcium current for illustrative purposes.

calcium in the pacemaker action potential oscillation.

At this stage, it would not be inappropriate to consider the model overfit. We have used a biophysical model with 44 parameters to fit a single oscillator waveform. A good fit would not be surprising, so it is important to validate the dynamics of our model against additional data. To this end, we consider the pacemaker dynamics during two different experimental manipulations: low concentration of extracellular sodium (decreased E_{Na}), and pharmacological block of Na^+ and K^+ channels (Smith and Zakon 2000).

3.3.2 Model Validation: Effects of E_{Na}

To test the new pacemaker model, we compared its dynamics under conditions that differed from those in the model fitting process. In the study of dynamical systems, qualitative changes in behavior produced by small changes in a system parameter are referred to as bifurcations (Strogatz 2014). One particular example of a bifurcation relevant to pacemaker dynamics is the transition between an oscillating state and a rest state (non-oscillating), and vice-versa; the nature of this transition depends on the system properties as well as the particular parameter that is varied.

One classic way in which oscillations can arise is through a Hopf bifurcation. The hallmark of a Hopf bifurcation is that the transition from an oscillating state to rest (or vice-versa) involves a discontinuous jump (i.e. as a system parameter is varied, there

is an abrupt change in frequency from some minimum value to zero) (Strogatz 2014). There are two kinds of Hopf bifurcations: one that exhibits a hysteresis and one that does not. Hysteresis can manifest in many ways, in the case of a Hopf bifurcation, hysteresis appears as a bistable system i.e. at a given parameter value the system can be oscillatory or not. Bifurcations presenting with hysteresis are known as *subcritical* Hopf bifurcations, whereas those without are *supercritical*. An alternative type of bifurcation (the homoclinic bifurcation) involves a continuous transition from rest to oscillating state along with a gradual change in oscillation frequency (i.e. rest can be thought of as an oscillation with infinite period) (Strogatz 2014). In summary, characterizing the transition between oscillating and non-oscillating states can provide a test of system dynamics (Smeal, Bard Ermentrout, and White 2010).

Lowering the equilibrium potential of sodium (E_{Na}) via changes in extracellular Na^+ concentration typically leads to cessation of action potential generation. We thus used this parameter to explore the transition between oscillating and non-oscillating states in both our pacemaker model and in experimental pacemaker preparations. In our model, we can manipulate E_{Na} directly. In our experiments, low- Na^+ ACSF was washed in to dilute the control ACSF, thereby gradually decreasing E_{Na} . Under ideal mixing conditions, the sodium concentration of the bath should obey an exponential diffusion equation 3.2 where r is the flow rate

$$[Na_{out}^+](t) = [Na_{out}^+]_0 e^{-\frac{t}{\tau}} \quad (3.2)$$

E_{Na} is given by the Nernst equation (eq 3.3; therefore by substitution we have that

$$E_{Na} \propto \log \frac{[Na_{out}^+](t)}{[Na_{in}^+]} = -k \frac{t}{r} + \alpha \quad (3.3)$$

where $\propto$ represents proportionality, and k and α are lumped constants. This implies that E_{Na} should decrease linearly in time, and since we do not have a direct measure of E_{Na} , time should be a good proxy.

In figure 3.3, we show the transition between oscillation and rest in both model and experiments. Our experimental analysis reveals that pacemaker frequency decreases over time, with an abrupt shift to the rest state (for simplicity we define rest to have zero frequency), as extracellular sodium concentration (i.e. E_{Na}) decreases (Figure 3.3A). To account for variability between experiments, we normalize the time scale such that the PN ceases to oscillate at time $t=1$. Measurements from individual preparations are

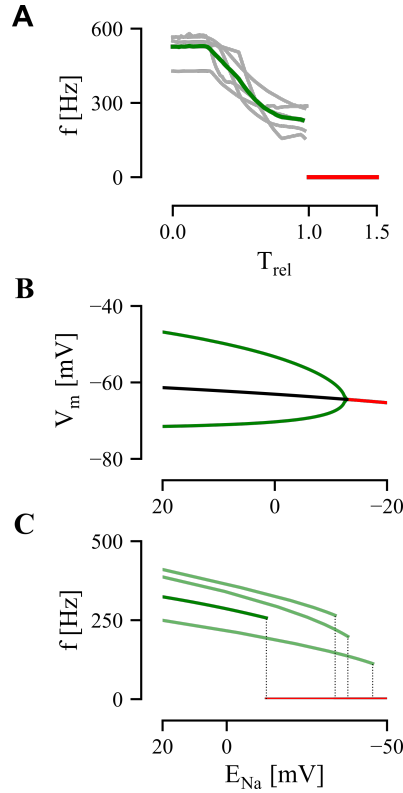


Figure 3.3: Data and model bifurcation analysis. (A) Relative time-series of pacemaker frequency as Na-free ACSF is washed in (see Methods) for 5 different pacemaker preparations. Green trace represents average (individual preparations in gray) and red trace represents cessation of firing. $T=1$ represents bifurcation point. (B) Orbit diagram for model bifurcation analysis with respect to E_{Na} . Green trace is action potential extrema. Black trace is unstable fixed point and red trace is stable fixed point. Black-Red intersection point is the Hopf bifurcation. (C) Frequency analysis of the model Hopf bifurcation. Dark green line represents model in figure 3.1C(i). Light green lines represent results from other model fits, figure 3.1C(ii-iv). Red line represents cessation and dotted lines show the bifurcation of each model.

shown in grey, with the mean shown in green ($N=5$ fish). On average, we see that the oscillation stops at ~ 260 Hz (figure 3.3B).

For the pacemaker model, we compute a bifurcation diagram showing the system's state (membrane potential, V_m) for different values of E_{Na} using XPP (Ermentrout 2002) (figure 3.3B). As E_{Na} decreases, the model neuron transitions from a oscillating (membrane potential extrema in green) to rest (red) at a bifurcation point corresponding to $E_{Na} = -12.8$ mV with no hysteresis. To distinguish a Hopf from a homoclinic bifurcation, we measured the frequency of the oscillation as E_{Na} decreases in figure 3.3C (dark green trace). The oscillation frequency follows a square-root-like curve until a discontinuity at $E_{Na} = -12.8$ mV, after which the cell stops firing: characteristic of a Hopf bifurcation

(Strogatz 2014). In other words, we can say that as E_{Na} is increased, our model undergoes a supercritical Hopf bifurcation at $E_{Na} = -12.8\text{mV}$. We observe qualitatively similar dynamics for the other model fits (figure 3.1C, light green traces).

While both the models and recordings undergo a sudden loss of spiking, a feature consistent with a Hopf bifurcation, other features of the model dynamics do not match the data. First, the manner in which frequency decreases with decreasing Na^+ is very different, as indicated by an increasing versus decreasing second derivative (compare figure 3.3A and 3.3C). This is possibly due to nonlinear changes in E_{Na} in the experiments resulting from variations in mixing and diffusion through the tissue; this would affect the detailed time-course of E_{Na} but the relation between E_{Na} and time will still be monotone. Secondly, we note that the experimental data spans a larger frequency range ($\sim 525\text{Hz} \rightarrow \sim 230\text{Hz}$; a drop of $\sim 60\%$) whereas the model spans 380Hz - 260Hz , a drop of 30% (although for the other model fits we see $40\text{-}5\%$ drops). This could be due to several factors, but one interesting possibility is that the pacemaker sensitivity to Na^+ is higher due to the presence of a persistent sodium current that underlies frequency control. It is important to note however, that despite these quantitative differences, both model and experimental systems show similar dynamics, with each exhibiting a Hopf bifurcation.

3.3.3 Model validation: Pharmacological Manipulations

In a similar manner, we can also consider how PN dynamics change as individual currents are manipulated. Smith and Zakon showed that blocking either I_{Na} or I_K channels results in firing cessation in experimental preparations (Smith and Zakon 2000). Importantly, they measured action potential waveform parameters as the channel blocker was washed in (i.e. as an increasing fraction of the channels are blocked). These data can thus provide another means of model validation.

We simulated this gradual channel block in the pacemaker model by manipulating the conductance of the appropriate channel as $G_{ion} \rightarrow (1-b)G_{ion}$ where b is a number between 0 and 1; control ($b = 0$) represents no block, while $b = 1$ represents complete block. We demonstrate the effects of progressive block of either sodium (left) and potassium (right) channels in figure 3.4A (block level, $b = 0$ to $b = 0.7$). As in the E_{Na} experiments, we performed a bifurcation analysis in XPP (Ermentrout 2002) and found that both of these bifurcations are supercritical Hopf bifurcations (not shown). The reader familiar with bifurcation analyses may note that these decreases in g_{Na} appear to result in a continuous frequency drop, but over a larger parameter range there is in fact a discontinuous drop

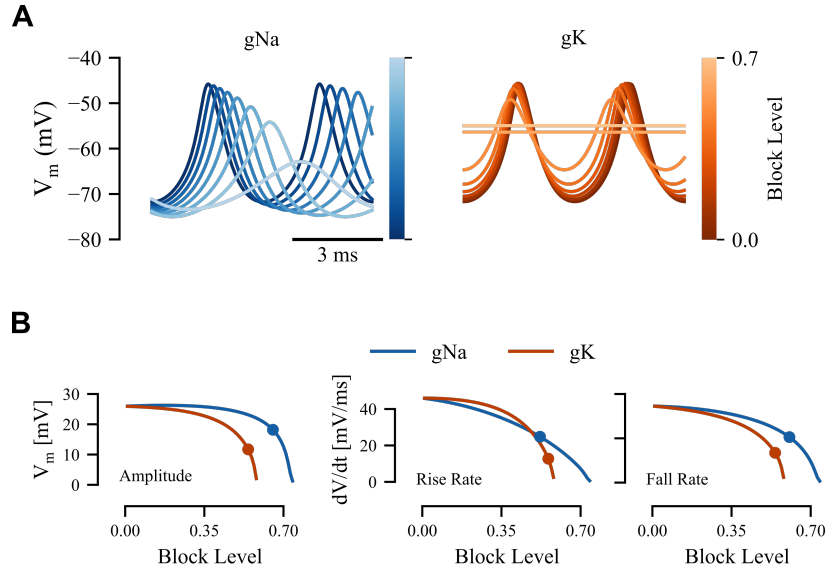


Figure 3.4: Response to progressive block of Na^+ and K^+ channels. (A) Model response to Na^+ channel block (g_{Na} , left) and K^+ channel block (g_{K} , right). (B) Action potential properties computed as a function of block level for peak-peak amplitude (left), action potential rise rate (center) and fall rate (absolute value; right). Dots represent block level with equivalent percentage change in each property from data reported in (Smith and Zakon 2000)

in frequency associated with a Hopf bifurcation.

Because we do not know the equivalent block level at the time the waveform properties were measured in the experiments, we use the following qualitative comparison based on three action potential waveform features. We consider how these features vary as the block level is increased (figure 3.4B), and what block level is required to match experimental data (solid circle, figure 3.4B). A good model will be internally consistent in that the required block level should be consistent across all waveform features. In figure 3.4B we show the peak-to-peak amplitude, peak rise rate, and peak fall rate (taken as positive for symmetry with rise rate) for both sodium and potassium block as a function of block level. The equivalent block level (the block level that corresponds to the percent change noted in the original data) is indicated by a solid circle. The equivalent level for sodium block is 0.59 ± 0.06 (mean $\pm$ standard deviation) whereas that for potassium block is 0.55 ± 0.007 ; the low variability here suggests good model performance.

Overall, our analyses show that this new model captures the main oscillatory dynamics and action potential waveforms of pacemaker cells based on the underlying sodium and potassium currents. Further, the results suggest that oscillatory dynamics in pacemaker neurons arise in a specific manner (supercritical Hopf bifurcation) that may influence

network synchrony and stability (Hansel, Mato, and Pfeuty 2012; Ermentrout, Pascal, and Gutkin 2001).

3.4 Discussion

The pacemaker network (PN) of wave-type electric fish sets the timing of a neural oscillation which exhibits precision and stability far beyond that of any known biological oscillator (Moortgat et al. 1998; Lucas et al. 2019). To understand these dynamics, we have developed a biophysically relevant model of pacemaker neurons that reproduces the action potential waveform as well as the effects of various experimental manipulations. From a dynamical systems perspective, we show that our model undergoes a Hopf bifurcation as E_{Na} is decreased. A similar effect is seen experimentally when Na^+ is removed from the extracellular medium: oscillations stop with a minimum frequency ~ 260 Hz. While our data only shows the offset of spiking (and thus super and subcritical bifurcations cannot be distinguished), we do show a sudden stop in oscillation which rules-in a Hopf bifurcation and rules out any form of homoclinic bifurcation, where the birth of an oscillation can have an arbitrarily low frequency. In addition, we were not able to successfully recover a normal oscillation after low- Na^+ treatment, and thus could not differentiate between sub and supercritical bifurcations based on the presence of hysteresis. This could be due to a network bistability where the control Na^+ -level could permit oscillation or not. Further work is of course required. In addition, our model accurately reproduces the changes in waveform properties such as amplitude and peak slew rate caused by partial channel block.

Of particular interest in this study is the fact that our model was fit to data from two related species (*A. leptorhynchus* and *A. albifrons*). While there are known differences in cell counts, and frequencies (Elekes and Szabo 1985; Shifman and Lewis 2018; Elekes and Szabo 1981; Dunlap and Larkins-Ford 2003), little is known about the differences in pacemaker network dynamics between these species (Lucas et al. 2019). We show preliminary data to suggest that both species have an equivalent dimensionless action potential waveform (figure 3.1B) that can vary widely across amplitude, mean and frequency. The implication of this being that pacemaker cells in both species have similar dynamics. This is supported by the fact that the model was fit to these different waveforms within relatively narrow parameter bounds. Furthermore, experimental validations are done with data from both *A. albifrons* (E_{Na}) and *A. leptorhynchus* (channel block).

This model can also provide important insight into precision and synchrony in the PN. For example, fast, early currents such as I_{NaP} tend to decrease synchrony across a network (Hansel, Mato, and Pfeuty 2012) whereas some of the slow, late potassium currents (Hansel, Mato, and Pfeuty 2012; Ermentrout, Pascal, and Gutkin 2001) tend to increase network synchrony (Hansel, Mato, and Pfeuty 2012). Interestingly, we found that I_{NaP} was not required to explain pacemaker waveforms, but a delayed potassium current played a fundamental role. Further, the specific dynamics of individual neurons in a network can also influence network synchronization (Hansel, Mato, and Pfeuty 2012; Ermentrout, Pascal, and Gutkin 2001). In particular, neurons exhibiting supercritical Hopf bifurcations (also referred to as Type II excitability) can lead to more robust synchronization (Fink, Booth, and Zochowski 2011; Mofakham et al. 2016). Understanding the role of bifurcation structure in PN precision and synchrony will require future modeling and experimental work.

We acknowledge that our model is a single cell model fit to data from an intact pacemaker network. The impact of this is not clear; gap junctional strength is proportional to the voltage between cells, so in a synchronized network, the voltage difference between cells is low, hence coupling is minimal, with gap junctions serving primarily as an error-correcting entraining force. This suggests that, at least to first order, the network effects of gap junctions may be minimal. Nonetheless, given the model exhibits similar dynamics to those observed experimentally, it will provide a basis for future work focused on how intrinsic neuronal dynamics interact with gap junctional coupling to produce high temporal precision and synchrony in the pacemaker network.

3.5 Author Contributions

ARS and JEL conceived the project. ARS designed the model and performed the simulations with input from JEL. CMB and YS performed experimental recordings. ARS wrote the first draft; ARS and JEL edited the manuscript. All authors have read and approved the final manuscript.

3.6 Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

3.7 Acknowledgments

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3.8 References

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Appendix

3.A Supplemental Figures

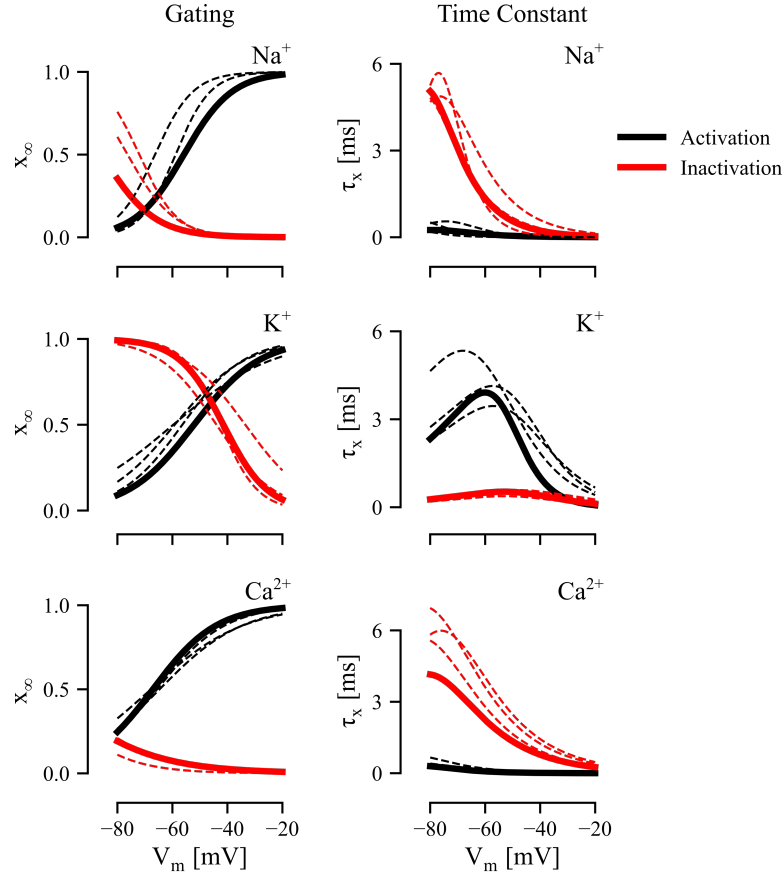


Figure 3.A.1: Voltage-dependence functions for each model current across all model fits. Thick lines represent canonical model in figure 3.1C(i) and dashed lines represent models in figure 3.1C(ii-iv). Gating functions (left) and time constant functions (right) with rows representing functions for sodium, potassium, and calcium descending.

3.B S1 Equations

$$\frac{dv}{dt} = -I_{Leak} - I_{Ca} - I_{Na} - I_K \quad (S3.1)$$

$$\frac{db}{dt} = \frac{b_\infty - b}{\tau_b} \quad (S3.2)$$

$$\frac{dg}{dt} = \frac{g_\infty - g}{\tau_g} \quad (S3.3)$$

$$\frac{dh}{dt} = \frac{h_\infty - h}{\tau_h} \quad (S3.4)$$

$$\frac{dm}{dt} = \frac{m_\infty - m}{\tau_m} \quad (S3.5)$$

$$\frac{dn}{dt} = \frac{n_\infty - n}{\tau_n} \quad (S3.6)$$

$$\frac{dq}{dt} = \frac{q_\infty - q}{\tau_q} \quad (S3.7)$$

$$I_{Leak} = G_{Leak}(v - E_{Leak}) \quad (S3.8)$$

$$I_{Ca} = G_{Ca}b^2g^2(v - E_{Ca}) \quad (S3.9)$$

$$I_{Na} = G_{Na}hm(v - E_{Na}) \quad (S3.10)$$

$$I_K = G_Kn^2q^2(v - E_K) \quad (S3.11)$$

$$\tau_b = \frac{S\tau_b}{\exp\left(\frac{\theta_{\tau_b}-v}{\sigma_{\tau_b}^2}\right) + \exp\left(-\frac{\theta_{\tau_b}-v}{\sigma_{\tau_b}^1}\right)} \quad (S3.12)$$

$$\tau_g = \frac{S\tau_g}{\exp\left(\frac{\theta_{\tau_g}-v}{\sigma_{\tau_g}^2}\right) + \exp\left(-\frac{\theta_{\tau_g}-v}{\sigma_{\tau_g}^1}\right)} \quad (S3.13)$$

$$\tau_h = \frac{S\tau_h}{\exp\left(\frac{\theta_{\tau_h}-v}{\sigma_{\tau_h}^2}\right) + \exp\left(-\frac{\theta_{\tau_h}-v}{\sigma_{\tau_h}^1}\right)} \quad (S3.14)$$

$$\tau_m = \frac{S\tau_m}{\exp\left(\frac{\theta_{\tau_m}-v}{\sigma_{\tau_m}^2}\right) + \exp\left(-\frac{\theta_{\tau_m}-v}{\sigma_{\tau_m}^1}\right)} \quad (S3.15)$$

$$\tau_n = \frac{S\tau_n}{\exp\left(\frac{\theta_{\tau_n}-v}{\sigma_{\tau_n}^2}\right) + \exp\left(-\frac{\theta_{\tau_n}-v}{\sigma_{\tau_n}^1}\right)} \quad (S3.16)$$

$$\tau_q = \frac{S\tau_q}{\exp\left(\frac{\theta_{\tau_q}-v}{\sigma_{\tau_q}^2}\right) + \exp\left(-\frac{\theta_{\tau_q}-v}{\sigma_{\tau_q}^1}\right)} \quad (S3.17)$$

$$b_\infty = \frac{1}{\exp\left(\frac{\theta_{b_\infty}-v}{\sigma_{b_\infty}}\right) + 1} \quad (S3.18)$$

$$g_{\infty} = \frac{1}{\exp\left(-\frac{\theta_{g_{\infty}}-v}{\sigma_{g_{\infty}}}\right) + 1} \quad (\text{S3.19})$$

$$h_{\infty} = \frac{1}{\exp\left(-\frac{\theta_{h_{\infty}}-v}{\sigma_{h_{\infty}}}\right) + 1} \quad (\text{S3.20})$$

$$m_{\infty} = \frac{1}{\exp\left(\frac{\theta_{m_{\infty}}-v}{\sigma_{m_{\infty}}}\right) + 1} \quad (\text{S3.21})$$

$$n_{\infty} = \frac{1}{\exp\left(\frac{\theta_{n_{\infty}}-v}{\sigma_{n_{\infty}}}\right) + 1} \quad (\text{S3.22})$$

$$q_{\infty} = \frac{1}{\exp\left(-\frac{\theta_{q_{\infty}}-v}{\sigma_{q_{\infty}}}\right) + 1} \quad (\text{S3.23})$$

