Fields Institute Summer Undergraduate Research Program: Modelling of Fetal Neurovascular Coupling

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1. Introduction

Neurovascular coupling is the relationship between neaurl activity of a fetus and the associated changes in cerebral blood flow. Understanding neurovascular coupling is important in order to help prevent disorders and

2. Background

2.1. Neuron Model

In order to better understand neuron activity in the brain, a model was created. The interest is not of the underlying principles of neuron activity, but instead the physical parameters of the neuron, as observed throughout the simulation, specifically, the mechanics of how sodium, potassium, chlorine, and calcium concentrations in the extra and intracellular cell membranes are related to the voltage of the neurons. The desired model realistically simulates the spikes in neuron voltage and chemical concentrations that are experimentally observed during brain activity. The main application of this study is to provide insight as to how seizures are formed and progress.

We have independently studied two different models. One is a simplistic model of one isolated neuron. [1] The second is a model of n excitatory neurons and n inhibitory neurons which are all coupled [2]. A schematic of the second situation is shown in figure 1.

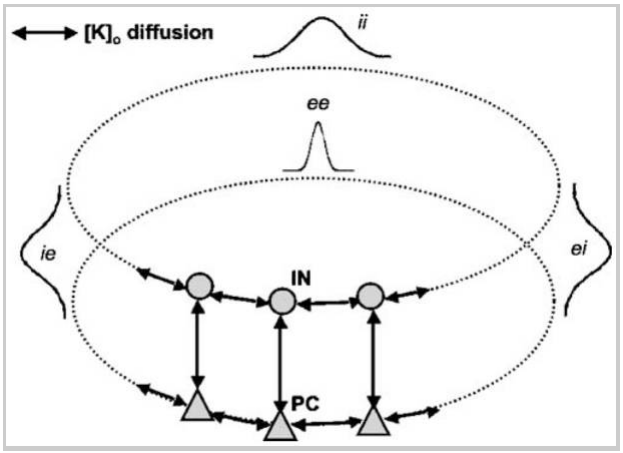

Figure 1: Schematic of excitatory and inhibitory neurons. [2]

2.2. Circulation Model

A model demonstrated by Beatrijs van der Hout-van der Jagt, et al [3], [4] was replicated. This model follows the blood flow through the system of a pregnant sheep and the fetus. The electrical analog of the system can be seen in Figure 2. As in a real system, the left ventrical of the mother pumps blood through the arteries. Some of this blood is then directed towards the uterine circulation while the rest is directed to the systemic circulation of the mother. Oxygen and nutrients in the blood that has been directed towards the uterine circulation is diffused across the placental membrane and enters the fetal circulation which follows a similar path. The fetus is subject to the additional pressure of the uterus, which is regulated

by a contraction model. The flow in the fetus is significantly symmetrical to that of the maternal system.

2.3. Data Analysis Model

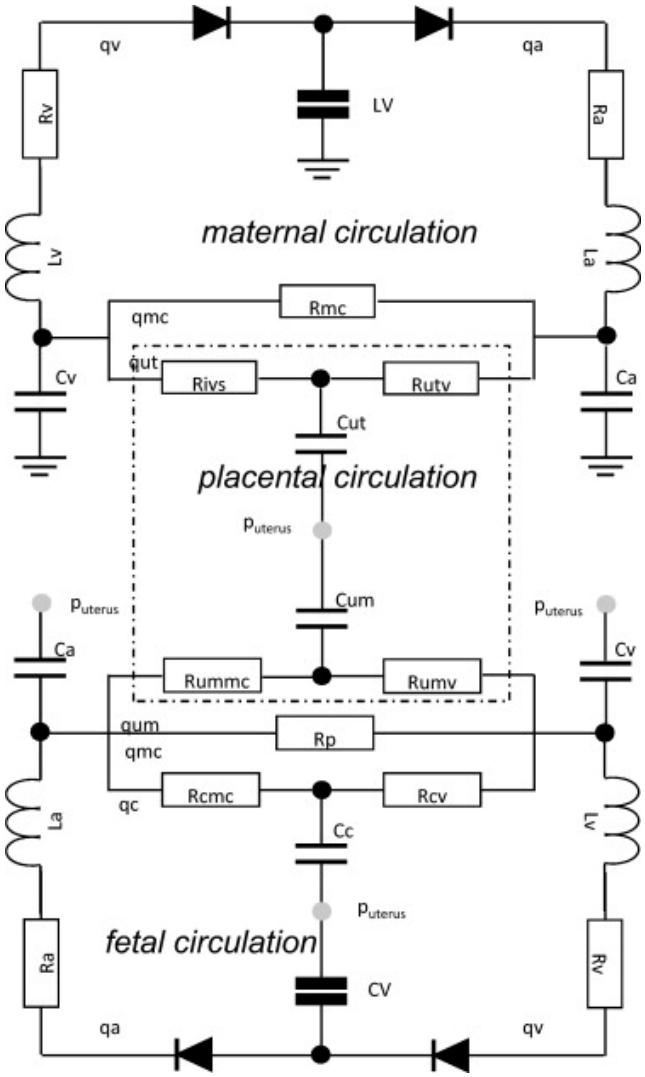

Figure 2: Electrical analog of blood flood system in the model. [3]