3.C Supplemental Tables

Table S3.1 Upper and lower bounds for parameter selection in the GA

Parameter	Lower Bound	Upper Bound	Unit
E_{Ca}	20.	30.	mV
E_K	-90.	-80.	mV
E_{Leak}	-90.	-80.	mV
E_{Na}	20.	30.	mV
G_{Ca}	0.	20.	mS
G_K	30.	70.	mS
G_{Leak}	0.	3.	mS
G_{Na}	30.	70.	mS
s_{τ_b}	100.	2.	ms
s_{τ_g}	5.	15.	ms
s_{τ_h}	5.	15.	ms
s_{τ_m}	100.	2.	ms
s_{τ_n}	5.	15.	ms
s_{τ_q}	100.	2.	ms
$\sigma_{\tau_b}^1$	10.	20.	mV
$\sigma_{\tau_g}^1$	10.	20.	mV
$\sigma_{\tau_h}^1$	5.	15.	mV
$\sigma_{\tau_m}^1$	5.	15.	mV
$\sigma_{\tau_n}^1$	5.	15.	mV
$\sigma_{\tau_q}^1$	10.	20.	mV
$\sigma_{\tau_b}^2$	10.	20.	mV
$\sigma_{\tau_g}^2$	10.	20.	mV
$\sigma_{\tau_h}^2$	5.	15.	mV
$\sigma_{\tau_m}^2$	5.	15.	mV
$\sigma_{\tau_n}^2$	25.	35.	mV
$\sigma_{\tau_q}^2$	20.	30.	mV
$\sigma_{b\infty}$	10.	20.	mV
$\sigma_{g\infty}$	10.	20.	mV
$\sigma_{h\infty}$	5.	10.	mV
$\sigma_{m\infty}$	5.	10.	mV
$\sigma_{n\infty}$	10.	20.	mV
$\sigma_{q\infty}$	5.	15.	mV
$\theta_{b\infty}$	-70.	-60.	mV
$\theta_{g\infty}$	-110.	-100.	mV
$\theta_{h\infty}$	-90.	-70.	mV
$\theta_{m\infty}$	-70.	-50.	mV
$\theta_{n\infty}$	-65.	-45.	mV
$\theta_{q\infty}$	-55.	-25.	mV
θ_{τ_b}	-100.	-80.	mV
θ_{τ_g}	-85.	-75.	mV
θ_{τ_h}	-90.	-60.	mV
θ_{τ_m}	-90.	-70.	mV
θ_{τ_n}	-65.	-45.	mV
θ_{τ_q}	-55.	-35.	mV

Table S3.2 Ionic Parameters for model fits. Canonical Model maps to Figure 3.1A, Model B-D maps to Figure 3.1B-D

Parameter	Canonical Fit	Model ii Fit	Model iii Fit	Model iv Fit	Unit
E_{Ca}	23.95	22.13	29.01	27.02	mV
E_K	-80.87	-87.12	-84.49	-89.02	mV
E_{Leak}	-88.91	-84.63	-88.95	-87.81	mV
E_{Na}	24.22	25.56	22.12	21.06	mV
G_{Ca}	14.28	4.13	1.99	2.57	mS
G_K	59.27	50.16	39.90	33.16	mS
G_{Leak}	1.13	1.98	1.11	2.17	mS
G_{Na}	63.13	52.48	48.66	61.82	mS

Table S3.3 Gating Parameters for model fits. Canonical Model maps to Figure 3.1A, Model B-D maps to Figure 3.1B-D

Parameter	Canonical Fit	Model ii Fit	Model iii Fit	Model iv Fit	Unit
s_{τ_b}	0.62	1.38	1.65	1.07	ms
s_{τ_g}	8.28	11.36	11.95	14.02	ms
s_{τ_h}	10.29	11.36	9.71	9.62	ms
s_{τ_m}	0.50	0.47	1.08	1.33	ms
s_{τ_n}	6.56	9.69	7.18	6.35	ms
s_{τ_q}	1.01	0.72	1.15	0.96	ms
$\sigma_{\tau_b}^1$	11.27	11.31	13.50	18.50	mV
$\sigma_{\tau_g}^1$	17.94	17.33	17.63	17.60	mV
$\sigma_{\tau_h}^1$	11.15	7.27	13.49	13.01	mV
$\sigma_{\tau_m}^1$	11.98	7.20	8.86	8.94	mV
$\sigma_{\tau_n}^1$	7.17	12.68	10.72	13.23	mV
$\sigma_{\tau_q}^1$	13.14	13.41	17.87	17.79	mV
$\sigma_{\tau_b}^2$	12.62	15.89	17.79	18.41	mV
$\sigma_{\tau_g}^2$	14.99	17.95	15.38	17.56	mV
$\sigma_{\tau_h}^2$	10.26	7.80	11.14	8.17	mV
$\sigma_{\tau_m}^2$	13.52	7.70	12.87	14.10	mV
$\sigma_{\tau_n}^2$	26.62	32.07	33.81	31.13	mV
$\sigma_{\tau_q}^2$	25.15	25.97	28.51	22.07	mV
$\sigma_{b\infty}$	11.55	15.12	16.80	12.37	mV
$\sigma_{g\infty}$	18.38	12.71	16.72	18.55	mV
$\sigma_{h\infty}$	9.48	9.03	8.51	6.92	mV
$\sigma_{m\infty}$	8.78	6.91	6.33	9.08	mV
$\sigma_{n\infty}$	12.05	12.99	11.33	18.22	mV
$\sigma_{q\infty}$	8.03	6.71	11.40	10.39	mV
$\theta_{b\infty}$	-67.10	-64.67	-67.86	-65.61	mV
$\theta_{g\infty}$	-106.52	-106.48	-102.24	-106.40	mV
$\theta_{h\infty}$	-85.67	-84.66	-76.30	-72.08	mV
$\theta_{m\infty}$	-55.85	-66.36	-58.86	-55.27	mV
$\theta_{n\infty}$	-52.16	-59.15	-56.39	-59.78	mV
$\theta_{q\infty}$	-41.48	-42.43	-33.52	-43.99	mV
θ_{τ_b}	-83.44	-96.35	-88.60	-94.56	mV
θ_{τ_g}	-82.37	-83.12	-77.18	-82.55	mV
θ_{τ_h}	-82.53	-76.68	-77.66	-84.61	mV
θ_{τ_m}	-77.87	-85.17	-72.28	-85.84	mV
θ_{τ_n}	-52.65	-59.64	-47.93	-49.18	mV
θ_{τ_q}	-47.45	-46.91	-44.41	-45.09	mV

Chapter 4

Electric Field Effects Mediate Pacemaker Resynchronization in the Pacemaker Nucleus of the Weakly Electric Fish *Apteronotus leptorhynchus*

4.1 Introduction

Brain oscillations have received extensive attention in neuroscience literature in the context of both brain computation (Güntekin and Başar 2014; Cole and Voytek 2017; Benítez-Burraco and Murphy 2019; Mazaheri et al. 2018) and neuromodulation (Pevzner et al. 2016; Hanslmayr, Axmacher, and Inman 2019; Knudsen and Wallis 2020). Global recordings of brain activity such as electroencephalograms (EEG) and local field potentials (LFP) reveal oscillations at various frequencies. These recordings provide a spatially averaged measure of network activity, meaning only pronounced, and synchronous activity will contribute to the signal (Buzsáki, Anastassiou, and Koch 2012; Fries, Nikolić, and Singer 2007; Wijk, Beek, and Daffertshofer 2012; Singer 1999; Musall et al. 2014). Breaking these signals down into functional frequency bins, the classical brain-waves such as α and γ , suggests that oscillation frequency and level of synchrony are fundamental to brain state and computation (Singer 1999; Ahmed and Cash 2013; Salkoff et al. 2015). Synchronization plays many roles in the mammalian brain. Neural integration requires temporal synchrony of convergent inputs (Fries, Nikolić, and Singer 2007; Draguhn and

Buzsáki 2004), and is the basis of coincidence detection or synchrony coding (Singer 1999; Gupta, Singh, and Stopfer 2016; Brette 2012). At a larger scale, synchrony and coherence has been associated with cognition (Solomon et al. 2017), memory recall (Bocchio, Nabavi, and Capogna 2017), and visual perception (Harris and Gordon 2015).

In the treatment of synchrony and coupling, weakly coupled oscillator theory provides many key insights and methods for studying these systems (Izhikevich and Kuramoto 2006; Hoppensteadt and Izhikevich 1996; Smeal, Bard Ermentrout, and White 2010; Schultheiss, Prinz, and Butera 2012). The basis for weakly coupled oscillators is a collection of oscillators (periodically spiking neurons for example) with connections “weak enough” that coupling perturbations do not significantly affect oscillator amplitude. From the standpoint of weakly coupled oscillators, synchrony requires coupling between cells: a collection of free-running (uncoupled) cells will not synchronize (Glass 2001; Forger 2017). Additionally it is interesting to note that synchrony has been shown to emerge from Hebbian learning rules: “fire together, wire together” (Ratnadurai-Giridharann, Khargonekar, and Talathi 2015; Talathi, Hwang, and Ditto 2008). In other work similar synchronous neurons have been shown to be coupled preferentially (Knoblauch et al. 2012).

In general the conditions for synchrony can be quite complex, requiring not only considerations of network topology but the underlying dynamics of the cells themselves (Mofakham et al. 2016; Hansel, Mato, and Pfeuty 2012; Skinner 2013; Sritharan and Skinner 2012; Mancilla et al. 2007; Lewis and Skinner 2012). In the most general terms, a stable synchronous state requires a timing error to be propagated across the network with the phase of each cell advanced or delayed appropriately. The stronger or more dense the coupling, the faster these units will synchronize. This can be achieved through any number of mechanisms including common-mode entrainment, feedback inhibition, or gap junctions (Uhlhaas et al. 2009).

While there are neurocomputational benefits of synchrony, it cannot be the global dynamical attractor of the brain. If the brain were to globally synchronize it would convert from a dynamic computer into a clock: something beneficial for some local networks of pacemakers (see Chapter 3), but detrimental to brain computation. As such, synchrony is fleeting, with the brain constantly alternating between synchronous and asynchronous states.

In order to perform their roles in the brain, some networks synchronize after exposure to a stimulus (known as event-related synchronization; ERS). For example this occurs

in the motor cortex when actively inhibiting motor activity (Aoh et al. 2019). Event-related desynchronization (ERD) is the opposite, in the sense that a signal will cause normally synchronized networks to desynchronize (Başar 2012). While many hypotheses have been proposed, the role of ERD remains unclear, but it is seen during increased cortical excitability (Meirovitch et al. 2015), periods of attention (Başar and Gölbaşı 2014; Pfurtscheller, Neuper, and Mohl 1994), and stimulus perception (Silas, Tipple, and Jones 2019). This notion of event-related (de)synchrony establishes a dynamic in which a network, given some input, switches between synchronized and desynchronized to perform a computation. It could be argued then that the speed of this switching is critical, and in ERD for example, recovery back to synchrony should be as quick as possible.

The timescale of ERD recovery should be related to the coupling strength between the neurons and networks involved, as this is a convergence to the synchronous attractor (Forger 2017). But does network coupling always describe recovery rate from a transient desynchronization? Weakly electric fish generate an oscillatory electric field to sense their environment (electric organ discharge; EOD) (Møller 1995). The timing of the EOD is controlled by the PN. The PN comprises ~ 150 oscillating and synchronized neurons with phase lags ($\sim 2\text{-}5\%$ of the oscillator period) (Lucas et al. 2019; Moortgat, Bullock, and Sejnowski 2000; Dye 1987; Moortgat et al. 1998; Zupanc 2017; Elekes and Szabo 1985). This synchrony is behaviourally modulated during electrocommunication, with electric fish sporadically producing signals called chirps. Chirps involve a transient increase in EOD frequency and decrease in EOD amplitude, while lasting only a few 10s of milliseconds (Lucas et al. 2019; Smith et al. 2016; Hupe and Lewis 2009). Mechanistically, this results from a transient desynchronization of the PN (Lucas et al. 2019; Dye 1988; Dye et al. 1989). The rapid resynchronization would predict strong, dense coupling between cells, but connections in the PN mediated through gap junctions are sparse and weak (Lucas et al. 2019; Moortgat, Bullock, and Sejnowski 2000). How therefore does the PN recover so quickly from desynchronization?

If recovery time in the PN cannot be explained by coupling strength (gap junctional conductivity) or coupling density (Lucas et al. 2019; Moortgat, Bullock, and Sejnowski 2000), then either these coupling metrics have been underestimated or stronger functional coupling is achieved by another means. One possibility is through electric field effects. Electric field effects (often referred to as ephaptic coupling) (Arvanitaki 1942; Anastassiou 2014; Jefferys 1995) occur when endogenous electric fields (generated by

neuronal networks) affect the dynamics of the networks themselves. In neighboring axons with oscillatory discharges, electric field effects in oscillators can serve an entraining and synchronizing function (Shifman and Lewis 2019; Bokil et al. 2001; Goldwyn and Rinzel 2016). Given this, we suggest that the fish’s own electric field will affect the PN’s dynamics (Lucas et al. 2019) (additionally see Chapter 3). In this work we show that by considering the electric field from the fish’s discharge we are able to recover the rapid timescale of transient desynchronization without increasing experimentally measured levels of gap junctional coupling in the PN.

4.2 Methods

4.2.1 Modeling Methods

Our modeling approach consists of a pacemaker network (PN), an electric field (EOD) proxy, and a chirp (transient desynchronization) mediated by synaptic inputs.

Pacemaker Network

The pacemaker nucleus is a collection of 2 principle cell types: pacemaker cells and relay cells (Lucas et al. 2019; Moortgat, Bullock, and Sejnowski 2000; Smith, Lu, and Zakon 2000; Ellis and Szabo 1980). It is believed that pacemaker cells are endogenous oscillators, whereas the relay cells transmit the timing signals to the electric organ and do not oscillate (see Chapter 3). For this reason, we focus on a reduced network of pacemaker cells.

We base our pacemaker model on an existing model of a 300Hz pacemaker cell in *Apteronotus* (see Chapter 3). Readers familiar with *Apteronotus* may notice this frequency is low compared to the typical EOD frequency. This is due to the experimental recordings on which the model was fitted; they were performed at room temperature which is several degrees Celsius lower than the fish normal environmental conditions, resulting in a lower frequency ($Q_{10} \sim 1.5$; (Dunlap, Smith, and Yekta 2000)); this is not believed to change anything other than dynamical time scale (see Chapter 3). This original model was a single compartment and therefore by Kirchhoff will be unaffected by electric fields. To this end, neurons were created as in figure 4.1a with a spherical soma, and three tapering axon sections, measuring 165 μ m in total. We have additionally elected to maintain an active, oscillating axon. However, in considering the electric field

properties, these design decisions should not impart any significant effect on our results (see Discussion).

Pacemaker cell somas were randomly distributed within a 1mm diameter sphere (figure 4.1b), similar to the distribution seen within the real pacemaker (Zupanc 2017). Because the electric field due to the EOD is expected to be uniform within the PN (Supplemental figure 4.A.1), the field is modelled with parallel plate electrodes situated at the PN poles at $\pm 600\mu\text{m}$ from the center. All cells are oriented parallel to the electric field (see Discussion).

In the fish, pacemaker cells are connected primarily via axo-axonic and axo-somatic gap junctions (Elekes and Szabo 1981) with an approximate 4% density (~ 900 total connections for 150 pacemakers) (Moortgat, Bullock, and Sejnowski 2000). In our model, cells are connected by symmetric gap junctions at their distal end (grey dotted lines figure 4.1b); since all neuron compartments are oscillators, we don't make the distinction between axo-axonic and axo-somatic. Networks were randomly generated with the probability of one cell being connected to another given by a variable parameter (4%, 7% and 10%; see Results). The only constraint is that the networks be connected, i.e. generated connectivity graphs with isolated sub-networks were recomputed until the network is connected.

Electric field (EOD proxy)

Considering that the EOD oscillation is driven by the PN, and the resulting EOD field feeds back onto the PN, we use a proxy EOD signal mirroring PN activity for electrode playback. We define the state of the entire PN to be the mean membrane potential of all pacemaker cells at a given time. If the network is fully synchronized (figure 4.1c left), then the membrane potential averaged over the network will be similar to that of an individual cell. If the network is desynchronized, then the network activity over the network will be closer to the mean of the membrane potential over an oscillation cycle (figure 4.1c right). We linearly map the PN state onto the EOD signal such that the peak AP amplitude maps to -1 and the trough maps to $+1$. The EOD is then scaled by a constant to determine the strength of the electric field [V/m]. This means that during synchrony the field will be at full strength and when the network is desynchronized the field strength will be near zero (figure 4.1c lower panels) (see Discussion).

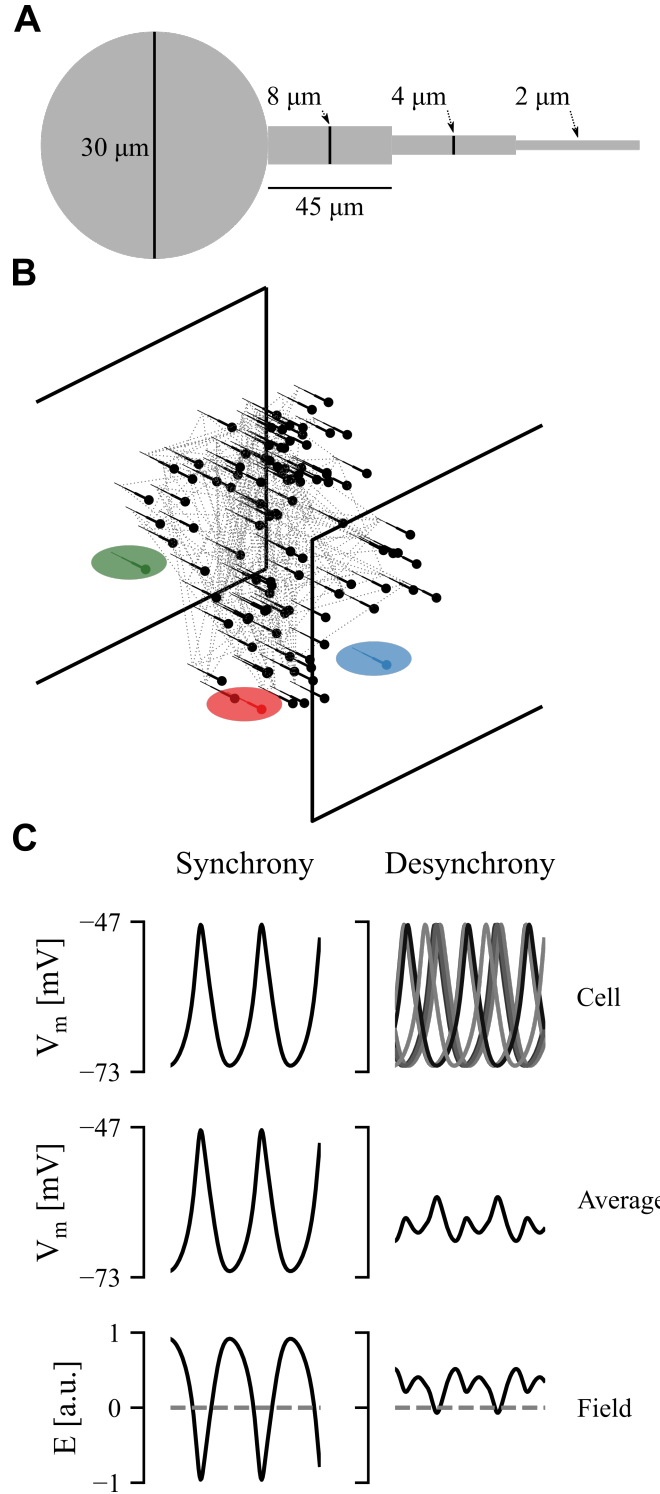


Figure 4.1: Computational model overview. (A) Neuron schematic featuring a 4 section neuron with a 30 μm soma and 135 μm axon tapering from 8 μm to 2 μm . (B) Network 100 cells are oriented parallel to the field from two parallel plate electrodes (black outline) spanning the virtual PN. Cells are coupled via gap junction (grey dashed lines). 3 example cells are used in later examples (red, green, blue). (C) Field control schematic. Synchronized PN (left) and desynchronized PN (right) are shown. First row shows distribution of action potentials (greyscale for display purposes). Second row shows mean over cells as a function of time. Last row shows EOD field map.

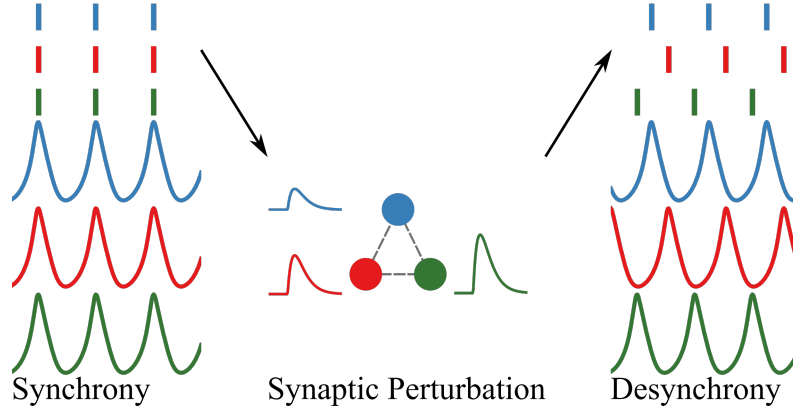


Figure 4.2: Schematic of transition between synchrony and desynchrony via synaptic perturbation. A gap junctional coupled network receives a random amplitude perturbation to each cell disrupting synchrony. Above raster represents activity in example cells from figure 4.1.

Chirp (synaptic perturbation)

In vivo, chirps (a form of transient desynchronization) are created by higher-order brain regions synaptically perturbing a subset of pacemaker cells, thereby desynchronizing the network (Lucas et al. 2019; Dye 1988). We model this with a chemical synapse to all cells. The synaptic perturbation is described by an alpha synapse with a time constant (τ) of 1ms and a random conductance chosen uniformly between 0mS/cm² to 10mS/cm² for each cell, sufficient to desynchronize the network. The initial conditions for the model network is the synchronized state (“pre-chirp”), and at 5ms simulation time a chirp is created by triggering the synapses and desynchronizing the network (figure 4.2). The simulation is then run for a further 145ms (150ms total).

Parameter Variability

In order to account for the effects of variation in cell position, connectivity and initial conditions, 10 cell collections were constructed, where we define a cell collection as a unique set of cell positions, orientations and chirp strengths. Then for each of the three coupling densities (4%, 7%, 10%), we create three sets gap junction connectivities for each of three coupling strengths (0.5nS, 1.0nS, 1.5nS). This yields 270 distinct networks which are then used for each field strength (i.e. in comparing between field strengths the underlying networks are unchanged).

Field Modeling

Each model network is run once without the feedback field (or ephaptic effects between cells), and then re-run six times with maximal field amplitude varying between 1V/m and 21V/m. These amplitudes are again somewhat arbitrary as the intracranial EOD field strength has not been measured, nor do theoretical models account for local heterogeneity which will affect the local field (Shifman, Longtin, and Lewis 2015). We’ve picked our field scale based on LFP scales. On the low end, 1V/m has been shown to efficiently entrain neurons *in vitro* (Anastassiou et al. 2011). Additionally it is known that 2–4V/m has been shown endogenously in cortex (Fröhlich and McCormick 2010) and this scale induces millivolt level changes in both hippocampal (Deans, Powell, and Jefferys 2007) and cortical neurons (Anastassiou et al. 2011; Fröhlich and McCormick 2010). At the upper end, 21V/m is smaller than the maximum field strength seen during epileptic LFPs (Queiroz et al. 2009; Weiss and Faber 2010).

Simulations were performed using the E_LFENN framework (Shifman and Lewis 2019), as such it should be noted that ephaptic effects between cells are included (cell-cell electric field effects), however these field strengths are small relative to the EOD field strength.

4.2.2 Measuring Network Synchrony

For this work, we measure synchrony with the Kuramoto order parameter (r) (Izhikevich and Kuramoto 2006; Forger 2017; Kuramoto 1984). r is a number between 0 and 1, with 0 representing perfect asynchrony (uniform spacing of all spike phases), and 1 representing perfect synchrony. An example representation of the mapping between phase (θ) distribution and r is shown in figure 4.3A. For illustrative purposes we have measured the Kuramoto index from the three sample cells in figure 4.2, at different phase distributions. Cell phase is defined uniformly between spike (peak) times, with the Kuramoto index (r) defined as

$$r \equiv \left| \frac{1}{N} \sum_{j=1}^N e^{i\theta_j} \right| \quad (4.1)$$

with figure 4.3A showing the intuition for equation 4.1. If the cell phases (θ) are taken to be uniformly distributed over a range $[0, \Delta]$ (what we will define as a raster width of size Δ), then Figure 4.3B shows the mapping between the raster width for 100 cells and the equivalent order parameter; as can be seen it is fairly linear between

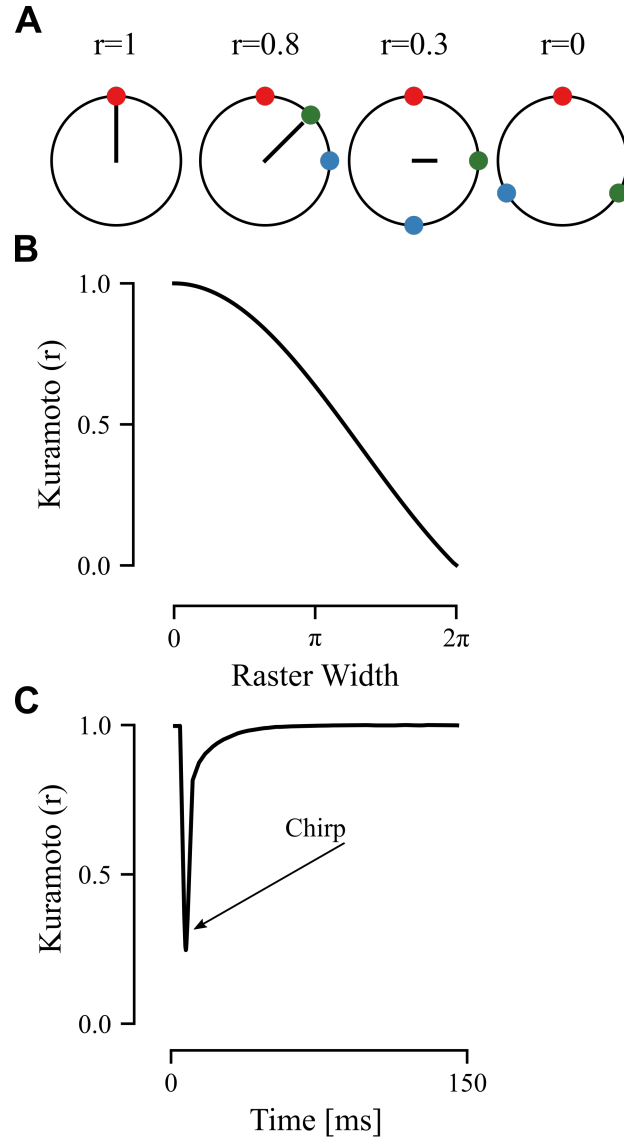


Figure 4.3: Kuramoto definition. (A) Representation of phase and order parameter r on the unit circle, phases are of example cells in figure 4.1. (B) Map from order parameter r to Raster Width (see text for definition). (C) Example model response in synchrony measure from a chirp applied at 5ms.

a raster width of 0 (perfect synchrony) and 2π (completely desynchronized), so the Kuramoto index can be considered a “synchrony fraction”. An example model response to synaptic perturbation is shown in figure 4.3C, where the network starts completely synchronized ($r=1$), desynchronizes due to the synaptic inputs (chirp), and then begins to resynchronize.

4.3 Results

We explore the possibility that electric field feedback from the EOD to the pacemaker nucleus (PN) decreases PN resynchronization time by modeling the closed-loop interaction between the PN and EOD. As described in the Methods, all simulations involve an initial 5ms of synchrony followed by a transient desynchronization from a synaptic input to the model networks. As noted previously, there is some degree of uncertainty about the coupling density and strength of the pacemaker network. Original experimental results suggested 4% and 5nS coupling (gap junctions) whereas subsequent computational models considered values as high as 10% and 15nS. For this reason, we’ve performed our simulations over a range of connectivity levels.

4.3.1 Electric Field Effects Promote Resynchronization

In figure 4.4 we show a matrix of results on how resynchronization dynamics change with various parameters. To begin, we will focus on the bottom left panel (figure 4.4) which corresponds to experimental coupling levels (4% connection density and 5nS conductance). We show Kuramoto traces as in figure 4.3C for several electric field strengths with dark-blue to light-blue representing low to high strength (black trace represents the null condition with electric field removed). Note that the null trace obscures results of the lowest field strength (1V/m). As we can see, without electric field effects, or very weak field effects, re-synchronization occurs in 50–100ms, much too slowly to reproduce *in vivo* studies. Additionally, we want to highlight the red and yellow dashed-lines representing 12ms and 30ms post stimulus (for an approximately 300Hz oscillator this is 4 and 10 cycles respectively). As field strength is increased, we see a faster and faster return to synchrony (see region between 12 and 30ms lines; this will be quantified in the next section).

The remaining panels in figure 4.4 show similar results for increases in gap junctional conductance (0.5nS–1.5nS) across rows, and increases in coupling density (4%–10%)

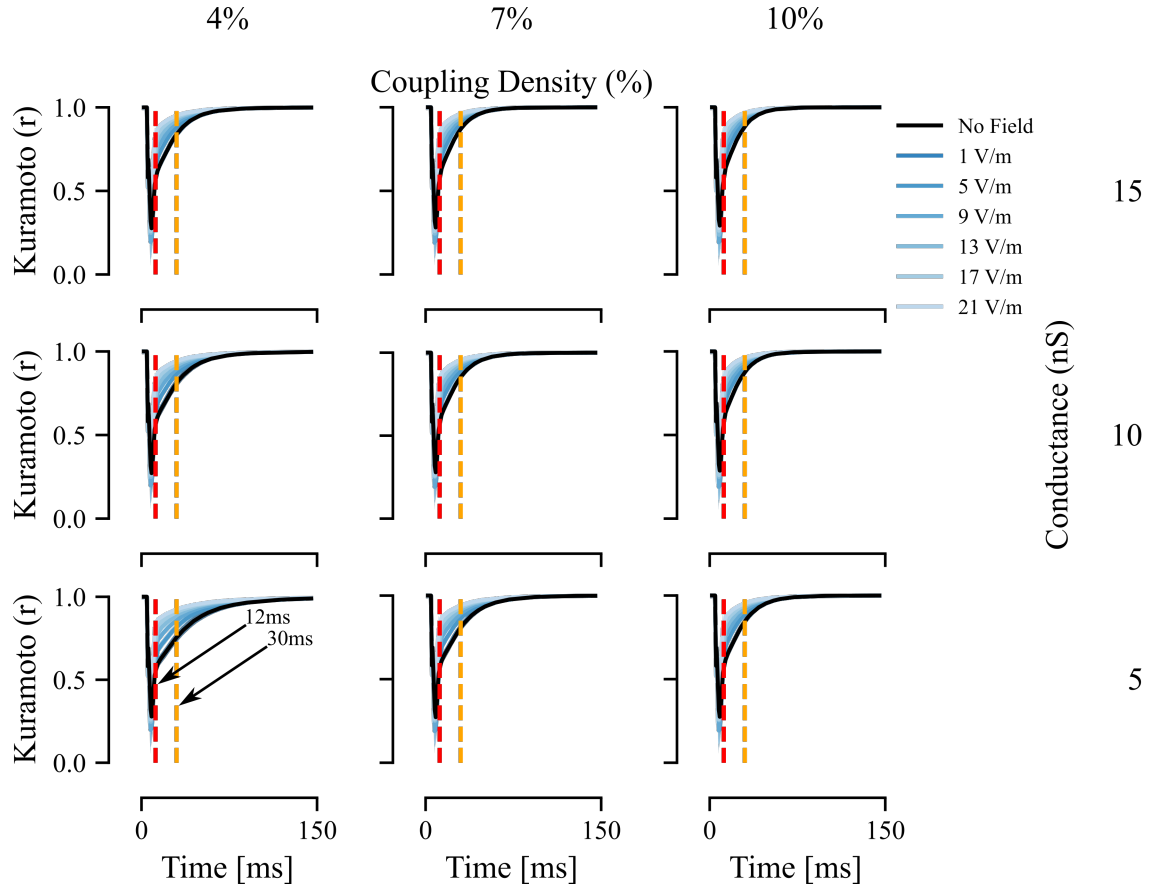


Figure 4.4: Model response to chirp as a function of field strength (legend inset upper right). Gap junction strength is varied across rows, and density is varied across columns. Red and yellow lines represent 12ms and 30ms time point at which r is measured in later figures (annotation bottom left).

across columns. Looking across the diagonal, we see that as overall coupling strength increases, resynchronization speed increases but significantly less dramatically than with increasing feedback field strength (compare traces within a panel).

4.3.2 Quantifying Synchrony Convergence

Using the time points (12 and 30ms) extracted in figure 4.4, we measure the mean and variance of the Kuramoto synchrony index for each condition in figure 4.5 using the same format with coupling density on the columns and coupling strength (conductance) on the rows. For each time point, we also show the mean of the null Kuramoto index i.e. with no electric field effects (dashed and solid black lines: 12 and 30ms respectively). The Kuramoto index at each time point as a function of field strength is presented as mean $\pm$ s.d. (solid and filled areas) (statistics taken across networks and connectivity). Of note is the nearly identical curves across coupling (compare null lines, particularly the 30ms line across coupling density shows the weak effect of connectivity). This is due to the fact that the electric field effects dominate any network coupling effects.

Interestingly, electric field effects cause a nearly 60% increase in synchrony ($r \sim 0.5 \rightarrow r \sim 0.8$) within 12ms (across all baseline connectivities). In fact, this benefit is so pronounced that $r \sim 0.8$ is where the control networks (null) would be at the second 30ms time point (distance between red and yellow control/dashed lines). By 30ms we see, even for intermediate field strength, synchronization to $r > 0.9$, which is relatively high synchrony (100 cells with normally distributed phase s.d.=5% has $r=0.95$).

4.3.3 Measuring Convergence Time

In order to highlight the effect of field effects, we quantify the time to synchrony in figure 4.6. Here we define synchrony as recovering to a Kuramoto synchrony of $r \geq 0.9$. We overlay all 9 experimental conditions with color denoting the connection density and intensity shades indicating conductance strength. Lines represent the mean of the resynchronization time.

In the weakest coupling (experimental) case, we see a convergence time of >60 ms which is decreased by $\sim 50\%$ via electric field effects. For all other coupling strengths we see similar relative gains ($\sim 50\%$ convergence time decrease) but with these results being within the target <30 ms. Again we see that increasing field effect strength is a much stronger contributor to resynchronization time than coupling strength (with the exception of the jump from the weakest (4%, 5nS) coupling to all other parameters).

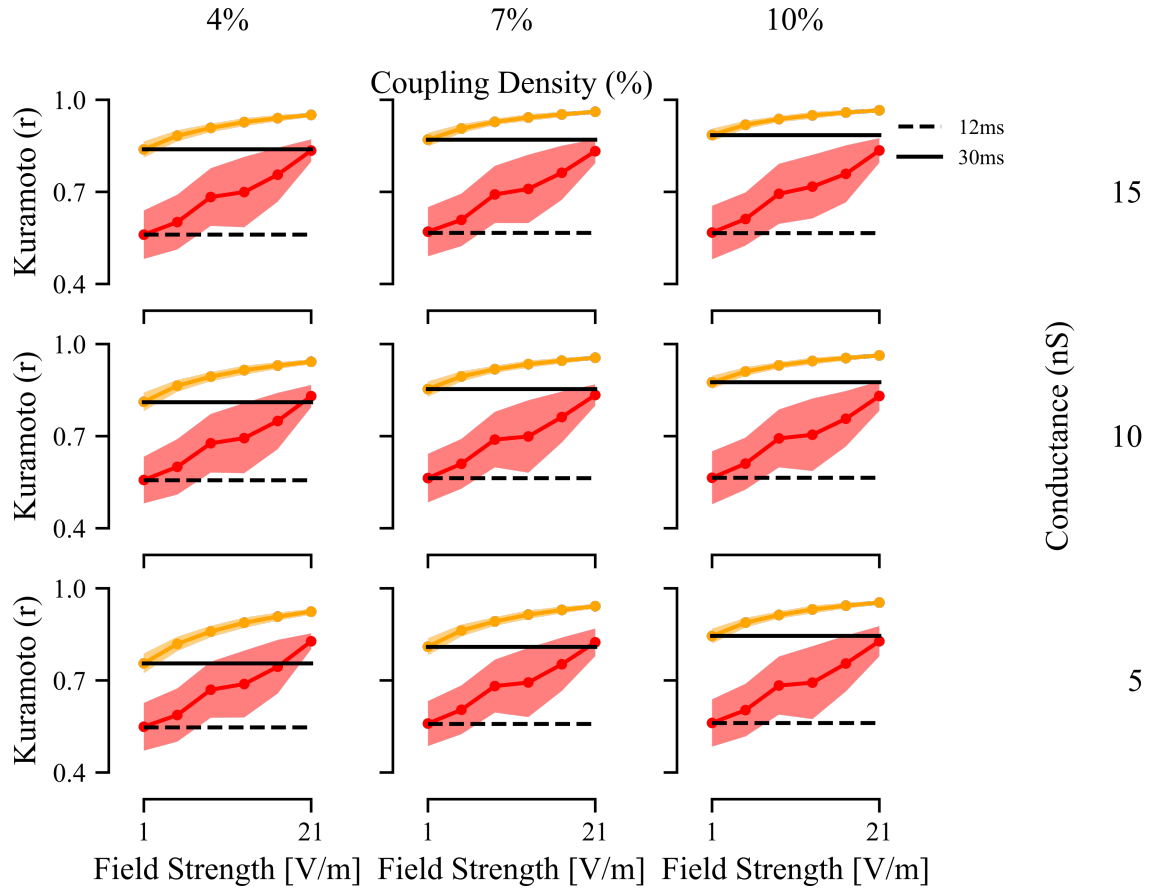


Figure 4.5: Synchronization convergence as a function of field strength. Like figure 4.4 gap junction strength is varied across rows, and density is varied across columns. Red and yellow lines represent 12ms and 30ms time points at which r is measured. Dashed line and solid lines are mean r when no field is applied at 12ms and 30ms respectively (legend upper right). Results are plotted as mean $\pm$ s.d. Extreme similarity in plots arises from field effects dominating coupling effects.

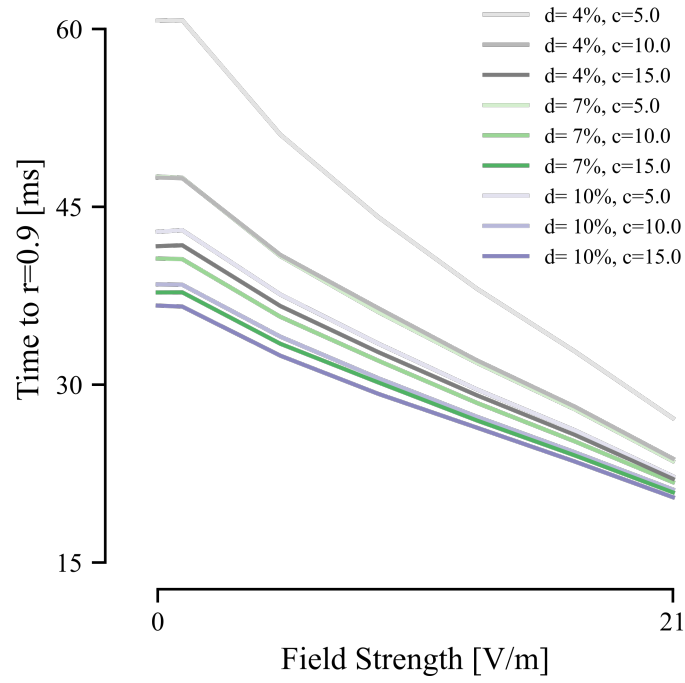


Figure 4.6: Time to synchrony ($r=0.9$) for all modeled networks. Color is given by combinatorial map with light to dark representing low to high coupling density, and green to purple representing low to high coupling strength. Note flat line between 0V/m, and 1V/m showing near zero effect size for very weak fields.

4.4 Discussion

The pacemaker nucleus (PN) of the weakly electric fish undergoes transient desynchronization (Lucas et al. 2019; Moortgat et al. 1998; Turner et al. 2007) in a process akin to event related desynchronization (ERD) (Meirovitch et al. 2015; Güntekin and Başar 2016). Interestingly, the transient in these fish can be as short as 30ms, however, weakly coupled oscillator theory, and computational modeling would predict much longer synchronization times given the experimentally measured coupling (Lucas et al. 2019; Moortgat et al. 1998). In the past, computational work has addressed this mismatch by simply increasing the coupling strength (Lucas et al. 2019; Moortgat, Bullock, and Sejnowski 2000).

The PN, under normal circumstances, has a single frequency. Since it is also fully synchronized, it can be abstracted as a single pulse generator. This generator then drives an electric organ, creating an electric organ discharge EOD. While the exact nature of this drive is unclear (direct drive, or an entrainment mechanism), the PN and the EOD are coupled 1-to-1 (Markham 2013; Salazar, Krahe, and Lewis 2013), i.e. every spike in the PN corresponds to a cycle of the EOD. Since this 1-to-1 coupling means the PN and EOD have the same frequency, then feedback entrainment from the EOD to the PN is feasible (Escalona, José, and Tiesinga 2002). Additionally the PN sits within a fairly uniform electric field that is due to the EOD (Shifman, Longtin, and Lewis 2015) (additionally 4.A.1). It has been well-established that electric fields can entrain axons (Shifman and Lewis 2019; Goldwyn and Rinzel 2016; Bokil et al. 2001) and neurons (Anastassiou et al. 2011; Fröhlich and McCormick 2010). Can the feed-back of the electric organ entrain its own control circuitry?