Fetus is connected with mother body by umbilical cord. Mother brings oxygen and other nutrients to fetus via umbilical cord. However, umbilical cord might be blocked in the process of labor. In case of blocking, fetus doesn't have adequate oxygen or other necessary elements. Therefore, it might damage fetal bodily functions especially brain functions. Mathematically, a linear system of ordinary differential equation which models micro-environment in fetus can be built. Some important outputs of that model are heart rate (HR), blood pressure (BP), pressure of oxygen (PO) and pressure of carbon dioxide (PCo2). Some models also have other outputs such as Electroencephalography (EEG) and Electrocorticography (ECoG).

For Qiming Wang's model, it is modeling HR, BP, PO and PCo2. However, there might be something missing is the model. But, we don't know what they are. The missing part might significantly affect outputs. Therefore, we manually delayed some parts in the model. Let's denote the reduced model as WD and denote the original model as WOD. We want to compare the differences between outputs of those two models.

Statistically, a feasible way to achieve that goal is to compare the relationship among HR, BP, PO and PCo2 in each model. I regarded HR as response variable and others were explanatory variables. The main reason why I did this way was that HR is easiest

to record in practical. But BP, PO and PCo2 sometimes may not be recorded easily. Moreover, BP, PO and PCo2 sometimes may not be recorded in equal time space. Therefore, it was better to set HR as response variable. There was also same situation of EEG and ECoG. In that model, HR was response variable and EEG and ECoG were explanatory variables.

3. Model and Methods

3.1. Neuron Model

The single neuron model can be understood as follows: The neuron is inside of a chemical bath with sodium, potassium, chlorine, and calcium; each one has an intrinsic ionic current, and the potassium and sodium additionally have an associated pump to them. The sodium and potassium currents have associated gating variables, n and h respectively, which regulates the rate of current flow. These gating variable are a function of the current voltage of the neuron. There is also a separate equation which models the pump that is being used for the sodium and potassium. It is a function, naturally, of the concentrations of sodium and potassium. The rate of change of sodium is completely determined by the pump and its intrinsic current. The potassium, however, has an additional Glia current and diffusion current. Glia cells remove potassium from the extracellular space. The glia current is a function of the potassium concentration. Finally, the potassium also has the potential to diffuse away from the extracellular space. This diffusion current is again, a function of the concentration of potassium. In total, we keep track of six dynamic variable: Voltage, sodium, potassium, calcium, and 2 gating variables n and h. The applicable single neuron equations are as follows:

$$I_{Na} = -g_{Na}[m_\infty(V)]^3 h(V - V_{Na}) - g_{NaL}(V - V_{Na})\,.$$

$$I_K = -(g_K n^4 + \frac{g_{AHP}[Ca]_i}{1 + [Ca]_i})(V - V_K) - g_{KL}(V - V_K)\,.$$

$$I_{Cl} = -g_{ClL}(V - V_{Cl})\,.$$

$$I_{pump} = (\frac{\rho}{1 + exp((25.0 - [Na]_i)/3.0)})(\frac{1.0}{1.0 + exp(5.5 - [K]_o)})\,.$$

$$I_{glia} = \frac{G_{glia}}{1.0 + exp((18 - [K]_o)/2.5)}\,.$$

$$I_{diff} = \epsilon([K]_o - k_{0,\infty})\,.$$

$$C\frac{dV}{dt} = I_{Na} + I_K + I_{Cl}\,.$$

$$\frac{dq}{dt} = \phi[\alpha_q(V)(1 - q) - \beta_q(V)q], q = n, h\,.$$

$$\frac{d[Ca]_i}{dt} = \frac{-0.002 g_{Ca}(V - V_{Ca})}{1 + exp(-(V + 25)/2.5)} - [Ca]_i/80\,.$$