In this work, we have shown with a modeling approach that the EOD feedback entrains the PN, and can rescue experimentally measured resynchronization times with little to no requirement for increasing coupling parameters.

4.4.1 Realism

In order to simplify the actual PN we’ve made some approximations that we will discuss in the following.

Axon taper

A uniform (straight with equal impedance) axon in a spatially uniform electric field will not experience any effect from a uniform electric field (except for at the boundaries) (Shifman and Lewis 2019; Anastassiou et al. 2010; Holt and Koch 1999) as the ephaptic current (related to the spatial derivative of the field) is zero. In the PN, the axons of pacemaker cells are quite wide and meander in all directions. The result is that each point along the axon will experience a different electric field magnitude in the direction of the axon and hence the axon can couple to the field. Modeling these spatially complex axons is quite complicated hence we’ve imposed coupling by creating a tapering axon (non uniform impedance). While this is not believed to represent the actual axons, it provides a reasonable abstraction to facilitate modeling.

Axon orientation

We have aligned our cells with the extracellular field which is not realistic (see above). To see how much of an effect this has had, we have re-done much of this modeling work while allowing neuron azimuth and elevation (about the soma) to be free parameters from $[-\pi, \pi]$. In fact, these results were only quantitatively distinguishable from the results presented herein (i.e. graphs looked visually identical; data not shown). There are two reasons for this. Firstly, in the rotational range $[-\pi, \pi]$ half of the time the cell will merely be facing “backwards” in the field. Since both the soma and axon are oscillators (same dynamics), the field is only pushing current backwards through a similar system: in one orientation current is pushed soma $\rightarrow$ axon, the other orientation is axon $\rightarrow$ soma. This symmetry reduces this condition to cells being in an angle within $[-\pi/2, \pi/2]$. In this case, half of the cells will have the orientation $[-\pi/4, \pi/4]$. Since the field effect is related to component of the field parallel to the axon (Shifman and Lewis 2019; Goldwyn and Rinzel 2016; Tveito et al. 2017) (in this case $\sin(\theta)$), there will have be an electric field effect 71% as strong as in non-rotated case ($\sin(\pi/4)$). Since half of the cells receive a mostly intact feedback, and gap junctions homogenizing the network: it is not surprising that these results are robust to rotation.

Chirp Dynamics

In this work we have modeled the chirp as dropping the EOD amplitude to near zero. While it is true that during a chirp, EOD amplitude decreases (Lucas et al. 2019), it usually does not decrease to that extent. As a result we underestimate the field

strength after the chirp, which will serve to delay synchronization and thus we expect our resynchronization times to be conservative estimates.

4.4.2 Electric Fish Implications

There are some interesting details which came about during the model development. For example, the knowledgeable reader may have noted that the map used to create the virtual field implies that the EOD is out of phase with the PN. We had initially performed simulations with the EOD in phase, and interestingly this field disrupted synchronization. This raises questions about EOD control: Is this a phase locking effect where the PN and EOD are oscillators affecting each other? Alternatively, does the PN drive the EOD and the combination of propagation, and spinal delays amounts to some odd multiple of phase delays (π , 3π , $\dots$)? Another option is this phase difference relates to an unknown local field geometry, or current flow? While we do not have any of these answers, the PN-EOD phase map will be part of the answer for determining how the electric organ is controlled.

4.4.3 Implications on Connectivity

Most importantly we have shown that electric fields can modulate the functional connectivity of a network. In the case presented here we show that a weak electric field of 21V/m is capable of increasing the apparent coupling strength by a large degree (more so than by increasing coupling density by $2.5\times$ coupling strength by $3\times$). Additionally, above we have discussed how in a well-behaved field this can be robust to extreme variations in geometry (far more than would be seen for example in cortex, hippocampus, or within axon tracts). Lastly, we have discussed how the same techniques can be used to disrupt synchrony. This is of interest in neuromodulatory treatments of epilepsy where functional hypersynchrony underlies epileptiform activity (Jiruska et al. 2013; Rao and Lowenstein 2015). In summary the functional connectivity of a network, in some conditions, is not solely mediated by its topology but also by its geometry in sufficiently strong (biologically plausible) electric fields.

4.5 Competing Interests

We have no competing interests.

4.6 Contributions

ARS and JEL conceived and planned the simulations. ARS implemented and performed the simulations with input from JEL. ARS and JEL wrote the manuscript. All authors read and approved the final manuscript.

4.7 Acknowledgement

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4.8 References

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Appendix

4.A Supplemental Figures

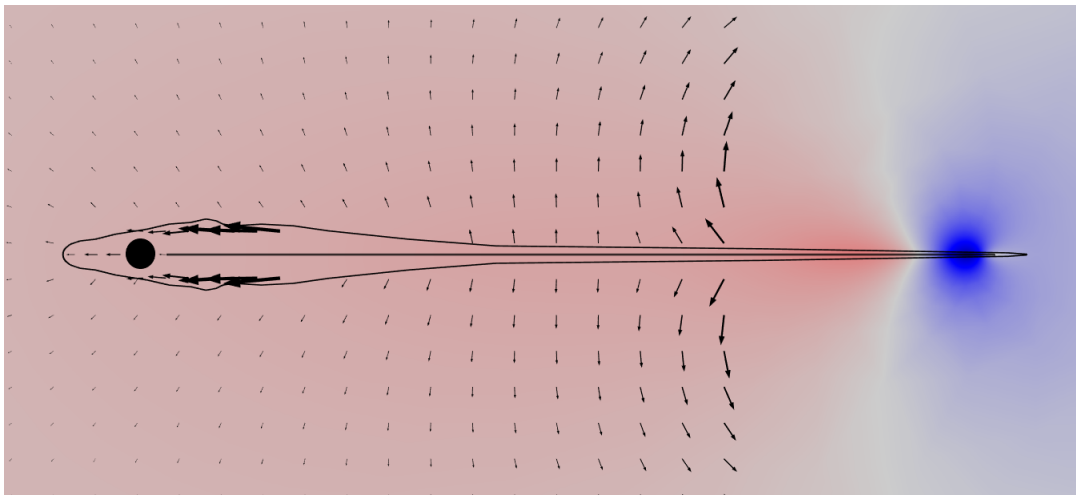


Figure 4.A.1: PN inside the EOD of *Aptereronotus*. Simulation of one phase of the EOD with the approximate location of the PN (black dot, not to scale). Color maps EOD negative-positive (blue-red). Field vectors (black arrows) inside the fish near the PN are approximately uniform

Part II

Macro-scale Bioelectric Fields

Chapter 5

The Complexity of High-Frequency Electric Fields Degrades Electrosensory Inputs: Implications for the Jamming Avoidance Response in Weakly Electric Fish¹

Abstract

Sensory systems encode environmental information that is necessary for adaptive behavioural choices, and thus greatly influence the evolution of animal behaviour and the underlying neural circuits. Here, we evaluate how the quality of sensory information impacts the jamming avoidance response (JAR) in weakly electric fish. To sense their environment, these fish generate an oscillating electric field: the electric organ discharge (EOD). Nearby fish with similar EOD frequencies perform the JAR to increase the difference between their EOD frequencies, i.e. their difference frequency (DF). The fish determines the sign of the DF: when it has a lower frequency ($DF > 0$), EOD frequency is

¹A. R. Shifman and J. E. Lewis (2018). “The Complexity of High-Frequency Electric Fields Degrades Electrosensory Inputs: Implications for the Jamming Avoidance Response In Weakly Electric Fish”. In: *J. R. Soc. Interface* 15.138, pp. 1–11

decreased and vice versa. We study the sensory basis of the JAR in two species: *Apteronotus leptorhynchus* have a high frequency (ca 1000 Hz), spatio-temporally heterogeneous electric field, whereas *Eigenmannia sp.* have a low frequency (ca 300 Hz), spatially uniform field. We show that the increased complexity of the *Apteronotus* field decreases the reliability of sensory cues used to determine the DF. Interestingly, *Apteronotus* responds to all JAR stimuli by increasing EOD frequency, having lost the neural pathway that produces JAR-related decreases in EOD frequency. Our results suggest that electric field complexity may have influenced the evolution of the JAR by degrading the related sensory information.

5.1 Introduction

Weakly electric fish sense their environment using a self-generated electric field (EOD: electric organ discharge) (Moller 1995). Perturbations to this field enable the perception of objects and other fish even in the dark, a behavior called electrolocation (Lissmann 1958; Bennett 1971b). The EOD of wave type electric fish is quasi-sinusoidal, oscillating with a frequency (EODf) that varies across individuals and species. When two fish approach one another, their EODs will interfere, resulting in amplitude modulations with a frequency equal to the difference between the two interacting EODfs (i.e. difference frequency, DF). When the DF is small, these amplitude modulations can mimic those used for electrolocation, effectively “blurring” the electrosensory scene (Heiligenberg, Baker, and Matsubara 1978; Heiligenberg 1991). When exposed to a small DF, many species perform a jamming avoidance response (JAR): the lower-frequency fish perceives a $DF > 0$ and decreases its EODf, while the higher-frequency fish perceives a $DF < 0$ and increases its EODf, effectively increasing the magnitude of the DF (Bullock, Hamstra, and Scheich 1972a; Stamper et al. 2012; Carlson and Kawasaki 2007).

Here, we consider two species of the gymnotiform order, *Apteronotus leptorhynchus* (EODf ~ 600 -1100Hz) and *Eigenmannia virescens* (EODf ~ 200 -600Hz), that respond differently to JAR-related stimuli (Alves-Gomes et al. 1995; Turner et al. 2007). When a conspecific EOD results in a $DF < 0$, both species increase their EOD frequency, in a JAR-consistent manner. However, a $DF > 0$ produces distinct responses: *Eigenmannia* decrease their EOD frequency (as expected), but *Apteronotus* increase their EOD fre-

quency (the so-called non-selective response, NSR (Dye 1987; Bastian, Schniederjan, and Nguyenkim 2001)). In other words, *Eigenmannia* can change EOD frequency appropriately in response to either a negative or positive DF, whereas *Apteronotus* responds with an increase in EOD frequency regardless of the sign of the DF (Dye 1987; Heiligenberg et al. 1996). Interestingly, *Eigenmannia* will change EODf in response to the complex envelopes resulting from multiple fish (social envelope response, SER (Stamper et al. 2012; Stamper, Fortune, and Chacron 2013)). A similar behavior has not yet been described in *Apteronotus*, but it appears they are unlikely to experience such envelopes and may even actively avoid them (Stamper et al. 2010; Tan et al. 2005).

The differences in JAR-related behaviors between *Eigenmannia* and *Apteronotus* can in part be explained by neuroanatomy. While both species have neurons in the midbrain that respond selectively to the sign of the DF (sign-selective neurons) (Rose and Canfield 1991; Rose 2004; Rose and Heiligenberg 1986), *Apteronotus* lacks the neural pathway necessary to decrease EOD frequency from baseline levels (Heiligenberg et al. 1996; Rose 2004). How these species differences have evolved is not clear, but the underlying selective pressures are apparently much more diverse than might be expected for a behavior whose sole function is to avoid jamming. First of all, *Sternopygus*, which is thought to represent the ancestral condition (Rose 2004; Tagliacollo et al. 2016; Smith et al. 2016), is a wave-type electric fish that does not produce a JAR, but nonetheless has sign-selective neurons (Rose and Canfield 1991; Rose, Keller, and Heiligenberg 1987). In addition, EOD frequency and its modulation over different time-scales are apparently under sexual selection; this has led to sexual-dimorphic frequencies and communication signals that vary significantly, even between closely-related species (Smith et al. 2016; Ho et al. 2010). This, along with predation (Stoddard and Markham 2008), has resulted in an expansion of EOD frequencies to higher than 2 kHz in some species (Turner et al. 2007; Tagliacollo et al. 2016; Smith et al. 2016). Further constraints involved in high-frequency EOD generation are thought to have driven the transition from a myogenic electric organ (involving a neuromuscular-like synapse; as in *Eigenmannia*) to a neurogenic organ comprising only neuron-like cells (as in *Apteronotus*) (Bennett 1971a). This transition is also associated with an increase in the spatiotemporal complexity of the resulting electric fields (Shifman, Longtin, and Lewis 2015), which are very different in *Eigenmannia* and *Apteronotus* (figure 5.1): a spatially uniform oscillating dipole in the former (Assad et al. 1998), and spatially heterogeneous traveling wave in the latter (Shifman, Longtin, and Lewis 2015). We suggest that there may be a relationship between the spatiotemporal

features of the EOD and the evolution of the JAR through the impact on the quality of the related sensory inputs.

To perform an effective JAR and change EODf in the correct direction, the fish must determine the sign of the difference frequency (DF). To do this reliably, it is necessary to track the time-varying amplitude modulations and phase differences between signals at different body locations (Heiligenberg, Baker, and Matsubara 1978; Heiligenberg 1991; Stamper et al. 2012; Carlson and Kawasaki 2007). These fish have no efference copy of their EOD (Bullock, Hamstra, and Scheich 1972a; Bullock, Hamstra, and Scheich 1972b), so some body locations must serve as a timing reference (e.g. at a location where the modulation is minimal). For two interacting fish, the amplitude modulation will be periodic in time with a frequency equal to the DF. The phase of the combined signal is also modulated periodically at the same frequency, but with a different temporal pattern. When the amplitude modulation is plotted as a function of phase difference, a closed curve (ellipse-like trace) is formed; this is traditionally referred to as a Lissajous plot (Heiligenberg 1991; Carlson and Kawasaki 2007; Heiligenberg and Bastian 1980) (see figure 5.2). The direction of rotation of this curve is determined by the sign of the DF (for $DF > 0$, the rotation is counter-clockwise; and for $DF < 0$, the rotation is clockwise) (Heiligenberg, Baker, and Matsubara 1978; Bullock, Hamstra, and Scheich 1972a; Stamper et al. 2012; Carlson and Kawasaki 2007). In this paper, we show that the spatial heterogeneities of a complex EOD confound the sensory information arising from phase and amplitude modulations, and thus limit the accuracy with which the sign of the DF can be determined. This sensory limitation could adversely affect JAR performance and thus impact the evolution of this behavior in some species.

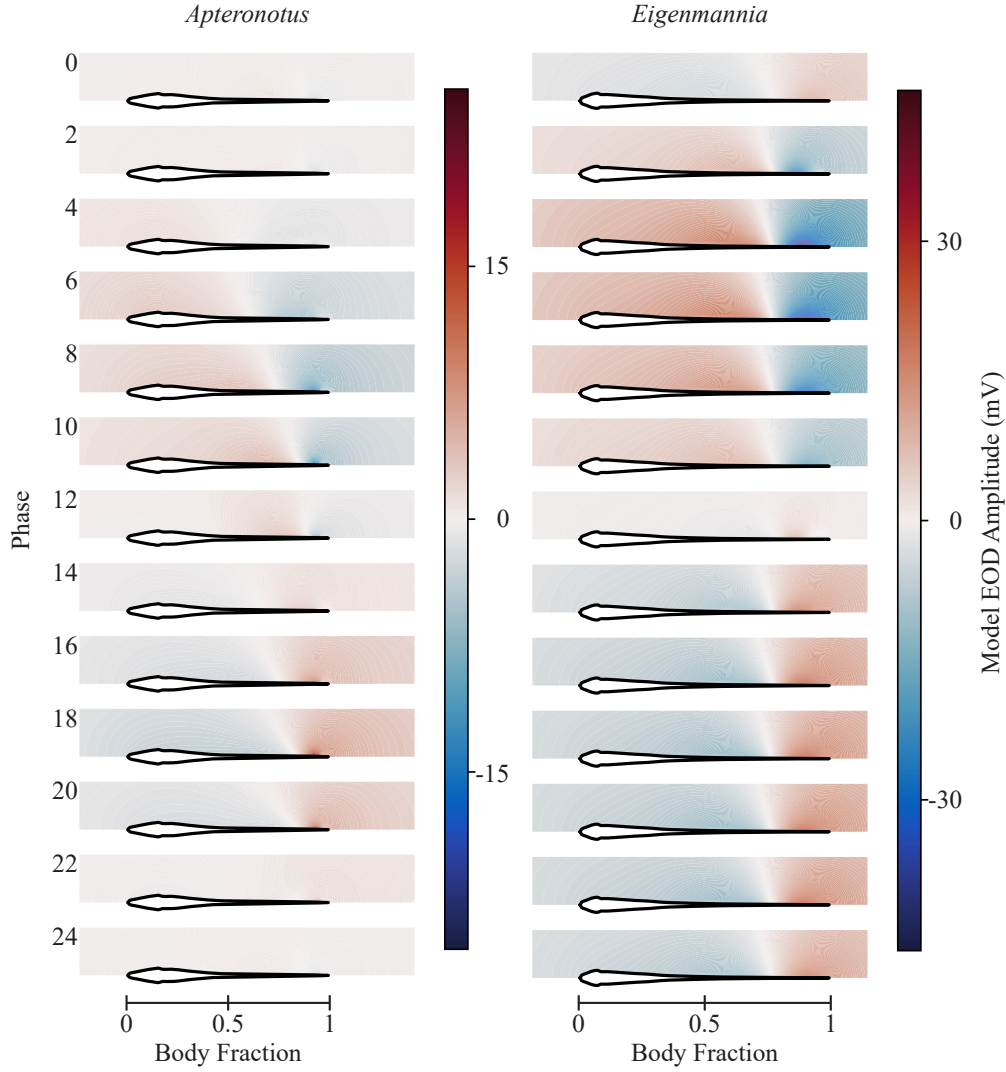


Figure 5.1: Spatiotemporal evolution of the EOD in both *Eigenmannia* and *Aptereronotus*. Panels show model outputs (voltage map) for 12 phases of one EOD cycle over a representative domain 5cm from the left of the nose to 30cm to the right; rostral-caudal length is shown as body fraction in a 26cm *Eigenmannia* (EODf=300Hz) and a 21cm *Aptereronotus* (EODf=600Hz). Voltage scale (mV) is indicated by the colorbar on the right in each case; note that the “zero-line” is visible as a white (0 V) line separating positive (red) and negative (blue) regions.

5.2 Methods

5.2.1 Modeling the electric field

We perform a detailed comparison of the spatiotemporal features of jamming signals between *Eigenmannia* and *Apteronotus* using computational models. We have previously developed a model for the time varying electric field of a 21 cm long *Apteronotus leptorhynchus* (Shifman, Longtin, and Lewis 2015), and describe here a similar model for *Eigenmannia*. In brief, a 2D cross-section of the *Eigenmannia* body (26 cm in length) was divided into 3 compartments: skin, body, and electric organ. The contour of the fish (not including fins) was an idealized approximation of the tracings provided by C. Assad and B. Rasnow (Assad et al. 1998; Rasnow and Bower 1996) and was symmetrical about the rostro-caudal axis. The length of each model was given by the original tracings from the Assad and Rasnow recordings. The skin comprised a 100 μ m layer and the electric organ was defined as a 0.01cm x 22cm rectangle centered about the rostro-caudal axis and beginning 3cm from the tip of the nose. The electrical conductivities for each body compartment were taken from the *Apteronotus* model (Shifman, Longtin, and Lewis 2015; Babineau, Longtin, and Lewis 2006). To replicate the experimental recording conditions, the fish model was placed in a 70cm x 70cm “tank” with water conductivity of 200 μ S/cm (Assad et al. 1998; Assad 1997), and a reference (ground) electrode in the corner of the tank nearest the head.

As in previous studies, we used a finite element approach (COMSOL Inc) to model the electric field (Shifman, Longtin, and Lewis 2015; Babineau, Longtin, and Lewis 2006; Babineau, Lewis, and Longtin 2007; Kelly et al. 2008); we solved the forward quasi-electrostatic (QES) problem: Poisson’s equation (equation 5.1), in which the voltage (Φ) in space with conductivity (σ) is calculated from the current density ($\vec{J}$). The lateral edges of the electric organ were defined as boundary current sources with the current following equation 5.2. Note that in *Eigenmannia*, the electric organ is enveloped by a resistive sheath (Bennett 1971a), which would bias current flow parallel to the rostral-caudal axis in a manner that may not be consistent with these boundary conditions. Nonetheless, since our model accurately reproduced the spatiotemporal variations in the EOD and electric field (see following), it was sufficient to address the JAR-related questions in this study. Future work will be aimed at understanding the current generating properties of the electric organ itself.

$$\nabla \cdot \sigma \nabla \Phi = -\vec{J} \quad (5.1)$$

Due to the relatively simple dipolar nature of the EOD in *Eigenmannia* (Assad et al. 1998; Assad 1997), the current density on the organ was defined as the sum of two Gaussian curves, as was done previously for a single-phase model in *Apteronotus* (Babineau, Longtin, and Lewis 2006; Babineau, Lewis, and Longtin 2007). Each Gaussian curve had 3 free parameters: amplitude (A), peak center (c), and standard deviation (σ), with the current density function $J(x)$ as given in equation 5.2.

$$J(x) = A_1 e^{\frac{-(x-c_1)^2}{2\sigma_1^2}} + A_2 e^{\frac{-(x-c_2)^2}{2\sigma_2^2}} \quad (5.2)$$

The model was fit to previously recorded EOD data, kindly provided by C. Assad and B. Rasnow (Assad et al. 1998; Rasnow and Bower 1996). The EOD was sampled at 25 timepoints over one EOD cycle, and spatially interpolated (linear, over triangular mesh) to 0.2cm resolution within 2cm lateral of the fish, and 0.6cm resolution outside that region. This variable density implicitly weights data points closer to the body, allowing for better fits to the increased heterogeneities in this region (Shifman, Longtin, and Lewis 2015). The fitting procedure involved finding the parameters for the current density (equation 5.2) that minimized the sum of squared error (SSE, equation 5.3) between model potential (Φ^m), and recorded potential (Φ^r). Optimization was performed using the Nelder-Mead simplex algorithm (Nelder and Mead 1965) which was implemented in the Java Apache Math Library through COMSOL's JAVA API. In order to compare the error across phases, the SSE was normalized (normalized root mean squared error, NRMSE; equation 5.4).

$$\text{SSE} = \sum_{i=1}^n (\Phi_i^m - \Phi_i^r)^2 \quad (5.3)$$

$$\text{NRMSE} = \frac{\sqrt{\frac{\text{SSE}}{n}}}{\max(\Phi^r) - \min(\Phi^r)} \quad (5.4)$$

To bias continuity of the current density solutions between each EOD phase, the solution (optimized current) for one phase was used as the initial condition for the fitting algorithm at the next phase. Note that the recorded data for phase 2 was uncharacteristically discontinuous in comparison to the rest of the data, and was therefore excluded from the optimization. Once fitting was complete, the solutions for each phase were

stored as a numerical lookup table, with a temporal resolution of 25 points per EOD cycle and a spatial resolution of 1000 points over the electric organ.

5.2.2 Amplitude and phase modulations in multiple sine waves

Electric fish generate a quasi-sinusoidal, oscillating electric field. The fields (EODs) of multiple fish with different frequencies sum to create an amplitude-modulated signal; as in previous studies (Heiligenberg, Baker, and Matsubara 1978; Heiligenberg and Rose 1985), we illustrate this using sine waves that represent the EODs of two fish (equation 5.5). The reference (or carrier) frequency is F_0 (i.e. receiving fish), and the modulating frequency is F_1 (neighbouring fish) with a difference frequency $DF \equiv F_1 - F_0$ (Carlson and Kawasaki 2007) (this is the standard convention in which a positive DF indicates that the neighbouring fish has the higher EOD frequency). When the DF is non-zero, an “apparent frequency” appears (the beat frequency). In the time domain, this results in a beat (amplitude modulation) at a frequency $|DF|$ (where $|\cdot|$ denotes absolute value). *Eigenmannia* is able to sense differences in EOD periods as low as 400 ns (i.e. $DF \sim 0.036$ Hz in a 300 Hz fish) (Rose and Heiligenberg 1985; Carr, Heiligenberg, and Rose 1986). For a relatively small modulating signal, the amplitude modulation is given by equation 5.6 (Stamper et al. 2012), where α , F , and ϕ represent the amplitude, frequency and phase shift respectively. In general, the modulating signal will be smaller than the carrier as electric fields decay over space and the self-generated EOD is generally larger than that sensed from neighboring fish (Stamper et al. 2012). It should be noted that for more complicated signals (more than two sine waves, or harmonics present) these analytic forms are not always applicable, so in the case of the simulated EODs, the AM, and later the envelope (when multiple DF s are present) is calculated using peak tracing (see later).

$$S(t) = \alpha_0 \sin(2\pi F_0 t + \phi_0) + \alpha_1 \sin(2\pi F_1 t + \phi_1) \quad (5.5)$$

$$AM(t) = \sqrt{\alpha_0^2 + 2\alpha_0\alpha_1 \cos(-\phi_0 + \phi_1 + 2\pi(F_1 - F_0)t) + \alpha_1^2} \quad (5.6)$$

A second order effect of amplitude modulation is phase modulation; the modulating signal effectively pushes the phase of the carrier around in time. This phase modulation is given by equation 5.7 for pure sine waves, where ω_0 and ω_1 is the angular frequency of fish 1 and 2 respectively and α_0 and α_1 are their respective amplitudes (Stamper et al. 2012). Again, in general for complex signals, an analytic form of the phase is not

applicable, so the phase ϕ of a signal x is given by the angle of the Hilbert transform $\bar{x}$ (equation 5.8). The phase difference $\Delta\phi$ between the modulated signal and a reference signal $x(t)$ is given by equation 5.9. The phase modulation is shown in figure 5.2(B).

$$\phi(AM(t)) = \frac{\omega_0 + \omega_1}{2}t + \arctan\left(\frac{\alpha_0 - \alpha_1}{\alpha_0 + \alpha_1} \tan\left(\frac{\omega_0 - \omega_1}{2}\right)\right) \quad (5.7)$$

$$\phi(x(t)) = \arctan\left(\frac{\text{Im}(\tilde{x})}{\text{Re}(\tilde{x})}\right); \quad \tilde{x} \equiv \left(x \star \frac{1}{\pi t}\right)(t) \quad (5.8)$$

$$\Delta\phi(AM, x) = \phi(AM) - \phi(x) \quad (5.9)$$

In our analyses, we calculated the AM and envelope by tracing the local minima. The differential phase modulation was calculated by equation 5.9 and sampled at these minima. For the Lissajous plots shown in figures 5.4 and 5.6, the reference signal was taken at a single body location (50%); for the JAR model (see below), the unperturbed signal at each body location served as the reference signal for that location. The choice of the 50% point was arbitrary; however, the Lissajous plots are similar regardless of point chosen. Given the modulations to both phase and amplitude, the sign of the DF can be unambiguously determined. The amplitude modulation as a function of phase forms an enclosed orbit, or Lissajous plot (figure 5.2B) with the direction of rotation denoting the sign of the DF (clockwise: $DF < 0$, and counter-clockwise: $DF > 0$) (Stamper et al. 2012; Carlson and Kawasaki 2007). While normally these are plotted in Cartesian coordinates, we used polar coordinates (the comparison is shown in figure 5.2B). Although small phase modulations are clear when portrayed in Cartesian representations, large modulations can lead to discontinuities in these plots. Polar representations are much easier to interpret in general, due to the continuous phase wrapping.

As noted earlier, interactions involving more than two fish involve additional considerations. For example, with three sine waves, not only are there DF s between each of the three signals, there are also the differences between each DF (DDF s) (Stamper et al. 2012). When one modulating sine wave produces a positive DF and the other produces a negative DF , the Lissajous plots will trace out modulations that oscillate between positive and negative DF s. In this case, the Lissajous plots will form rotating “hypotrochoid-like” patterns with the net rotation given by the difference between the two DF s (the DDF) (Stamper et al. 2012; Partridge and Heiligenberg 1980).

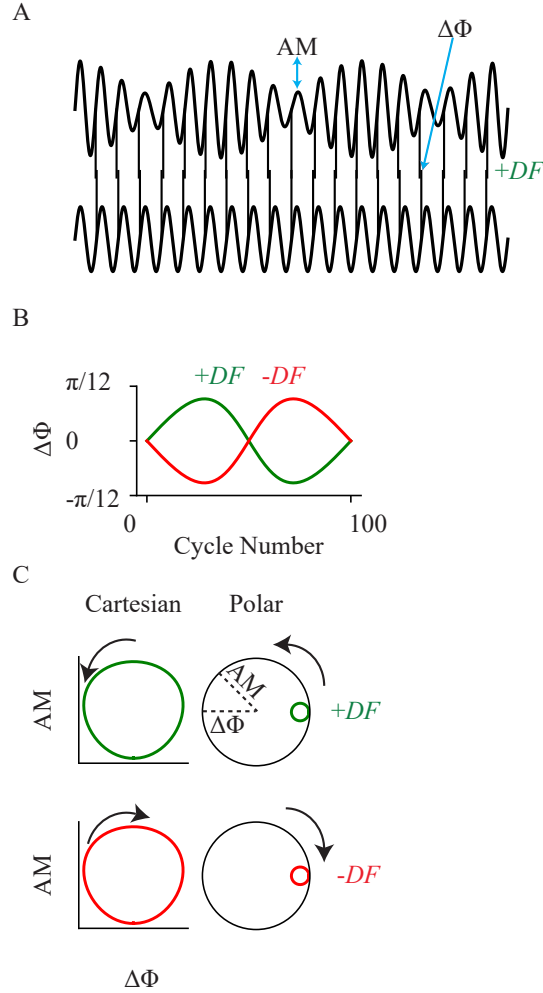


Figure 5.2: Computational rules for the jamming avoidance response (A) Schematic illustration showing the phase precession of an AM signal (upper) due to a +DF, relative to an unmodulated carrier (lower); the $\Delta\Phi$ is illustrated by the offset between pairs of vertical lines that indicate zero phase in each signal. (B) Phase modulation $\Delta\Phi$ over an AM cycle for both +DF (green) and -DF (red). (C) Lissajous plots shown in the traditional Cartesian coordinates (left) as well as the polar coordinates used in this study (right). In both representations, $\Delta\Phi$ is the phase modulation, and the AM is the envelope of the amplitude modulated signal. The arrows indicate the direction of rotation, which uniquely determines the sign of the DF.

5.2.3 Calculating JAR-related sensory inputs

To investigate the JAR in the laboratory, a pair of transverse electrodes (orthogonal to the body) is typically used to mimic another fish (Stamper et al. 2012; Carlson and Kawasaki 2007; Partridge and Heiligenberg 1980). We replicate this experimental paradigm in our models, using two transverse electrodes to deliver a sine wave stimulus at frequencies of $\pm 1\%$ that of the model fish. Specifically, we used EOD frequencies of 300Hz (*Eigenmannia*) and 600Hz (*Apteronotus*) with DFs of $\pm 3\text{Hz}$ and $\pm 6\text{Hz}$ respectively (i.e. $\text{DF} = \pm 1\%$). These DFs typically result in JARs with similar magnitudes in each species (Bullock, Hamstra, and Scheich 1972a; Heiligenberg et al. 1996). The stimulus was calibrated so that the potential across the electrodes was equal to the peak-to-peak amplitude of the fish’s head-tail EOD; this resulted in a peak modulation-depth (contrast) on the order of 60%. The electrodes were positioned at 14cm lateral to the body (on both sides) and at a rostral-caudal location (nose at 0cm) of 10cm for *Eigenmannia* and 8cm for *Apteronotus*; note that the body lengths for the *Eigenmannia* and *Apteronotus* model fish are 26cm and 21cm respectively. We also consider interactions among three fish (Stamper et al. 2012; Partridge and Heiligenberg 1980). In this case, the electrode stimulus is the sum of two sine waves with different frequencies (representing two different fish). In *Apteronotus*, the baseline DF between each sine wave and the receiving fish (which had $\text{EODf} = 600\text{Hz}$) was 103Hz and -97Hz ($\text{DDF} = +6\text{Hz}$) and -103Hz and +97Hz ($\text{DDF} = -6\text{Hz}$). This was halved in *Eigenmannia* to match the 300Hz EODf of the receiving fish, with baseline DFs of 51.5Hz and -48.5Hz ($\text{DDF} = +3\text{Hz}$) and -51.5Hz and +48.5Hz ($\text{DDF} = -3\text{Hz}$). To simplify further discussion, we will refer to this condition as $\text{DDF} = \pm 1\%$. In this three-fish case, the peak-to-peak stimulus amplitudes were scaled, as in the two-fish case, such that the maximal amplitude of the electrode signal was equal to the head-tail EOD amplitude.

To evaluate the sensory information underlying the JAR, we use a well-established model (Partridge and Heiligenberg 1980) in which EOD amplitude and phase modulations can be used to predict the relative magnitude and sign of the JAR. The model directly maps phase and amplitude modulations onto JAR magnitude (figure 11 in (Heiligenberg and Bastian 1980), and figure 9 in (Partridge and Heiligenberg 1980)). We calculated this mapping by using the previously-described fits to behavioral data (Partridge and Heiligenberg 1980). The phase and amplitude modulations are determined at different body locations and through this mapping, each provides an estimate of JAR magnitude. Despite this model being developed for *Eigenmannia*, it allows us to char-

acterize the quality and reliability of sensory inputs in both species of fish, but does not imply that the neural algorithms underlying the JAR are the same. As a point of note, due to windowing effects of the Hilbert transform used to calculate the phase differences, the first and last 8 cycles of the AM cycle were excluded to eliminate errors.

5.3 Results

5.3.1 Eigenmannia Model

In previous work, we developed a finite-element model (FEM) of the spatiotemporal electric field generated by *Apteronotus* (Shifman, Longtin, and Lewis 2015). To compare the electric signals available for sensing by *Eigenmannia* and *Apteronotus*, we developed a similar model of the *Eigenmannia* EOD (see Methods). The fitting error for the *Eigenmannia* model, as compared to the experimentally-measured potentials, was $2\% \pm 0.15\%$ NRMSE (mean $\pm$ SD). Overall, the EOD of *Eigenmannia* is relatively uniform and dipolar in nature (figure 5.1). The zero-crossing (white band where the sign of the EOD changes in space, i.e. voltage is zero) is relatively static in space over the EOD cycle. In contrast, the zero-crossing in *Apteronotus* oscillates in space near the tail. Furthermore, the fraction of time that the EOD has a multipolar topology is much greater in *Apteronotus* than in *Eigenmannia* (note that at phase 12, both fish have a multipolar EOD). Given the accurate models of the spatiotemporal EOD of these species, we were able to compare the sensory signals that would be available to each during a JAR experiment.

5.3.2 JAR-related sensory inputs for experiments involving two and three fish

In typical experiments involving the JAR, a pair of transverse electrodes are used to deliver a sine wave stimulus that mimics one or more fish. We considered similar stimuli, using a pair of transverse electrodes (see Methods) to deliver a signal with a DF equal to 1% (i.e. 6Hz for *Apteronotus* and 3Hz for *Eigenmannia*). In figure 5.3, we show the resulting amplitude modulations (AMs) in each species at different rostral-caudal locations; these locations were also used as representative locations in the following analyses. While the AMs at each location were quite similar between the two species, there were also apparent differences, suggesting that the available sensory information

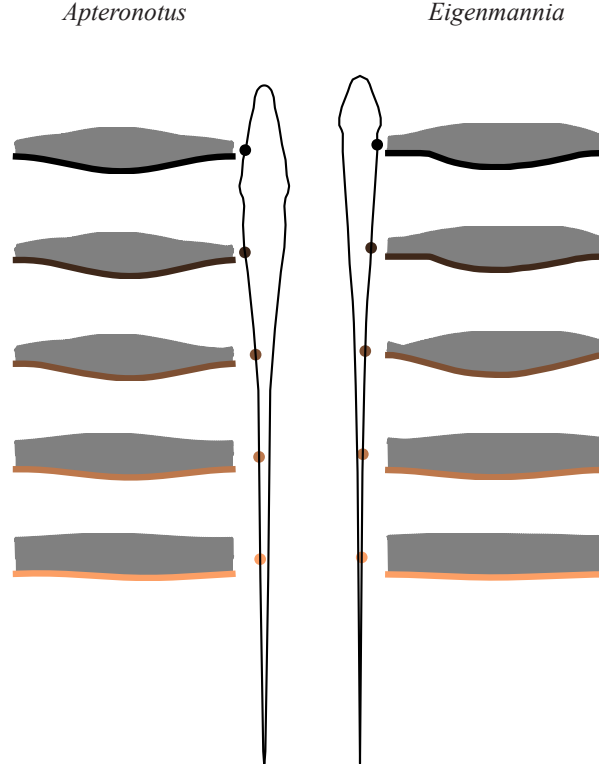


Figure 5.3: Sample amplitude modulated waveforms arising from a two-fish paradigm for *Aptereronotus* (left) and *Eigenmannia* (right). The length of each fish is normalized (body fraction) to facilitate comparison. The AM is created by a pair of transverse electrodes playing a sine wave with DF 1% below the EODf (600Hz and 300Hz respectively). Waveforms are sampled at a body fraction of 0.1, 0.25, 0.4, 0.55, and 0.7 (dark to light colors respectively); the lower envelope is highlighted, and one AM cycle is displayed.

differs between the two species of fish. In the following, we look more closely at the phase and amplitude modulations to examine the information content of these signals.

As described previously (Heiligenberg, Baker, and Matsubara 1978; Heiligenberg 1991; Partridge and Heiligenberg 1980), to determine the sign of the DF and produce the appropriate JAR, the fish must determine the amplitude and relative phase of the modulated signal with respect to its own unperturbed EOD. In figure 5.4, we compare the phase and amplitude modulations at multiple body locations for a DF of 1%. In these Lissajous plots, the radial angle indicates the phase difference between the modulated signal and the reference signal (taken here as the unperturbed EOD at 50% body length, see Methods), and the radius represents the relative amplitude of the AM (note that each plot was scaled independently to its own maximum radius). While some of these Lissajous plots form simple loops, others show more complicated double-loops (see *Eigenmannia* at 25% body fraction for example); these doublets occur when the AM

depth is large (α_0 is similar to α_1 ; Eqns 5.5–5.8; the resulting phase precession can span the entire circle causing the double-loops to appear. In general, the results in figure 5.4 are consistent with the theory and previous experiments (Heiligenberg, Baker, and Matsubara 1978; Carlson and Kawasaki 2007): the sign of the DF unambiguously determines the direction of rotation in both species.

We next considered what happens with three fish. In a natural setting with more than two fish, the sensory signals underlying the JAR become more complicated. For example, when one fish is joined by two other fish, two DFs can arise with respect to the receiving fish. In addition, the difference between the DFs (DDF) can also result in relevant modulations; this is referred to as the “social envelope” (Stamper et al. 2012). When the DDF is small enough (similar to a DF that would produce a JAR), *Eigenmannia* will change EODf in a manner predicted by the JAR, producing a social envelope response, SER. It is not known if *Apteronotus* will respond similarly but in a natural setting they do not usually create social envelopes (Stamper et al. 2012; Stamper et al. 2010; Tan et al. 2005). Nonetheless, we can use our models, as in the previous section, to explore the effects of social envelopes on the sensory information available for a SER.

The social envelopes are shown in figure 5.5 (the three-fish analog of figure 5.3). The high-frequency modulation occurs at the DF (approximately $\pm 15\%$ of the EODf) and the slow envelope (smaller than that in the two-fish case) occurs at the DDF (approximately 1% of the EODf). To explore how a fish would perceive this DDF, we show the resulting Lissajous plots in figure 5.6 (the three-fish analog of figure 5.4). The previously-predicted hypotrochoid-like patterns (see Methods) were most apparent for large amplitude modulations (e.g. 25% in *Eigenmannia*) (Stamper et al. 2012; Partridge and Heiligenberg 1980). Such patterns are due to the superposition of a positive and negative DF (counter-clockwise and clockwise rotations respectively) and in both species, the net direction of rotation (given by the dominant DF) gives the appropriate sign of the DDF. In general, the Lissajous plots for *Eigenmannia* in both two-fish and three-fish conditions (figure 5.4, 5.6) encompass a larger area than those for *Apteronotus*, indicating deeper, and hence, more robust modulations. This suggests there is a higher signal-to-noise ratio for JAR-related sensory inputs in *Eigenmannia*. In the next section, we considered how this might relate to the robustness of these sensory inputs.