$$\frac{d[K]_o}{dt} = -0.33I_K - 2\beta I_{pump} - I_{glia} - I_{diff}\,.$$

$$\frac{d[Na]_i}{dt} = 0.33\frac{I_{Na}}{\beta} - 3I_{pump}\,.$$

The neuron network model is more complicated. Keep in mind that each neuron in the network is an individual system, and so we will need an entire set of equations for each of the n excitatory neurons and n inhibitory neurons. We begin with the same initial set up: the neurons are all in the same chemical bath as before, and the same currents and gating variables are in place. There is no explicit chlorine current this time, and instead there is a leak current which represents all leaks in the neuron, i.e. from the potassium and sodium pump as well as the entirety of the chlorine pump. There is also the synaptic current term. This can be understood as follows: each neuron interacts with every other neuron in the system. The strength of the interaction is determined by the distance between the two neurons. So, the synaptic interaction between two adjacent neurons is strong compared to the interaction of two neurons which are far apart. The interaction between two excitatory neurons is different than between two inhibitory ones, and both are different than an excitatory-inhibitory interaction. This synaptic current is also regulated by a synaptic efficacy term s, which is a function of the voltage of the neuron. Another current term we have is the external current. This is from the external voltage that is applied locally to a certain portion of the neuron ring and only for a certain period of time. The final additional current term is a random term which may at any point add or take away from the neuron voltage with equal probability. Its also important to note that the calcium concentration of the inhibitory neurons is always assumed to be zero.

The governing sodium equation is precisely the same as in the single neuron model. The potassium equation is quite different however. We now have a diffusion of potassium between a given neurons and all of its immediate neighbours. For example, if we have 10 excitatory neurons and 10 inhibitory ones, than excitatory neuron number 5 will experience diffusion of potassium with excitatory neurons number 4 and 6, and inhibitory neuron number 5.

In total, each neuron in the network has 8 parameters to keep track of: voltage, sodium, potassium, calcium, n, h, s and eta. The applicable neuron network equations are as follows:

$$I_{Na}^{e/i} = -g_{Na}[m_\infty^{e/i}(V^{e/i})]^3 h^{e/i}(V^{e/i} - V_{Na}^{e/i})\,.$$

$$I_K^{e/i} = -(g_K[n^{e/i}]^4 + \frac{g_{AHP}[Ca]_i^{e/i}}{1 + [Ca]_i^{e/i}})(V^{e/i} - V_K^{e/i})\,.$$

$$I_L^{e/i} = -g_L(V^{e/i} - V_L^{e/i})\,.$$

$$I^e_{syn} = -\frac{(V^e_j - V_{ee})}{N}\sum_{k=1}^{N} g^{ee}_{jk} s^e_k \chi^e_{jk} - \frac{(V^e_j - V_{ie})}{N}\sum_{k=1}^{N} g^{ie}_{jk} s^i_k \chi^i_{jk}\,.$$

$$I^i_{syn} = -\frac{(V^i_j - V_{ei})}{N}\sum_{k=1}^{N} g^{ei}_{jk} s^e_k \chi^e_{jk} - \frac{(V^i_j - V_{ii})}{N}\sum_{k=1}^{N} g^{ii}_{jk} s^i_k \chi^i_{jk}\,.$$

$$I^{e/i}_{pump} = (\frac{1.25}{1 + exp((25.0 - [Na]^{e/i}_i)/3.0)})(\frac{1.0}{1.0 + exp(8.0 - [K]^{e/i}_o)})\,.$$

$$I^{e/i}_{glia} = \frac{G_{glia}}{1.0 + exp((18 - [K]^{e/i}_o)/2.5)}\,.$$

$$I^{e/i}_{diff} = \epsilon([K]^{e/i}_o - k_{0,\infty})\,.$$

$$C\frac{dV^{e/i}}{dt} = I^{e/i}_{Na} + I^{e/i}_K + I^{e/i}_L + I^{e/i}_{syn} + I^{e/i}_{ext} + I^{e/i}_{rand}\,.$$

$$\tau^{e/i}\frac{ds^{e/i}}{dt} = \phi\sigma(V^{e/i})(1 - s^{e/i}) - s^{e/i}\,.$$

$$\frac{d\eta^{e/i}}{dt} = \gamma^{e/i}(V^{e/i} - V_b) - \tilde{\gamma}\eta^{e/i}\,.$$

$$\frac{d[K]^{e/i}_o}{dt} = 0.33I^{e/i}_K - 2\beta I^{e/i}_{pump} - I^{e/i}_{diff} - I^{e/i}_{glia} + \frac{D}{\Delta x^2}([K]^{e/i}_{o(+)} + [K]^{e/i}_{o(-)} + [K]^{e/i}_o - 3[K]^{e/i}_o)\,.$$

$$\frac{d[Na]^{e/i}_i}{dt} = 0.33\frac{I^{e/i}_{Na}}{\beta} - 3I^{e/i}_{pump}\,.$$

The single neuron model was implemented with relative ease. We simply input all the equations and parameters into MatLab and use an ODE solver to simulate the data with appropriate initial conditions. A matrix y is produced where the columns of y represent the progression of each physical parameter. The only real problems that arose with this implementation is just basic troubleshooting and physical parameter adjustments. Once these minor problems were resolved, we were able to get reasonable spiking patterns.

The network neuron model was more difficult to implement. Originally, we had wanted to produce a program in which the user could choose which neuron he or she wants to observe, and that MatLab would run this simulation independently. However, because the simulation for a specific neuron needs information from adjacent neurons, we need to run all the simulation for all the neurons simultaneously. What we eventually implemented was a series of 2*n*8 differential equations. The first n are the voltage equations for the excitatory neurons. The next n are the voltage equations for the inhibitory neurons. The next n are the s equations for the excitatory neurons, and the next n are the s equations for the inhibitory neurons, and so on.

It was more difficult to troubleshoot this model. The first problem we encountered was the emergence of complex model in the output. We realized immediately that imaginary numbers could only be produced by the logarithm that was in our model. We therefore double checked all terms involved with the logarithms until we found the source of this problem. The last problem we discovered was certain values growing too quickly and too much. Specifically, we noticed that the potassium concentrations were growing to much greater values than we saw in the single neuron value. After some thoughtful investigation, we realized that he size scale of one of our coefficients was incorrect and needed to be much smaller. Once that was fixed, the model was running seemingly correctly; we had all the neurons experiencing reasonable spiking patterns.

3.2. Circulation Model

There are several components to the circulation model. The first is the circulation itself. Blood flow in the system is driven by the pressure difference between compartments:

$$\frac{\partial q}{\partial t} = \frac{\Delta p - Rq}{L}$$

Near the heart, an additional parameter is modelled that indicates if the heart valves are open or closed. They are closed when there is a negative or zero pressure difference across the valve and open for positive pressure difference. These valves prevent backflow of blood into the systemic circulation.

Inertance of the blood is modeled in the arteries of both the maternal system and the fetal system according to:

$$\Delta p = L\frac{\partial q}{\partial t}$$

Elsewhere, the following holds:

$$\Delta p = Rq$$

The oxygenation of fetal blood was modeled as shown in Figure 3. The assumed constant oxygen concentration of the maternal arteries and flow of that blood in the uterine system controlled the oxygen concentration into the fetal circulation. The oxygen distribution was determined by considering convective transport in the vessels, diffusion in the placenta, and metabolic uptake in all compartments as follows:

$$\frac{d(cO \cdot V)}{dt} = q(cO_{in} - cO) - \dot{O}_{diff} - \dot{O}_{met}$$

As in reality, there is no blood flow between the mother and fetus. Oxygen and nutrients diffuse across the membrane in the placenta according to:

$$\dot{O}_{diff} = D(pO_{2,ivs} - pO_{2,um})$$

The blood flow in the fetus is affected by the uterine pressure as well. Pressure in the uterus changes with contractions. The contractions are modeled so that they are periodic with a period of three minutes one minute of contraction and then two minutes of resting. There is a continuous transition between regimes.

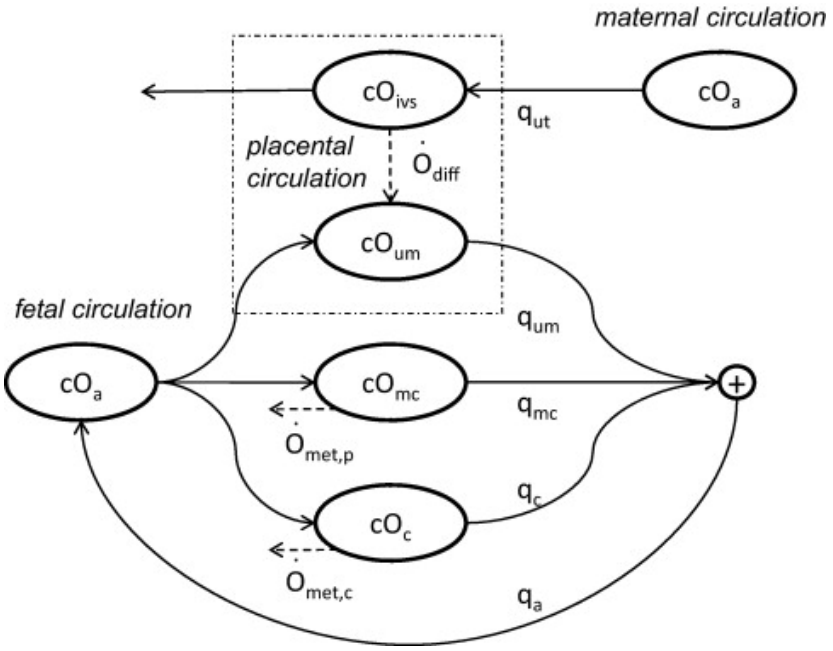

Figure 3: Model of fetal oxygenation flow. [3]

In order to have a complete system of equations, and assuming blood to be incompressible, the following holds:

$$\frac{dV}{dt} = q_{in}(t) - q_{out}(t)$$

The circulation model was implemented using the MatLab solver, *ode*45.