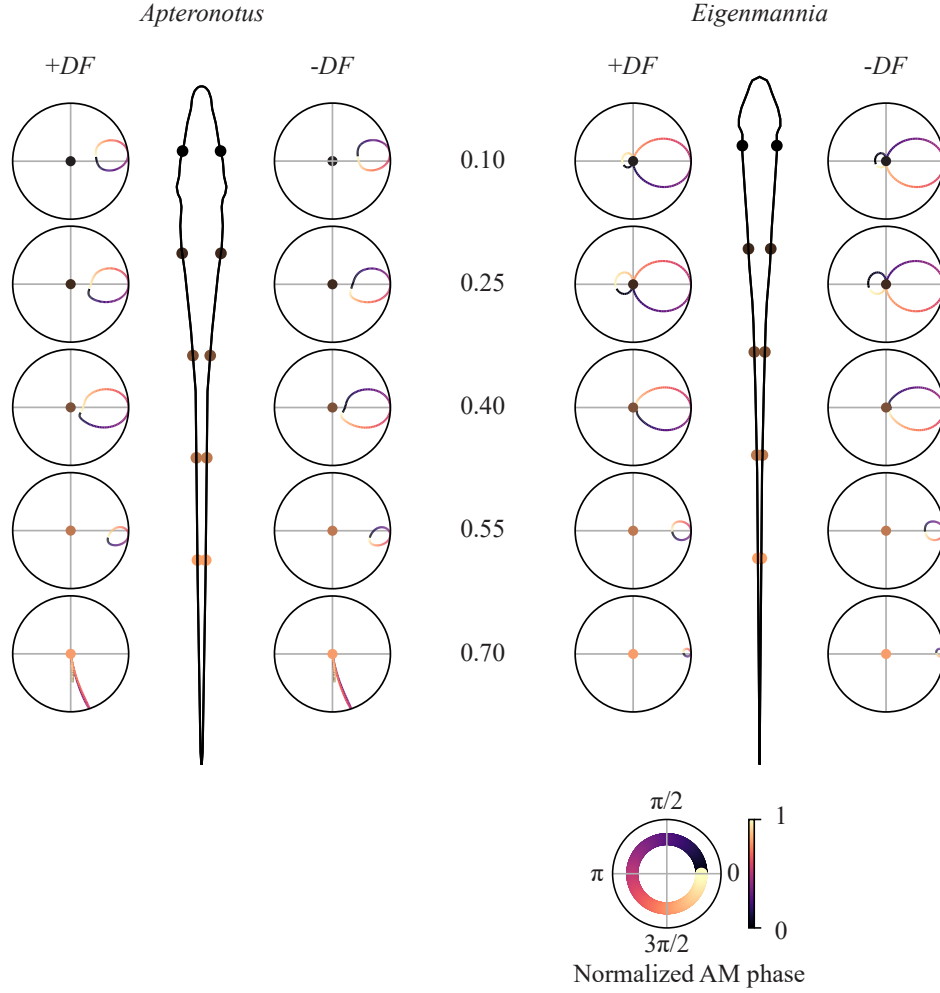


Figure 5.4: Analysis of the JAR-related sensory inputs in a two-fish condition. Polar plots for phase and amplitude modulations in both species of fish at body locations as indicated (center, same locations as those in figure 5.4). A pair of transverse electrodes play a sine wave with $DF \pm 1\%$ of the EODf. The angle of the polar plot is the phase modulation over time, and the radius is the absolute value of the lower envelope (AM). The arrow indicates rotational direction, and temporal progression through the AM cycle is indicated by the colorbar (beginning: black; end: yellow). The modulation is calculated using a reference location at body fraction of 0.5

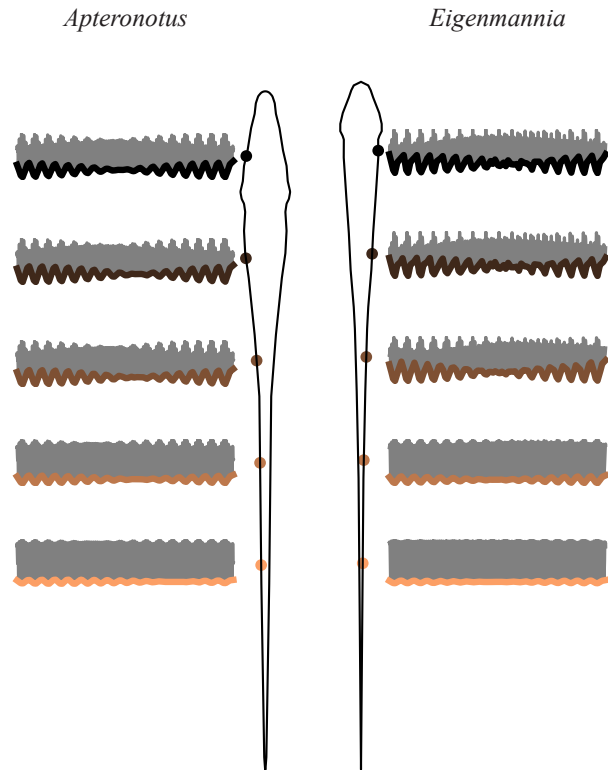


Figure 5.5: Sample amplitude modulated waveforms arising from a three-fish paradigm for *Aptereronotus* (left) and *Eigenmannia* (right). Similar to figure 5.3 except the AM is created by a pair of transverse electrodes playing two sine waves with DDF 1% below the EODf (600Hz and 300Hz for *Aptereronotus* and *Eigenmannia* respectively).

5.3.3 Predicting the quality of JAR-related sensory inputs

The Lissajous plots described in the previous section suggest that the quality of sensory information available for the JAR is higher in *Eigenmannia*. More reliable sensory inputs should lead to the production of a more robust JAR with larger magnitude. We tested this by adopting a previously-described behavior-based model of the JAR ((Partridge and Heiligenberg 1980); see Methods). The algorithm that fish use for the JAR is well-accepted (Heiligenberg, Baker, and Matsubara 1978), and involves the phase and amplitude modulations represented in figures 5.4 and 5.6 as inputs. The JAR model maps these inputs onto the relative magnitude of a JAR; a larger JAR represents increased certainty in the decision process and thus we considered JAR magnitude as a proxy for the reliability of sensory inputs. Figure 5.7 shows the JAR magnitude at different locations along the body in both *Apteronotus* and *Eigenmannia* for the two-fish condition. The data are presented as mean $\pm$ 1 SD over the different reference locations. The JAR prediction depends on the body location used for a reference, so our predictions show mean and SD (shaded) over all reference locations (figure 5.7). It is immediately apparent in *Eigenmannia* that the sensory input predicts the appropriate direction of the JAR (positive JAR for a negative DF and vice-versa) for almost all body locations (figure 5.7). Importantly, there is negligible overlap between the +DF and -DF condition, indicating relatively unambiguous sensory inputs. Conversely, in *Apteronotus* there is an extensive overlap between the two DF conditions, implying more ambiguous, or less robust sensory inputs.

As expected, extending this analysis to three fish introduced complexity: since the modulation rotates in the “wrong” direction at some points in time, the change in EODf produced by social envelopes should be reduced in magnitude (Stamper et al. 2012). We confirmed this using the same JAR model as the two-fish case (Partridge and Heiligenberg 1980). In *Eigenmannia* (at least in the front half of the body) the sensory inputs result in a smaller but reliable SER in the correct direction (figure 5.8). On the other hand, *Apteronotus* show a much more variable response due to contradictory signals arising from different body locations. Overall, as for the two-fish case, this analysis suggests that the sensory signals underlying the SER are also more reliable for *Eigenmannia*, and predicts a small unreliable SER, if any, in *Apteronotus*. Thus, it appears that the complex EOD topology exhibited by *Apteronotus* degrades sensory information in both JAR and SER contexts, and is one of the causes of a less reliable response in this species.

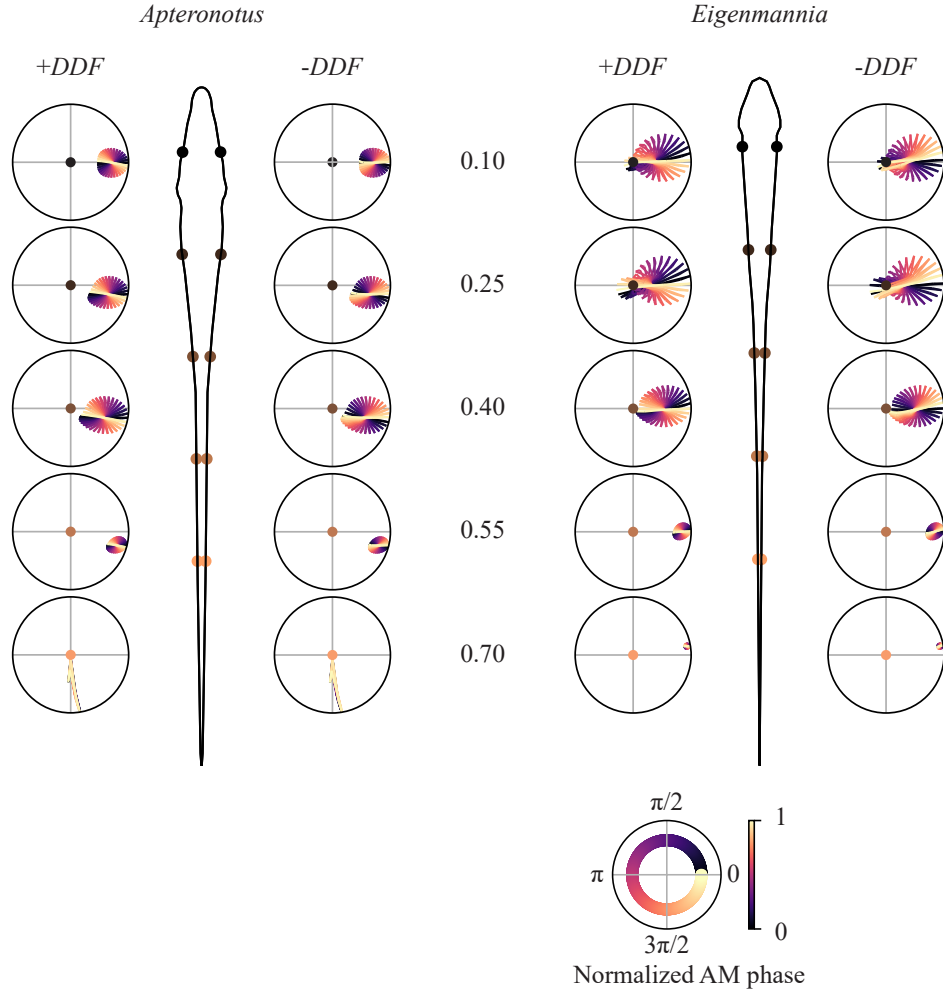


Figure 5.6: Analysis of the JAR-related sensory inputs in a three-fish condition. Polar plots for phase and amplitude modulations in both species of fish, similar to figure 5.4 except the pair of transverse electrodes plays the sum of two sine waves with $DDF \pm 1\%$ of the EODf.

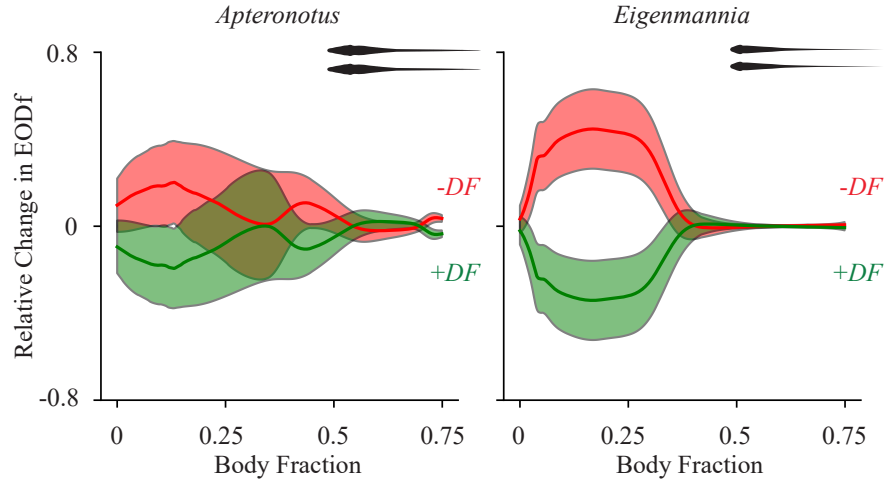


Figure 5.7: Normalized JAR predictions for the two-fish condition. Model predictions are based on the sensory information from the polar plots in figure 5.4. A positive JAR indicates a rise in frequency, and would be appropriate for a -DF. Multiple estimates of the JAR are calculated, each time using a different location along the body as a reference. Results are plotted as mean $\pm$ SD over the different reference locations.

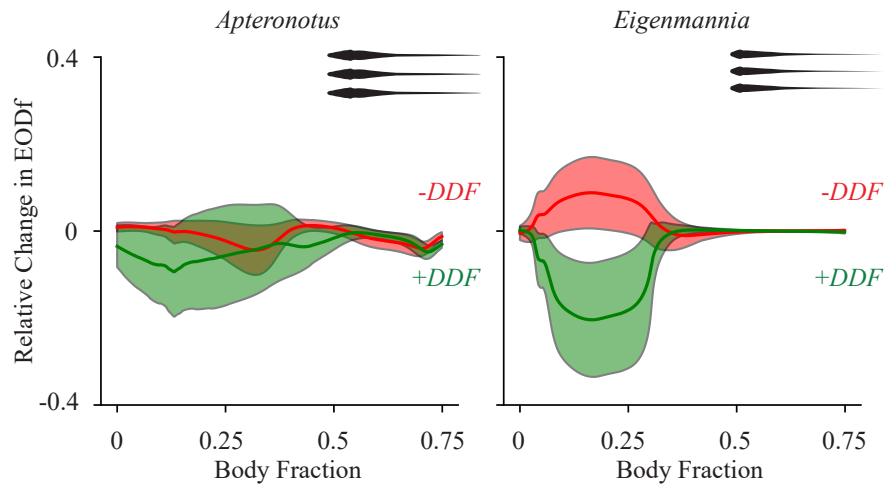


Figure 5.8: Normalized SER predictions for the three-fish condition. Model predictions are illustrated as in figure 5.7, but are based on the sensory information from the polar plots in figure 5.6.

5.4 Discussion

When weakly electric fish are presented with an oscillating electrical stimulus with a frequency close to that of their electric organ discharge (EOD), they perform a jamming avoidance response (JAR) (Heiligenberg 1991; Metzner 1999). The JAR involves shifting the EOD frequency (EODf) away from that of the stimulus and is thought to reduce the compromising effects of signal interference on electric sensing (Carlson and Kawasaki 2007; Bastian 1987). In this study, we compared the JAR-related sensory inputs available to two species: one (*Eigenmannia*) is able to produce a robust JAR in both directions (increasing and decreasing frequency), while the other (*Apteronotus*) only increases EOD frequency in the context of the JAR (Heiligenberg et al. 1996). Our analyses show that the spatially complex electric field of *Apteronotus* degrades the quality of sensory inputs, and thus suggests that the structure of the EOD may have influenced the evolution of the JAR and its corresponding neural circuits.

In this work, we used detailed models of the spatiotemporal EOD of *Eigenmannia* and *Apteronotus* to describe the sensory inputs across the body at high resolution. We found that for the experimental paradigm commonly used to explore the JAR, the sensory inputs available to *Eigenmannia* represent phase and amplitude modulations more accurately than those for *Apteronotus*. To illustrate this, we used an established model of the JAR in *Eigenmannia* for which each body location “votes” for an increase or decrease in EOD frequency based on local amplitude and phase modulations (Heiligenberg, Baker, and Matsubara 1978; Partridge and Heiligenberg 1980). While this allows us to characterize the reliability of the JAR-related sensory inputs, it does not imply that the same neural algorithm is used in the two species. At each location on the body, we calculated this vote for all possible reference locations to evaluate the variation in voting for a given stimulus (figure 5.7). In this context, the predicted JAR magnitude (normalized) provides a measure of reliability: more reliable sensory inputs lead to more certainty in the determination of the sign of the DF, which leads to a larger JAR magnitude. We found that in *Eigenmannia*, there was essentially no ambiguity (no overlap in JAR direction) between the +DF and -DF conditions, whereas in *Apteronotus* the two conditions resulted in significant overlap, especially in the mid-body, indicating that sensory inputs are far less reliable and can lead to an ambiguous response (figure 5.7).

When *Eigenmannia* are stimulated with social envelopes (amplitude modulations arising from three fish with very different frequencies), they systematically change EODf,

a behaviour called the social envelope response (SER). The JAR model we used was previously applied to situations involving multiple fish with very similar EOD frequencies (Partridge and Heiligenberg 1980), and the general phase-amplitude rotations were found to be consistent with behavior. Recent work has explored social envelopes resulting from EOD frequencies that differ much more, but involve second order differences (the DDF) less than 5Hz (the range of DF that would result in a JAR; (Stamper et al. 2012)). This work showed that the SER in *Eigenmannia* (response to a DDF) was similar to a JAR produced by a similar DF. While it is not known whether *Apteronotus* will respond to social envelopes, it has been suggested that they actively avoid them (Stamper et al. 2010). We showed that during social envelope stimulation, the previously described hypotrochoid-like curve confounds the determination of the DDF sign more in *Apteronotus* than in *Eigenmannia*. Over a fraction of each AM cycle, the rotation occurs in the “wrong direction” (opposite to that indicating the true DDF sign); in other words, the modulating signal contains features of both positive and negative DDFs, resulting in phase modulations more than an order of magnitude weaker than those from a pure DF (Stamper et al. 2012). In addition, these results showed that in *Eigenmannia*, there is essentially no overlap (ambiguity) in the predicted response for positive and negative DDFs over more than 30% of the body, whereas in *Apteronotus* the predicted responses overlap completely, suggesting that the sign of the DDF cannot be determined reliably (figure 5.8).

Interestingly, both *Eigenmannia* and *Apteronotus* will respond to pure AMs (no phase modulation), but in different ways. *Eigenmannia* decreases its frequency (Carlson and Kawasaki 2006), suggesting that a pure AM mimics a positive DF. Indeed, this response was explained by the dynamics of electrosensory receptors (Carlson and Kawasaki 2006): a pure AM induces a weak phase modulation in the electroreceptor T-unit response, leading to a counter-clockwise rotation in the Lissajous plot. This is essentially an electrosensory illusion of a +DF. On the other hand, *Apteronotus*, when presented with a pure AM, increases its frequency and then tracks the AM with small variations around this elevated baseline (Metzen and Chacron 2014). While the electroreceptors in *Apteronotus* are tuned to the higher frequencies typical of their EODs (Hopkins 1976; Metzner and Heiligenberg 1991), their dynamics are not likely so different to result in a Lissajous plot rotating in a direction opposite to that of *Eigenmannia*. That said, *Apteronotus* would then experience the same illusory +DF which would illicit an increase in EODf (non-selective response, NSR) (Dye 1987; Bastian, Schniederjan, and Nguyenkim 2001).

Why *Apteronotus* produces a JAR/NSR comprising only increases in EOD frequency is not clear. Furthermore, why would this behavior be maintained in an evolutionary context if it is not effective in avoiding a jamming stimulus? The JAR appears to have evolved at least twice in the Gymnotiform family (i.e. independently in *Apteronotus* and *Eigenmannia*) and another time in the Mormyrids (Heiligenberg 1991; Rose 2004; Kawasaki 1996; Albert and Crampton 2005). Although all species use the same computational rules to compute the sign of a DF (Heiligenberg 1991; Rose 2004; Kawasaki 1996), the neural implementation, circuitry, and specific behavioral responses vary. This suggests that the JAR has evolved under multiple selective pressures, in addition to the jamming effects of conspecific EODs on electrolocation. These could involve social structure (Tallarovic and Zakon 2002; Oestreich and Zakon 2005), electrocommunication (Smith et al. 2016), predation (Stoddard and Markham 2008) and signal energetics (Salazar, Krahe, and Lewis 2013; Lewis et al. 2014). Socially, *Eigenmannia* are gregarious, while *Apteronotus* tend to live alone or in small groups (Stamper et al. 2010; Tan et al. 2005), suggesting that JAR-related stimuli and social envelopes are less common for *Apteronotus*. In addition, *Apteronotus leptorhynchus* produce gradual increases in EODf during aggressive encounters, apparently as a dominance display (Tallarovic and Zakon 2005), while *Apteronotus bonapartii* perform a JAR to a DF of 100Hz (well out of the jamming range) (Ho et al. 2010). These observations suggest that frequency rises serve a communication purpose, similar to the transient changes in EODf involved in chirping (Turner et al. 2007; Smith et al. 2016). It has also been suggested that predation drove the evolution of the higher frequency EODs (Stoddard and Markham 2008). Generating a high-frequency EOD comes at a cost, both energetically and mechanistically: *Apteronotus* have lost the myogenic electric organ found in *Eigenmannia* in favor of a neurogenic organ and produce an electric field with much greater spatiotemporal complexity. Our present results suggest that field complexity leads to a degradation of the sensory information required to produce an effective JAR, identifying a novel aspect of JAR evolution. However, much more comparative work, involving phylogenetics, behavior and neurophysiology, will be necessary to understand all the factors that led to the diversity of JAR-related behaviors in wave-type electric fish.

5.5 Competing Interests

We have no competing interests

5.6 Authors' Contributions

ARS and JEL designed the simulation. ARS performed all simulations, and analyzed the results with input from JEL. ARS and JEL wrote the paper. Both authors read and approved the final manuscript.

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Chapter 6

py(FEM)²S Finite Element Modeling of Fish ElectroMotor Scenes

6.1 Introduction

Sensory systems provide a non-linear transformation (map) between some complex, high-dimensional set of inputs (the sensory scene) and a neural representation which is encoded for integration by the brain. Many sensory systems across the animal kingdom implement similar strategies. For example center-surround receptive fields are present in the mouse visual system (Niell [2015](#)), fish electroreceptive organization (Metzen et al. [2008](#)), and human mechanosensory systems (Purves et al. [2001](#)), as well as many others. Additionally combinatorial coding is seen in many systems such as fly olfaction (Grabe and Sachse [2018](#)), and mouse gustation (Roper and Chaudhari [2017](#)). This overlap in sensory transduction techniques suggests that studying a given sensory system in depth can uncover generalizable strategies and lead to insights that apply to many sensory systems.

While this map between the environment and a neural code may be easy to discuss in vague terms. Studying sensory systems can be quite challenging in terms of experimental, or theoretical practicality. In the visual system, the sensory surface (retina) is hidden within the eye making *in vivo* recordings challenging, often relying on optical methods (requiring genetic tools limiting recording scope) (Yin et al. [2013](#); Yin et al. [2014](#)), or field recordings such as electroretinograms that make interpretation in the context of neural coding problematic (Heikkinen, Nymark, and Koskelainen [2008](#); Pinto et al. [2007](#)). In the mammalian mechanosensory system, understanding sensory

inputs requires considerations of viscoelastic deformation of the skin (Pereira, Mansour, and Davis 1991; Silver, Freeman, and Devore 2001) creating complex theoretical barriers. One particularly interesting (exotic) sensory system that mitigates some of these challenges is the electrosensory system of electric fish.

Weakly electric fish generate an electric field in order to sense their environment (Moller 1995). Conductive objects will shunt this field and create a relatively high potential around the object. Conversely resistive objects diverge the field and form a relatively low potential nearby (Crampton 2019; Babineau, Longtin, and Lewis 2006; Shifman and Lewis 2018). Electrorceptors on the fish’s skin measure these electric potentials, forming the basis for the electrosensory system (Crampton 2019; Salazar, Krahe, and Lewis 2013; von der Emde G 1999). Historically research has focused on the field perturbation – the net effect of adding an object into the fish’s electric field. This is defined as the difference between the electric field with the object and without the object. This field perturbation is measured across the fish’s skin to form the so-called electric image (Heiligenberg 1977). Because these electric images can be experimentally measured (von der Emde G 1999; Fotowat, Harrison, and Krahe 2013; Emde et al. 1998; Pedraja et al. 2018) and the physics of the fish’s electric fields can be well approximated by electrostatics (due to their low frequency fields) (Babineau, Longtin, and Lewis 2006; Shifman, Longtin, and Lewis 2015; Assad, Rasnow, and Stoddard 1999; Rother et al. 2003) this system lends itself well to studying sensory inputs.