3.3. Data Analysis Model

I applied two non-parametric statistical regression techniques to deal with those data. One is generalized additive model (GAM) and another one is local polynomial regression (Loess). The basic idea behind these two methods is to smooth the data and then get approximate functions.

In statistics, a generalized additive model (GAM) is a generalized linear model in which the linear predictor depends linearly on unknown smooth functions of some predictor variables, and interest focuses on inference about these smooth functions The general form of GAM is described as following,

$$g(y_i) = f_1(x_{1t}) + \cdots + f_n(x_{nt})$$

function g is a link function. $f_1, \cdots, f_n$ are smoothing functions.

Local polynomial regression (Loess) is a strongly related non-parametric regression method that combine multiple regression models in a k-nearest-neighbor-based meta-model. The general form of Loess is described as following,

$$y_i = h(x_{1t}, \ldots, x_{nt})$$

h is a local polynomial function.

The main purpose is that we want to test whether the functional effect of explanatory

variables(BP, PO and PCo2) for response variable (HR) is statistically significant or not. In plain language, we want to judge if those explanatory variables really affect response variable.

In our case, the final model is described as following,
generalized additive model,

$$HR = f_1(BP) + f_2(PO) + f_3(PCo2) + f_4(BP * PO) \\ + f_5(PO * PCo2) + f_6(PCo2 * BP)$$

Local Polynomial Regression,

$$HR = h(BP, PO, PCo2, BP * PO, PO * PCo2, PCo2 * BP)$$

Multiplication terms BP * PO, PO * PCo2 and PCo2 *BP stand for interactive effect. More precisely, for example, BP * PO stands that BP interacts with PO. In other words, The effect of BP on HR depends on PO.

Similarly, for the model with EEG and ECoG, the final model is described as following.

$$HR = f_1(EEG) + f_2(ECoG)$$

Similarly, for the model with EEG and ECoG, two final models are described as following.

$$HR = f_1(EEG) + f_2(ECoG) + f_3(EEG * ECoG)$$
$$HR = h(EEG, ECoG, EEG * ECoG)$$

Finally, we could use many smoothing method to approximate regression equation above.

4. Results

4.1. Neuron Model

For the single neuron model, we wanted to reproduce the results of the paper we were studying. The paper produced a few different plots for different time scales and different parameter values. As seen in Figure 4a and APPENDIX On the short timescale, the spiking of each variable is rapid and consistent. On the long time scale, the voltage of the neuron experienced periods of intense spiking and periods of relative rest (figure 4c). By changing only the value of the tendency for potassium to diffuse, epsilon, and the tendency for glia cells to absorb potassium G_{glia} value, we can produce spiking in the same period of time (figures 4c, 4e and 4d). We are also able to produce a spiking pattern that is qualitatively different than the other patterns (figure 4). One interesting observation is that when we completely turn off all calcium contribution, we are not able to produce certain results (figure 4b). We were able to produce all the results of the paper with our model.

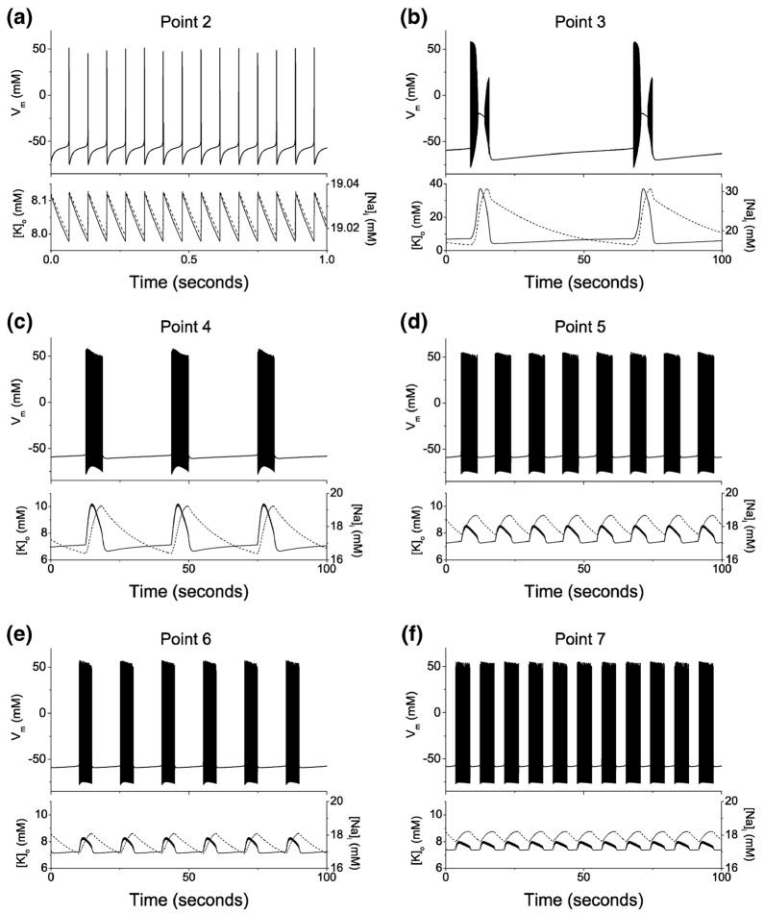

Figure 4: Results from the paper regarding single neuron model. [1] Replicated results can be found in the appendix due to space restrictions.

The network model had harder to gauge results. We did not have any results to compare our data to, so we had to use our judgement to some extent. One strategy we had to gauging our accuracy was decoupling the system; when we take away all terms which involve neurons interacting with one another, what we reduce the model to is essentially $2n$ single neuron simulations. If our decoupled model produces almost identical results as our single neuron model, than we will know that our model was probably correct. Once that was established, we recoupled the system again. The results of the coupled model are similar to the uncoupled model. Unfortunately, in order to truly the appreciate the difference between the couple and uncoupled model, we need to run the model for at least 100 seconds. Due to the lack of computational resources, we were not able to run the model for 100 seconds, even for only $n = 3$ neurons. Shown in Figures 5 and 6 are the qualitative behaviours of the 1st and 3rd neurons, respectively, in a model of 5 neurons using each of 100 ms, 1000 ms, and 10000 ms for the model. By looking at the 100ms model, we can see that the neurons which are closer to the middle (around neuron number 3) experience more spiking than neurons near the edge. This can be explained by noting that the external current applied to the model is a Gaussian centred at the middle neuron. So, the middle neurons experience more of the external current and so experience greater spiking.

Through our model, we were able to observe certain activities of neurons under different conditions. We saw spiking patterns for both the single neuron and the neurons in a network. In the future, this model could be used to observe brain activity under certain conditions, and perhaps be able to find out causes of seizures.

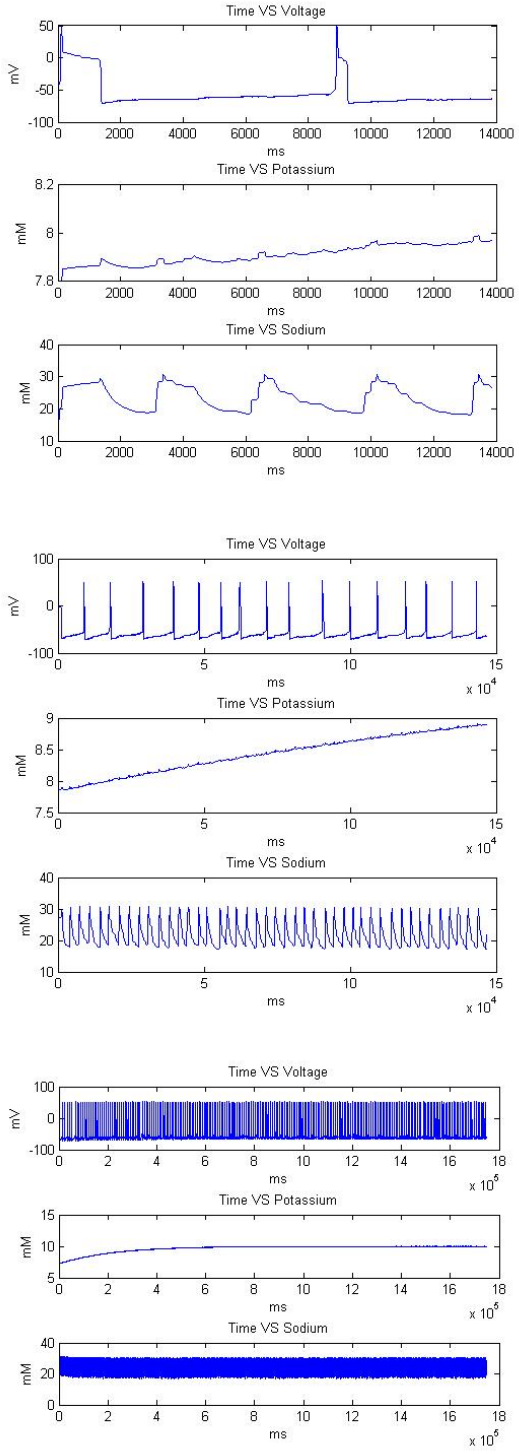

Figure 5: Top: 100 ms model of the 1st neuron in a 5 neuron model. Center: 1000 ms model of the 1st neuron in a 5 neuron model. Bottom: 10000 ms model of the 1st neuron in a 5 neuron model