Experimental studies of the electrosensory system are nevertheless limited by various physical constraints: limited number of simultaneous recording locations on the skin or the number of objects and complexity of the experimental scene. Additionally, there is the challenge involved with separating the effects of movement from sensing (under experimental conditions, movement is constrained and thus affects the natural sensory inputs (Fotowat, Harrison, and Krahe 2013; Hupe and Lewis 2009; Nelson and Maciver 1999)). However due to the simple physics, these constraints can be mitigated *in silico* to explore high-dimensional scenes and study a large number of experimentally inaccessible questions (Shifman and Lewis 2018; Babineau, Lewis, and Longtin 2007); (also see Chapter 4). For this reason, computational tools have been used ubiquitously in electric fish research for decades (Hoshimiya et al. 1980; Heiligenberg 1975). However, there are many limitations to existing tools such as financial and computational cost, tool flexibility, and the range of experimental conditions which can be studied. For this reason we’ve developed a new tool (py(FEM)²S: read “*py fems*”) which is both free and easily

scalable to high-performance computing (HPC), mitigating expense, while also being highly flexible. Additionally, we include a number of standard electric fish analyses thus minimizing the amount of additional work needed to study sensory physiology in this system.

6.1.1 Existing Technology

Previously, various computational models have been used to explore the electric fields across many species of electric fish. The main two methods have been the Boundary Element Method (BEM) (Rother et al. 2003; Assad 1997) and the Finite Element Method (FEM) (Babineau, Longtin, and Lewis 2006; Shifman, Longtin, and Lewis 2015). Both FEM and BEM have their merits and downsides. Proponents of BEM would highlight the computational efficiency when low surface area to volume ratio problems are studied, since the only relevant set of equations are on the boundaries between domains (Rother et al. 2003; Assad 1997; Williams, Rasnow, and Assad 1990). However importantly, when studying complex scenes, BEM has the downside that generally an infinite, or semi-infinite, domain is assumed so heterogeneities can be challenging to formulate and solve (Babineau, Longtin, and Lewis 2006; Assad 1997; Babineau 2006).

Conversely proponents of FEM would point out that any model which can be formulated in a weak form may be solved, and in general solutions can be more accurate (Babineau, Longtin, and Lewis 2006). This benefit comes at the expense of computational efficiency, to the point where historically only two-dimensional FEM models have been used (Babineau, Longtin, and Lewis 2006; Shifman, Longtin, and Lewis 2015). It should be noted here that electric fish models using BEM have typically been 3D (Rother et al. 2003; Assad 1997; Williams, Rasnow, and Assad 1990; Pedraja et al. 2014).

Existing Finite Element Models

The platform of choice for our previous work, and that of many others is COMSOL (COMSOL Inc., Burlington, MA) (Babineau, Longtin, and Lewis 2006; Shifman, Longtin, and Lewis 2015; Emde 2012). COMSOL is a general finite element solver, with the main appeal being its ease-of-use. It allows users to focus on model-building while keeping the computational details “under the hood”. This means that FEM techniques are available to most scientists many of whom will have a very limited background in computational methods.

Historically, most electric fish models have been conceptually simple e.g. a static,

straight fish with a simple nearby object (Babineau, Longtin, and Lewis 2006; Babineau 2006; Caputi, Aguilera, and Pereira 2011), and as such COMSOL made an excellent experimental platform. However as questions about sensory systems become more complex, so to do the geometric requirements for the FEM model. How does body morphology and pose affect the electrosensory inputs from a given scene? What does a sensory scene “look like” to a freely swimming fish? These questions are difficult to study in COMSOL for various reasons including a weak scripting interface for creating complex bodies (which in general would need to be computed numerically prior to building the model), and the challenges of scaling to high-performance computing (HPC) platforms. It should be noted that COMSOL does scale very well to HPC but due to licencing costs the financial burden is beyond that of most research groups.

For these reasons we’ve developed an electric fish oriented finite element solver, `py(FEM)2S`, which mitigates many previous modelling constraints while facilitating model development and analysis for electric fish specific questions.

6.1.2 Finite Element Modeling of Fish ElectroMotor Scenes

`py(FEM)2S` is a software tool for solving electric fish models with the finite element method. In this section we will highlight the benefits and features of `py(FEM)2S` over existing FEM tools.

We use the FEniCS platform as its computational backend. FEniCS is a well established, mature, and maintained FEM library (Logg, Mardal, and Wells 2012). Besides reliability, the other advantage of an open source FEM solver is that the per-processor cost is zero, i.e. HPC scaling is also free: reducing the barrier to larger and more complex problems.

`py(FEM)2S` while being a “code-based” tool is designed in such a way that model definition is similar to that in many software tools: we use a stepwise, sequential process to create fish and other objects. For example:

- Create fish body with head at (x, y)
- Create prey-like object at location (x, y)
- Rotate fish by angle θ
- etc ...

In this way, simple objects can be modeled with under 10 lines of code. We have implemented this by sacrificing CAD tools in favor of a constructive geometry based on simple objects (squares, circles, and polygons), which should be sufficient for a wide range of scientific questions. More complex scenarios can be implemented as composites of these simple objects. Fish geometry is handled internally and defined by the fish’s spinal pose (shape of midline), so natural fish shapes are implemented with exactly the same amount of effort as a straight fish, or any other geometric object. We have additionally included the notion of parameter sweeps allowing for flexible model development, testing, and exploration. Lastly, we’ve implemented a robust plotting library which interfaces well with model design. `py(FEM)2S` is also Paraview (Ahrens, Geveci, and Law 2005) compatible so users more comfortable with a graphical environment to explore their data can do so easily.

6.2 Methods

6.2.1 FEM Overview

We will first provide a cursory overview of terms and ideas in FEM tools to provide the reader with a basis for understanding subsequent sections. For a full FEM overview see chapter 2 in the FEniCS Book (Logg, Mardal, and Wells 2012). FEM solvers solve partial differential equations (PDEs), which are differential equations defined on multiple dimensions (instead of one-dimension such as time in ODEs). Areas (regions) in PDEs are commonly referred to as domains (the water domain, or the fish domain). At the interface between two domains (or the edge of a domain) is a boundary; the fish-water boundary is the fish’s skin where it meets the water. FEM tools discretize the domain into something called a mesh: a collection of vertices and edges over which the PDE is solved (approximated). In this way FEM discretization can be considered a higher-dimensional analogue of adaptive ODE methods (e.g. `ode45` for those familiar with MATLAB solvers). Figure 6.1 highlights these concepts. We have created a 2D model with a square background (named ‘bg’) and a circular foreground (named ‘fg’). Figure 6.1A shows the domains: the background domain is shown in purple and the foreground domain is in yellow. Figure 6.1B shows the boundaries with the background boundary (bg) in red and the bg-fg boundary in cyan. Lastly, figure 6.1C shows the computational mesh in grey (for ease of viewing we have added the geometry outline in black).

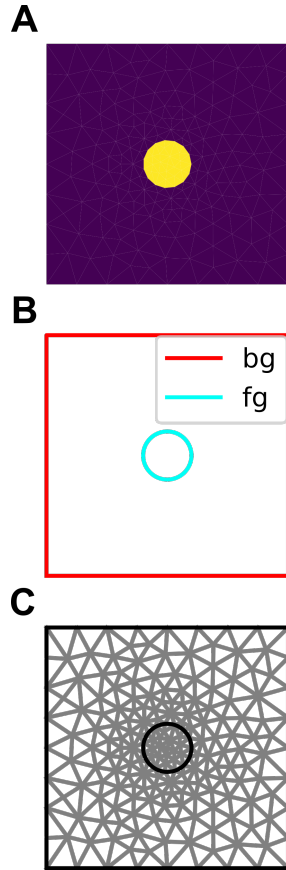


Figure 6.1: Schematic of relevant FEM terminologies. An example environment consisting of a square background (bg) and circular foreground (fg) is created. (A) Model domain definitions. (B) Domain boundaries. (C) computational mesh with geometry outline for visualization.

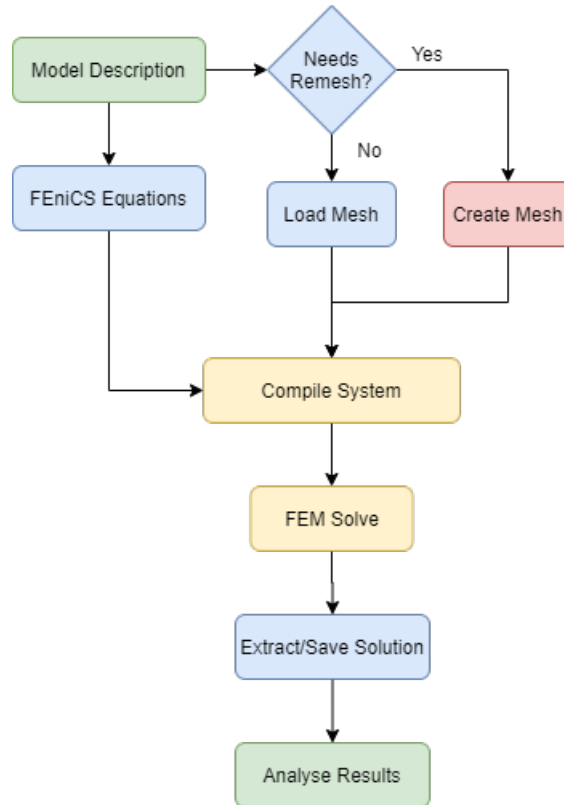


Figure 6.2: py(FEM)²S flowchart from user-specified model to analysis. User steps are green, py(FEM)²S steps are blue, external steps (GMSH) are red, and FEniCS steps are yellow. Users specify a model in py(FEM)²S which is then compiled and solved in FEniCS and parsed by py(FEM)²S for user analysis.

6.2.2 FEM Methods

py(FEM)²S is a wrapper around FEniCS. py(FEM)²S takes a simple model specification and then converts it into a computational structure that FEniCS can understand. Our modeling process is outlined in figure 6.2 with user steps (green), internal steps (blue), FEniCS steps (yellow), and external steps (red). The user specifies a model either through our API or a model description file (soon to be implemented). py(FEM)²S then takes this description and computes a mesh with GMSH (Geuzaine and Remacle 2009) or uses the previously computed mesh if the geometry has not changed. py(FEM)²S then builds the model equations. From here, FEniCS compiles (if necessary) and solves the model with its internal FEM solvers and passes the solution back to py(FEM)²S for analysis.

The FEniCS backend compiles models into parallel executable c-code for fast execution which will natively use available processing power and as such easily scales to HPC. Additionally, this compiled model is cached, so model updates that do not change model

structure (such as changing the conductivity parameter) do not require the model to be recompiled, increasing efficiency for parameter sweeps.

Electric Fish FEM Specifics

For electric fish FEM simulations the general equation used is the Poisson equation (eq 6.1) (Babineau, Longtin, and Lewis 2006; Shifman, Longtin, and Lewis 2015; Assad 1997), where σ is the (optionally anisotropic, and inhomogenous) conductivity tensor, Φ is the electric potential (voltage), and J is the current flux density.

$$-\nabla \cdot \sigma \nabla \Phi = J \quad (6.1)$$

Additionally, we define Neumann boundary equations providing a current source on a boundary, and Dirichlet boundary conditions describing voltage sources.

6.2.3 Defining Models

All models are derived from the *BaseFishModel* class (“code template”) which includes a fish, tank, ground electrode, and circular object in 2D similar to previous models (Babineau, Longtin, and Lewis 2006; Shifman, Longtin, and Lewis 2015). Additionally, the *BaseFishModel* defines all of the physics and boundary equations needed to define the Poisson Equation, the fish’s electric field, and the ground electrode. In Supplemental Code 6.A, a small object, modeled as a 0.2cm circle, is created and added to a new domain. This model templating is the basis for all py(FEM)²S models so that models can be fully described with minimal code and minimal duplication.

6.2.4 Included Functionality

Parametric sweeps

Exploring these types of models using parametric sweeps is critical from a scientific point of view, whether to simulate a moving object, a moving fish, or varying object conductivities. Thus, the ability to define a base structure and manipulate it parametrically should be straight-forward.

In py(FEM)²S we’ve implemented a mechanism for defining parameters in a model and then sweeping over them in both a combinatorial and linear way. A linear sweep would involve taking a set of parameters (for example x , y coordinates of an object) and

sweeping over them together e.g. $(x_0, y_0), (x_1, y_1), \dots, (x_n, y_n)$. In contrast, a combinatorial sweep handles all combinations of parameter values (for example prey conductivity and x position $(x_0, \sigma_0), (x_1, \sigma_0), (x_n, \sigma_0), (x_0, \sigma_1), \dots, (x_n, \sigma_n)$). We show an example in Supplemental Code 6.B; defining a parameter is as simple as adding it to the appropriate function call, and creating the sweep simply involves defining a parameter set (or several sets for that matter). Since parameter sweeps are independent, py(FEM)²S will additionally order simulations to minimize model compilation.

Saving Results

In py(FEM)²S, model solution data is saved into a single file with some machine-readable metadata files behaving as an index; we use an HDF file which has a file-system-like format. This means that loading the dataset (no matter how large) is nearly instantaneous, as only the parameters and some key features are loaded but without the solutions. Because a specific simulation can be loaded given only the parameters, the analysis cost scales linearly with the number of solutions, not the number of simulations performed. Thus, simulating various fish positions and poses from a 30 minute video but only analyzing four frames for a figure costs four load operations as opposed to 54000 (assuming 30fps). This is in contrast to other methods such as COMSOL where entire sweeps must be loaded at once, or where each simulation is stored separately which can cause issues with data management (Bhandari Neupane et al. 2019). As an example, previous work generated several thousand files with complex names indicating parameter values that needed to be managed (Shifman and Lewis 2018).

We address the data wrangling issue by the fact that the appropriate solution is loaded given the requested parameter set instead of wrangling file names to find the target. Additionally, since the dataset is maintained in parameter order, loading the 4th value of a parameter will always follow a numeric sort, not an alphabetical sort (i.e. 9<10 instead of “10”<“9”) which is a class of errors known to cause mistakes (Bhandari Neupane et al. 2019).

Plotting

Another important requirement of these modeling exercises is effectively visualizing the results. We have included a full plotting suite with support for both domain and boundary plots (scalar and vector valued), and mask selection (inclusive or exclusive). Additionally, we provide two files when saving 1D.xdmf (boundary functions) and 2D.xdmf

(domain functions); these are a superset of the XDMF format which allows all data to be plotted within Paraview i.e. you can import all of your data into a GUI for additional computation or more advanced plotting tools.

Electric Images

Computing electric images in COMSOL is a tedious and difficult process. Field perturbations are either defined by multistep physics creating sometimes hard-to-work-with solution nodes or multiple physics definitions with duplications. The two solutions (with and without the object) are subtracted to compute the field perturbation. Images are then either computed automatically by defining extrusions between inner and outer skin boundaries or by saving the internal skin separately from the external skin, then interpolating and computing the difference post hoc (leading to even more files to analyse).

In py(FEM)²S, objects can optionally be given background conductance (i.e. the conductance of water, or the conductance that the region would have when the object is removed). When background conductance is specified the electric image is automatically computed for both the left and right side of the fish and the field perturbation domain function is saved along with the electric image. Note that it is not yet possible to import the electric image into Paraview.

6.3 FEM Results

In this section, we consider a previous fish model (Babineau, Longtin, and Lewis 2006) and highlight how easy it can be implemented in py(FEM)²S. The reader should note that the code presented illustrates the basic structure but the more detailed oriented code required for stylizing or making high quality figures is not shown.

6.3.1 Classical Electric Fish Modeling: the Electric Image

Many previous electric fish model analyses focus on the electric image due to some object with different conductivities at different locations relative to the fish.

Here, we create a 21cm fish and create a 1mm object 2cm lateral to the fish similar to previous models (Babineau, Longtin, and Lewis 2006; Nelson and Maciver 1999). We combinatorially sweep the rostrocaudal locations of the object from 0 to 8cm in steps of 2cm as well as an object conductance (σ_{obj}) equal to either 1/100, 1/2 or 10 $\times$ that of water (σ_w) (15 total simulations). In figure 6.3 we show how the electric image waveform

changes as a function of object location and conductivity. Near the head, images are nearly unimodal but as the object moves down the body they become trimodal, showing the previously described “Mexican-hat” waveform (Caputi et al. 1998; Budelli and Caputi 2000). Note the sign inversion of the electric image between $\sigma_{obj}/\sigma_w < 1$ and $\sigma_{obj}/\sigma_w > 1$, as the object switches from a relative resistor to a relative conductor. Also note that the provided code creates the “scientific content” of figure 6.3 (electric images) but does not produce figure 6.3.

```
import matplotlib.pyplot as plt
from pyFEM2S import *

class CanonicalModel(BaseFishModel):
    def add_geometry(self, prey_x, prey_cond, **kwargs):
        prey = Circle((prey_x, 2), 0.1)
        self.model_geometry.add_domain("prey", prey, sigma=prey_cond)

cond_set = ParameterSet({'prey_cond': [CanonicalModel.WATER_CONDUCTIVITY / 100,
                                       CanonicalModel.WATER_CONDUCTIVITY / 10,
                                       CanonicalModel.WATER_CONDUCTIVITY * 10]},
                        'cond')

x_set = ParameterSet({'prey_x': [0, 2, 4, 6, 8]}, 'x', rebuild_mesh=True)
EIP = ElectricImageParameters(domains=('prey',), value=CanonicalModel.WATER_CONDUCTIVITY)
sweep = ParameterSweep(cond_set, x_set)

IterativeSolver('CanonicalModel', 'results', CanonicalModel, sweep,
                fish_x=(0, 21), fish_y=(0, 0), image=EIP).run()

dataset = load('results/CanonicalModel')

x_color = ['red', 'green', 'blue', 'purple', 'orange']
cond_style = ['solid', 'dashed', 'dotted']

for style, cond in zip(cond_style, dataset.parameter_levels['cond']):
    for color, x in zip(x_color, dataset.parameter_levels['x']):
```

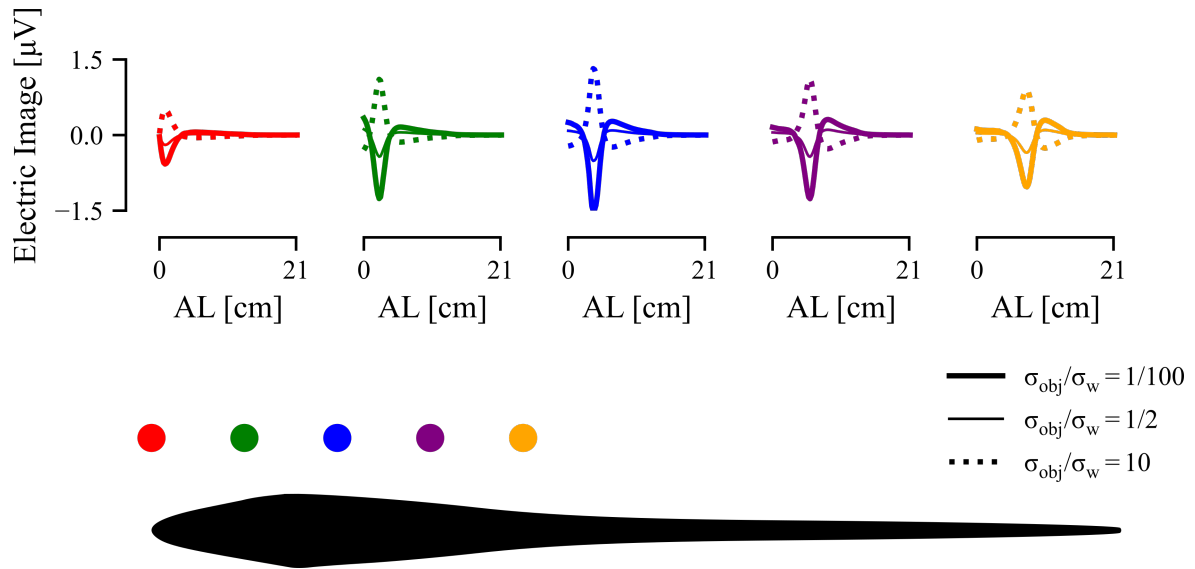



Figure 6.3: Electric image formation from objects in various rostrocaudal locations. Objects 0.5cm objects are placed at either 0, 2, 4, 6, 8cm from the tip of the nose (colored circles, bottom). For each object we compute the electric image as a function of skin arc-length (AL). We use a conductivity for each object either 100, 2, or 0.1 times smaller than that of water (0.1 times smaller is 10 times a better conductor).

```
data = dataset[f'x={x}'][f'cond={cond}']
right_image = data['ElectricImage'].load_data().right_tdp
right_arc_length = data['SkinStructure'].load_data().right_arc_length

plt.plot(right_arc_length, right_image, color=color, linestyle=style)
```

We can see that setting up a model with parameters can be done in as little as 4 lines. Additionally setting up a parametric sweep is another 4 lines and finally running, sweeping, and saving makes up a single line. This code greatly facilitates the reproduction of several classic figures in electric fish literature in 9 lines (10 lines, if imports are included). Additionally, this code provides an easier to read overview of a model than COMSOL as the model is still parcellated but within the same viewport.