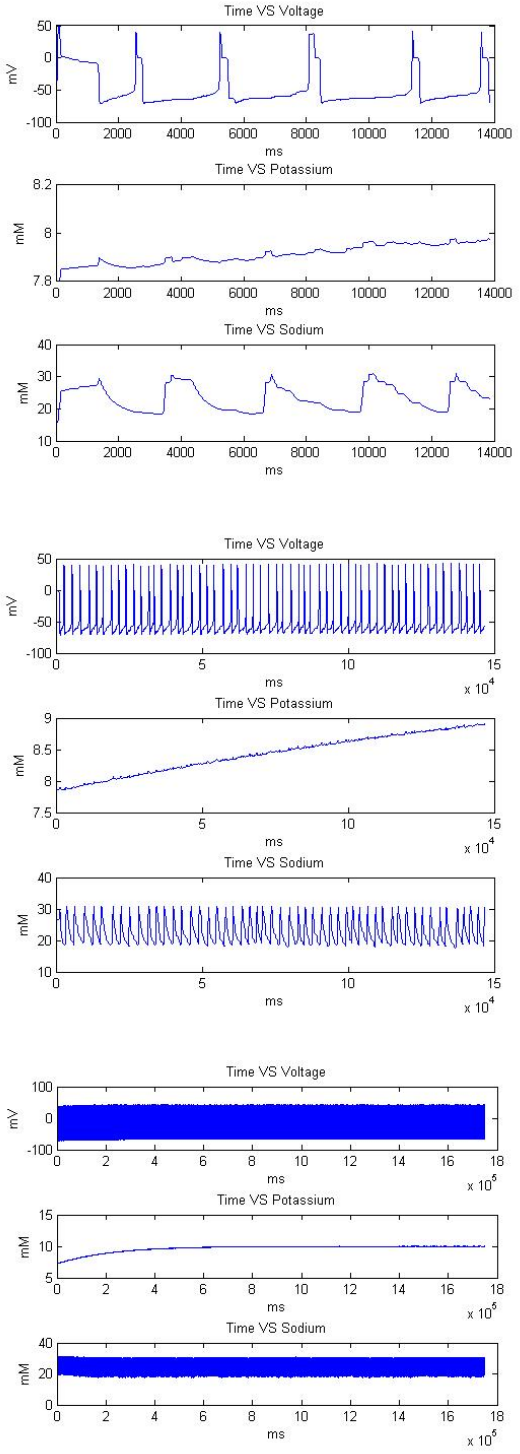

Figure 6: Top: 100 ms model of the 3rd neuron in a 5 neuron model. Center: 1000 ms model of the 3rd neuron in a 5 neuron model. Bottom: 10000 ms model of the 3rd neuron in a 5 neuron model

4.2. Circulation Model

As shown in Figure 7, the contraction results were replicated as in the paper. Figure 7a shows the relationship between time and the uterine pressure. Figure 7b shows the relationship between time and the resistance of the cerebral flow in the fetal brain.

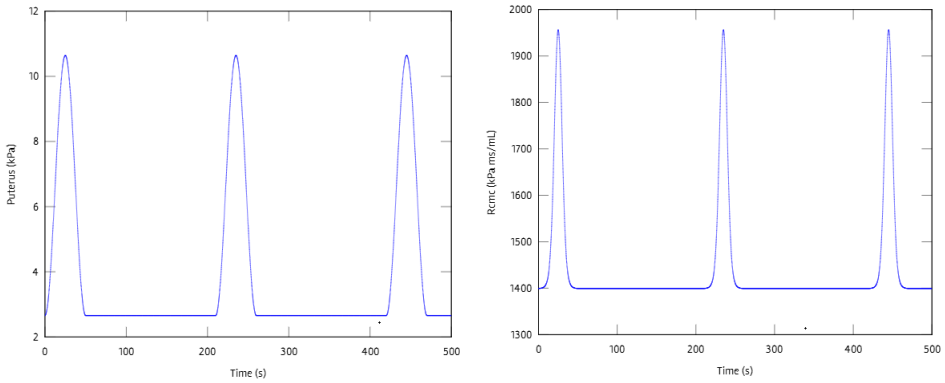

Figure 7: Left (a): Uterine pressure as a function of time. Right (b): Fetal cerebral resistance as a function of time.