6.3.2 Tail Bending

Another classic question with regards to electric fish modeling is how tail bending influences the electric image (Assad, Rasnow, and Stoddard 1999; Assad 1997; Sim and Kim 2011). We implement this in the example below.

```
import matplotlib.pyplot as plt
```

```

import numpy as np

from pyPRINCE import *

fish_x, fish_y = # code here

class BendingModel(BaseFishModel):

    def add_geometry(self, prey_x, prey_y, **kwargs):

        circle = Circle([prey_x, prey_y], 0.3)

        self.model_geometry.add_domain('prey', circle,

                                       sigma=self.WATER_CONDUCTIVITY / 10)

fish_set = FishPosition(fish_x, fish_y)
prey_set = ParameterSet({'prey_x': [2, 5, 10],

                        'prey_y': [3, 3, 5]},

                        'prey_position', rebuild_mesh = True)

sweep = ParameterSweep(fish_set, prey_set)

EIP = ElectricImageParameters(domains=('prey',), value=BendingModel.WATER_CONDUCTIVITY)

solver = IterativeSolver('BendingModel', 'results', BendingModel,

                        parameters=sweep, image=EIP).run()

dataset = load('results/BendingModel')

for ix in dataset.parameter_levels['FishPosition']:

    for iy in dataset.parameter_levels['prey_position']:

        plt.subplot(121)

        mask = plotting.generate_mask(dataset, include_domains=('skin', 'prey'),

                                     FishPosition=ix, prey_position=iy)

        plotting.plot_outline(dataset, FishPosition=ix,

                              prey_position=iy, mask=mask)

        data = dataset[f'FishPosition={ix}'][f'prey_position={iy}']

```

```

right_image = data['ElectricImage'].load_data().right_tdp
right_arc_length = data['SkinStructure'].load_data().right_arc_length

plt.subplot(122)

plt.plot(right_arc_length, right_image)

plt.subplot(121)

plt.xlim([-2, 22])

plt.ylim([-10, 10])

```

In this example, we assume that code already exists in your namespace to generate the body outlines (as this is not a problem specific to this toolkit). For a problem much more complex than the previous example, the model geometry setup is a very similar 4 lines and the sweep implementation is shortened to 4 lines total (as there is one less dimension to sweep).

In figure 6.4A we show a schematic of the simulation. An object is placed at one of three locations shown right of the fish. The fish’s tail bends in steps from ipsilateral to contralateral relative to the object (purple-to-green colorscale). In figure 6.4B-D, we show how tail bending affects the electric image (purple-green color matches tail state in panel A). Importantly, we show how tail bending introduces an amplitude modulation (AM) near the prominent points of the electric image (see insets in each panel for negative and positive peaks). Additionally, we highlight how the signal and amplitude change as the object moves rostrocaudally and laterally.

Much like the previous example, the data wrangling is already handled. As this is a more complex simulation, we have a more complex analysis. In the upper half of the iteration in the included code snippet, we show the included API for masking (inclusively) regions of interest (the skin and prey object) and plotting the outline. In the bottom half we show, as in the previous example, how to plot the electric image.

6.3.3 Realistic Motion

To this point we’ve been studying contrived models: perfect tail bending, straight fish. Real fish however exhibit a variety of behaviours (Stamper et al. [2012](#); Uyanik et al. [2019](#)). However, the underlying role that these movements play on the electrosensory scene is unclear. A non-FEM consideration in studying freely swimming fish is the time requirement to digitize (label) points on the fish to determine pose. This limits the length, and

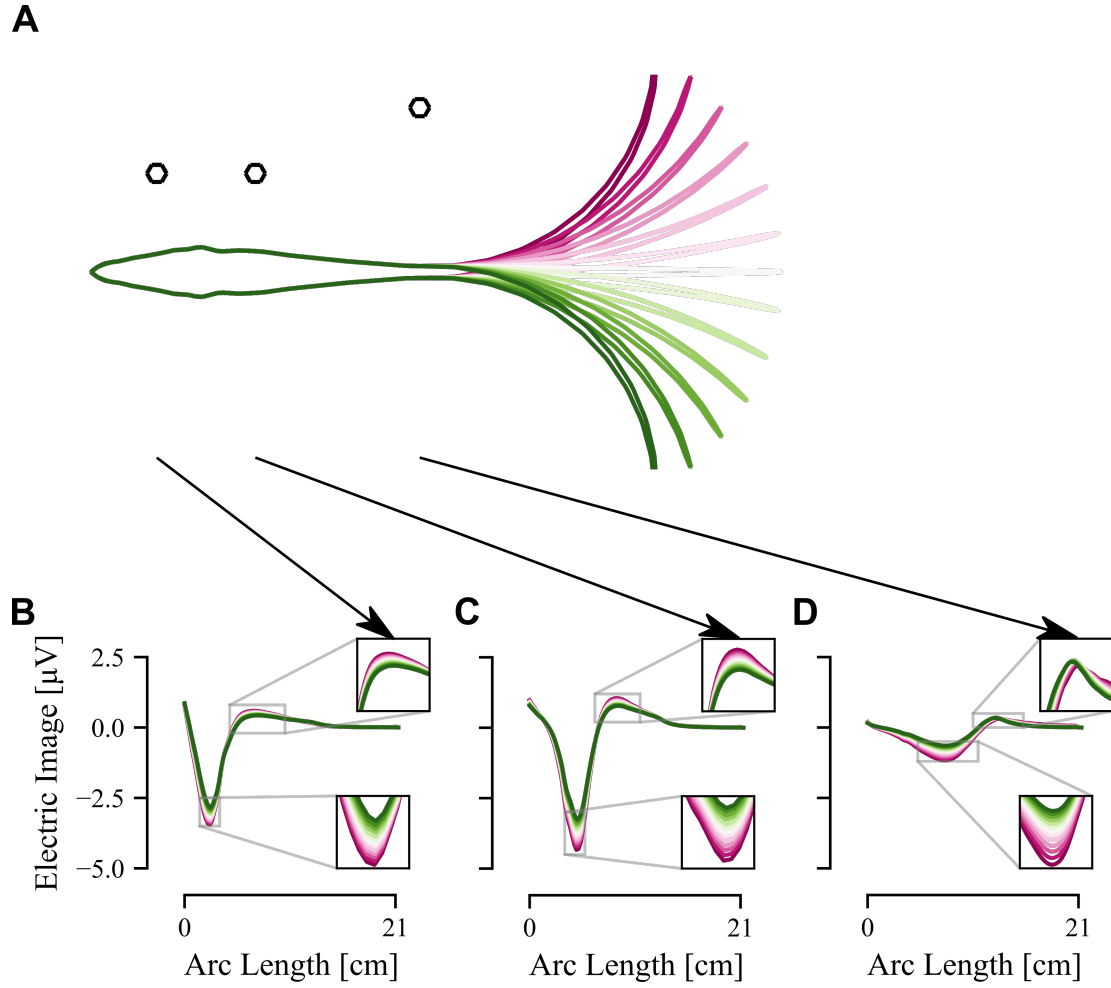


Figure 6.4: Electric Images During Tail Bending. (A) Schematic of tail bending with green representing the contralateral-most bend and pink representing the ipsilateral-most bend. Object locations are shown above fish. (B-D) Electric images for objects at location determined by arrow (B-D: left-right prey), amplitude modulations are highlighted at peak and trough via insets (grey).

number of videos and therefore experiments which can be studied. Recent developments in markerless pose estimation have greatly facilitated this step. DeepLabCut (Mathis et al. 2018) (DLC), for example, is a machine learning algorithm which is easily and efficiently trained and can extract fish poses with great accuracy. py(FEM)²S natively parses digitized fish from DLC. DLC outputs a single .h5 file, which when combined with coordinate information (pixel scaling, and origin location), is used by py(FEM)²S to automatically simulate the entire video. Note at this point analysis is done offline, i.e. it is not currently possible to model the electric field from real time video. This combination of automated digitization with automated FEM tools can facilitate the study of large, high-dimensional experiments. In figure 6.5 we show how this could work. For display, we have extracted three frames over two seconds of video showing a fish turning around within a rectangular plexiglass refuge (left panels). In the right panels, we show the computed electric field for each frame. Frames two and three are of particular interest as the reader can note how contorted the fish becomes. We have no issue in computing the field under these distortions. Additionally we highlight the degree to which the zero-potential line (white) becomes distorted which is known to have electrosensory impacts (Shifman and Lewis 2018; Heiligenberg 1977; Pedraja et al. 2018).

While this example involves a relatively simple electrosensory scene, it is similar to a commonly used experimental setup used to study tracking (Stamper et al. 2012) – one that has not yet been addressed extensively from a modelling perspective. Note however that additional objects could have been trivially added to the scene as in the previous examples. This is the main power of py(FEM)²S: each independent component is easy to use, and they can be stitched together without affecting other parts. For example, by swapping out the model specification to a model with an object or a different environment shape; the DLC parsing component is model-agnostic and hence would work the same.

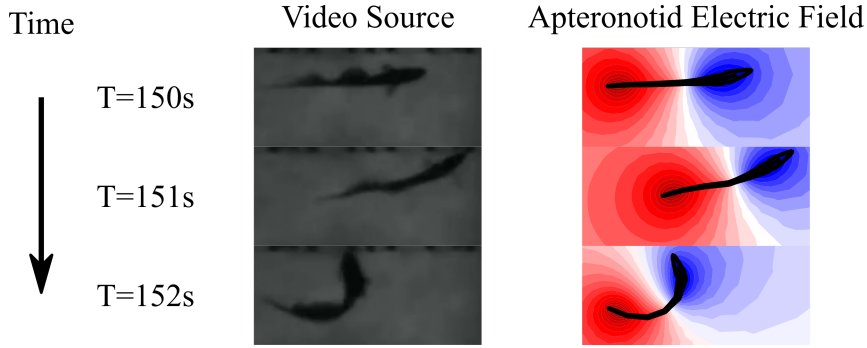


Figure 6.5: Fish EOD during realistic movement. (Left) we show three frames of a movie spanning 2 seconds showing the fish turning around. (Right) we show the same three frames with the electric field computed by $\text{py(FEM)}^2\text{S}$ after the movie was digitized by DeepLabCut (DLC).

6.4 Summary

In this work we’ve introduced $\text{py(FEM)}^2\text{S}$, a computational toolkit for modeling the electrosensory system of weakly electric fish. Models are defined geometrically and then solved via existing and efficient finite element models. The simulation results are stored in an easily accessible and efficient file for native analysis that interacts well with our plotting library. $\text{py(FEM)}^2\text{S}$ natively interprets digitized video from DeepLabCut (Mathis et al. 2018). Additionally, most model results can be visualized in Paraview: a free and interactive plotting environment. We believe that the combination of all these features mitigates the complexity of using a “code-based” environment while providing the benefit of fish-specific analyses and a highly flexible environment.

At this time, our finite element models and $\text{py(FEM)}^2\text{S}$ is limited to two dimensions. Historically, 3D FEM fish models have been too computationally expensive to be practical (in large part due to the skin domain, which is much smaller than the typical model scale), and thus BEM have been the choice for 3D work. However, more practical scaling to HPC (which is free with $\text{py(FEM)}^2\text{S}$) and the use of now standard FEM techniques, such as multiscale formulations or mortaring, can eliminate the skin domain, and mitigate the associated computational cost. This along with our use of a prototypical fish body, shaped by a spinal pose, should allow the extension of $\text{py(FEM)}^2\text{S}$ to 3D in the near future.

6.5 Competing Interests

We have no competing interests

6.6 Contributions

ARS and JEL conceived and designed the py(FEM)²S platform. ARS wrote py(FEM)²S software with input from JEL. ARS and JEL wrote the manuscript. MU performed experiments and digitized video. All authors read and approved the final manuscript.

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6.8 Data Availability

py(FEM)²S will be available on Github at <https://github.com/pyFEM2S> after publication.

6.9 References

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Appendix

6.A Supplemental Code 1

```
from pyFEM2S import *

class SupplementalCode1(BaseFishModel):
    def add_geometry(self, **kwargs):
        prey_object = Circle((5, 2), 0.2)
        self.model_geometry.add_domain("prey_domain", prey_object, sigma=1)
```

6.B Supplemental Code 2

```
from pyFEM2S import *

class SupplementalCode2(BaseFishModel):
    def add_geometry(self, prey_x=1, **kwargs):
        prey_object = Circle((prey_x, 2), 0.2)
        self.model_geometry.add_domain("prey_domain", prey_object, sigma=1)

prey_parameters = ParameterSet({'prey_x': [2, 3, 4]}, 'prey_location', rebuild_mesh=True)
ps = ParameterSweep(prey_parameters)
IterativeSolver('sweep_model', '.', SupplementalCode2, ps)
```

Part III

End Matter

Chapter 7

Discussion

Bioelectric fields arise naturally from all excitable tissues such as muscle, heart, or neurons. The biophysical basis for the activity in these cells is the action potential, large voltage excursions that take place across the cell membrane (Dayan and Abbott 2005). The action potential is created by large ionic current transients passing through the membrane, which give rise to electromagnetic fields (Buzsáki, Anastassiou, and Koch 2012; Gratiy et al. 2017; Hagen et al. 2018). In this work because spatial scales are small, and frequencies are low we omit the magnetic component of these fields and consider only the electrical component (Gratiy et al. 2017; Hagen et al. 2018). We show this derivation in the introduction (chapter 1).

The fields stemming from these tissues are broadly used in medicine as diagnostics, including electroencephalograms (EEGs) in brain, electrocardiograms (EC(K)Gs) in the heart, or electromyograms (EMGs) in muscle. However, the ultimate benefit of these techniques is limited by the level of understanding of the map between cellular dynamics (local) and field measures (global). In neuroscience particularly, bioelectric fields are used additionally as interpretation tools of brain dynamics (Pesaran et al. 2018; Buzsáki, Anastassiou, and Koch 2012). Because the action potential gives rise to an electric field, and the very same action potential is influenced by the extracellular potential, it follows that neural dynamics will be affected by these very same electric fields (Holt and Koch 1999; Anastassiou and Koch 2015; Anastassiou 2014; Weiss and Faber 2010).

Interestingly, the degree to which these electric fields affect neural dynamics is unclear (Anastassiou and Koch 2015; Weiss and Faber 2010; Jefferys 1995). These fields typically are treated as epiphenomena: solely indicative of underlying dynamics (the clinical or

LFP perspective). Despite this, there have been some studies showing that in niche cases, endogenous electric fields can play a role in neural dynamics (Goldwyn and Rinzel 2016; Furukawa and Furshpan 1963; Korn and Axelrad 1980; Han et al. 2018; Chiang et al. 2019), see (Weiss and Faber 2010; Anastassiou 2014; Jefferys 1995) for comprehensive reviews.

The goal of this work is to study electric field effects where they are most likely to be significant. We have used the electric fish *Apteronotus* (and *Eigenmannia* in chapter 5). The reason for this choice is that these fish create large, whole body electric fields in order to sense their environment (electric organ discharge; EOD). A result of this fact is that every neuron in their brain are immersed in a coherent non-local oscillatory electric field (Moller 1995; Assad 1997). Because of this global field, we show electric fields playing functional roles at the micro-scale and macro-scale (micron to centimeter). Specifically on the on the micro-scale we’ve developed computational methods (E_LFENN; Chapter 2) for modeling electric field effects. We’ve also developed a new model of the pacemaker cells (Chapter 3), which are responsible for controlling EOD timing. We then combine these tools and show how the EOD affects (entrains) its own pacemaker (Chapter 4). On the macro-scale we study the fish’s electric sense and behaviour. We first show that under jamming conditions (nearby fish with similar EOD frequencies), the spatiotemporal structure of the EOD dictates a fish’s ability to resolve the jamming condition due to additional harmonics (Chapter 5). We then develop a new set of computational tools (pyFEM²S; Chapter 6) which allow us to model fish in natural scenes with realist poses, allowing us access to questions about how fish shape their field geometry to facilitate sensing.

7.1 Oscillatory Dynamics and Electric Field Effects

The common theme underlying all of our studied electric field effects in axons, the PN, and the JAR, are oscillatory dynamics. Here we argue that oscillators are the best candidates for electric field effects (here we are using a strict definition of oscillator: a system equipped with a phase $\theta(t)$ where $\theta \pmod{2\pi}$ is T-periodic i.e. $\theta(t + \tau) \equiv \theta(t)$; we will relax this definition later). Why should this be the case? The answer lies in weakly coupled oscillator theory, and the phase response curve (PRC) (Smeal, Ermentrout, and White 2010; Schultheiss, Prinz, and Butera 2012).

Phase response curves (PRC) define how an oscillator responds to a perturbation.

Oscillators can (in principle) be reduced to two differential equations: the phase and amplitude of the limit cycle. We do not care about amplitude since our goal is the study of cellular and network timing, therefore we only consider the phase (Izhikevich 2000). In this formalism it is possible to describe how perturbations advance or retard the phase of a neural oscillator (see (Smeal, Ermentrout, and White 2010) for review). We will first consider a periodic pulse train which is locked to an external clock (note this can be extended to continuous perturbations via averaging). If this pulse train perturbs an oscillator, then the oscillator will drift relative to the perturbation until it reaches a zero-advance point ($\text{PRC}=0$; assuming such a point exists), locking it to the perturbation. It should be noted here that this does not necessarily scale to network level dynamics (Hansel, Mato, and Pfeuty 2012). This notion of periodic pulses causing the oscillator to slowly drift is a temporally compounding effect. In this example we have hidden the “oscillatory dynamics” discussed above in the pulse periodicity, which is a well understood mechanism for periodic entrainment (Roenneberg et al. 2010).

If we now consider the far opposite extreme: nonperiodic perturbation. The simplest case is an oscillator with a perfectly sinusoidal PRC, and perturbations happening with a uniform random temporal distribution (note this would be exponentially distributed for Poisson spiking). Over many cycles we would expect the net effect of weak perturbations to be zero. This is because when the perturbations are decorrelated in time, the odds of advancing or delaying are equal hence the longterm expectation is that there will be no net phase shift.

Focusing on systems with oscillatory (temporally compounding) effects has a particularly elegant benefit: the perturbation strength (e.g. ephaptic strength) dictates the convergence time to a stable, locked state. As long as the oscillatory dynamics are stable, then the absolute strength of the effect is irrelevant (the effect will be the same, just slower). Speaking with more natural environments in mind, as long as the convergence time is short relative to brain time scales, then ephaptic effects can be weak while still manifesting an effect, contrary to dogma that ephaptic effects are too weak to be relevant.

As a caveat on the focus on oscillatory dynamics we also suggest that the oscillator and perturbation should have similar frequency (the difference between the oscillator and perturbation frequencies; error frequency, should be small). Alternatively the ratio of perturbation to oscillator frequency should be close to an integer. In this work we have studied 1:1 locking and extending our results to N:1 locking is trivial – how-

ever polyrhythms (rational locking, N:M) is not trivial. There is a relationship between perturbation (or coupling) strength and the frequency error that can be entrained. Formally these are represented as “Arnold tongues” where coupling strength and the error frequency are related (Lowet et al. 2016; Escalona, José, and Tiesinga 2002). Broadly put, the stronger the perturbation is the the larger an error frequency can be entrained. We see this in fish electrosensory systems where nearby frequencies are entraining receptors, locking them to the beat (a harmful result in this context), and additionally (not shown) if the frequency range of a set of axons is too wide (we used $\pm 1\text{Hz}$, chapter 2) they will not entrain one another through electric fields. This is additionally why the PN-EOD system is so effective as their natural frequencies are 1:1 (or at least very close).

7.2 Other Sources of Field Effects

Despite our prior statement about oscillatory dynamics being a mediator of electric field effects, there is another option not studied here that has the potential to be a broadly acting mechanism.

Neurons are noisy, this due to a number of factors including synaptic input (Ermentrout, Galán, and Urban 2008). Importantly the type and statistics of this noise (including small amplitudes) can strongly impact neurons in a variety of ways such as stochastic resonance (Longtin 1993) (SR), or fluctuation-driven firing (FD) (Kuhn, Aertsen, and Rotter 2004; Rudolph and Destexhe 2003). If we consider that field potentials are, to an extent, spatially correlated, and reflective of synaptic activity then it is possible to imagine a framework where the LFP behaves as a spatially coherent noise source which has neurocomputational roles in the above mentioned modes (SR/FD). In this framework we imagine a set of weak oscillatory inputs giving rise to an oscillatory LFP. We then consider a neuron receiving subthreshold inputs. In this context, the synergy of LFP and synaptic input may be suprathreshold; a resonance if you will. Alternatively if we consider that weak membrane fluctuations as would be caused by the LFP are known to affect single cell encoding (Bernander et al. 1991), we can again argue for a mechanism where the LFP affects coding features – potentially by modulating spiking probabilities.

This idea is not without evidence, however this has not been studied in an endogenous field effect context. Stochastic resonance has implicated in exogenous field stimulation where evidence accumulation in is increased in human (Groen et al. 2018). There are also studies showing that neurons spike preferentially during different phases of the LFP

(Gupta, Singh, and Stopfer 2016). The authors interpreted their results as there being an optimal time for integration to occur (resulting from network state), and therefore the LFP arises from the network activity. Could the LFP feeding back to affect excitability partly underlie this as well? Another relevant example is the generation of γ -rhythms in cortex from spike synchrony (Salkoff et al. 2015), with the synchrony arising from inhibitory synaptic events. Does the phase of the γ -LFP synergize with this inhibition?

While these are certainly attractive ideas, it cannot be overstated there is no evidence for this and thus we can merely speculate at this mechanism. Further future work should be applied in this area.

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