Though the contraction model can be checked independently, the rest of the model relies on other parameters. Though volumes and oxygen concentrations are reasonable, they cannot be confirmed accurate due to other problems within the model. The pressure across the heart is unreasonable in magnitude, possibly caused by the sarcomeres getting too long. This unreasonable pressure continues to grow exponentially until MatLab throws an exception when arithmetic is attempted on a value at infinity.

4.3. Data Analysis

Since we used non-parametric regression techniques, we can't write the explicit equation. But we can do hypothesis testing of each functional effect and prediction. For Qiming's model, I built GAM for simulation data. Recall, we had two data set WOD and WD. For WOD, firstly I did model selection test. Then, there was strong evidence (p-value < 0.001) that we should include interaction terms in the model. Furthermore, all six functional effects were statistically significant (p-value < 0.0001). It means BP, PCo2 and PO did affect HR. Moreover, we can't separately consider BP, PCo2 or PO themselves because there were three interaction terms. Among BP PCo2 and PO, the effect of each of them on HR always depends on the other two. For WD, if we just considered three main effect BP, PCo2 and PO, BP was not statistically significant (p-value $= 0.09$). However, if we included three interaction terms, all six functional effects were significant. This was a interesting find. As I mentioned before, since BP PCo2 and PO may not be record all the time, I ran regression on two cases. One was BP PCo2 and PO was observed at equal space time point, another one was that BP PCo2 and PO was observed at sparse time point. I found consistent patterns in both cases. Overall, in the model with delay, something happened so that BP itself have no significant effect

on HR.

For the model with EEG and ECoG, all three functional effects were statistically significant (p-value < 0.01). Actually, it is very common sense that EEG and ECoG interact each other and have influences on HR.

To be honest, the way I dealt with these data set should be refined. For example, I also could do time series regression or functional data analysis. But because of limitation of data and time , those analysis cannot be done shortly. Therefore, I could use these techniques to deal with our data more properly in the future. Furthermore, I haven't finished analysis for Martin's experimental data. Since the data set is big, it was not easy to handle and analyze them. If I get opportunities after that, I'll try it again.

Appendix

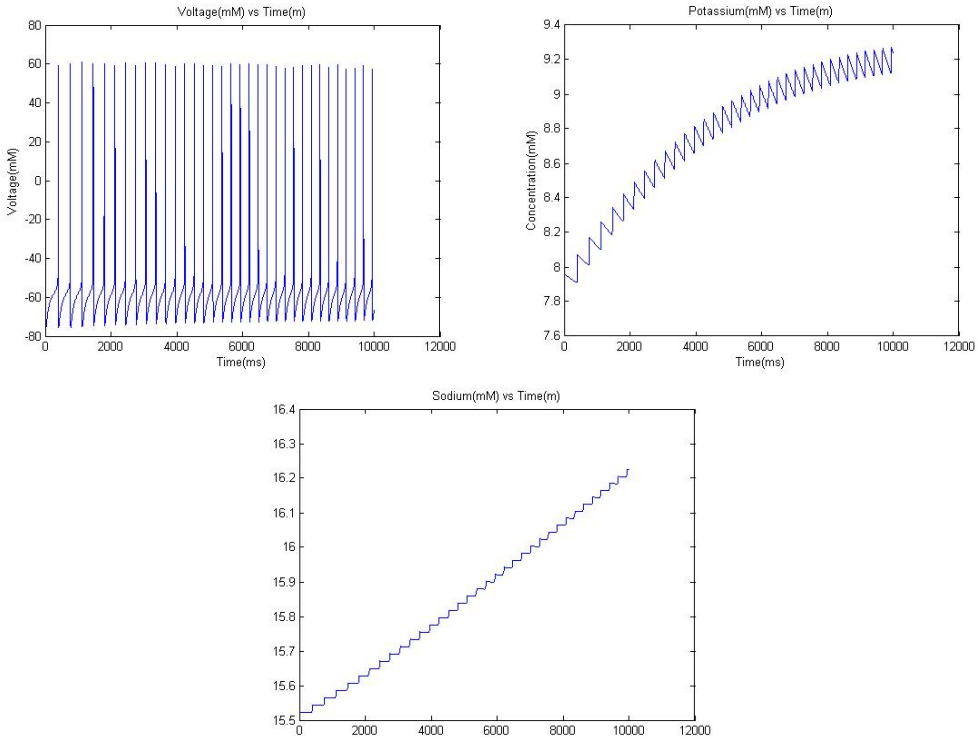

Figure 8: Replicated results of Figure 4a.

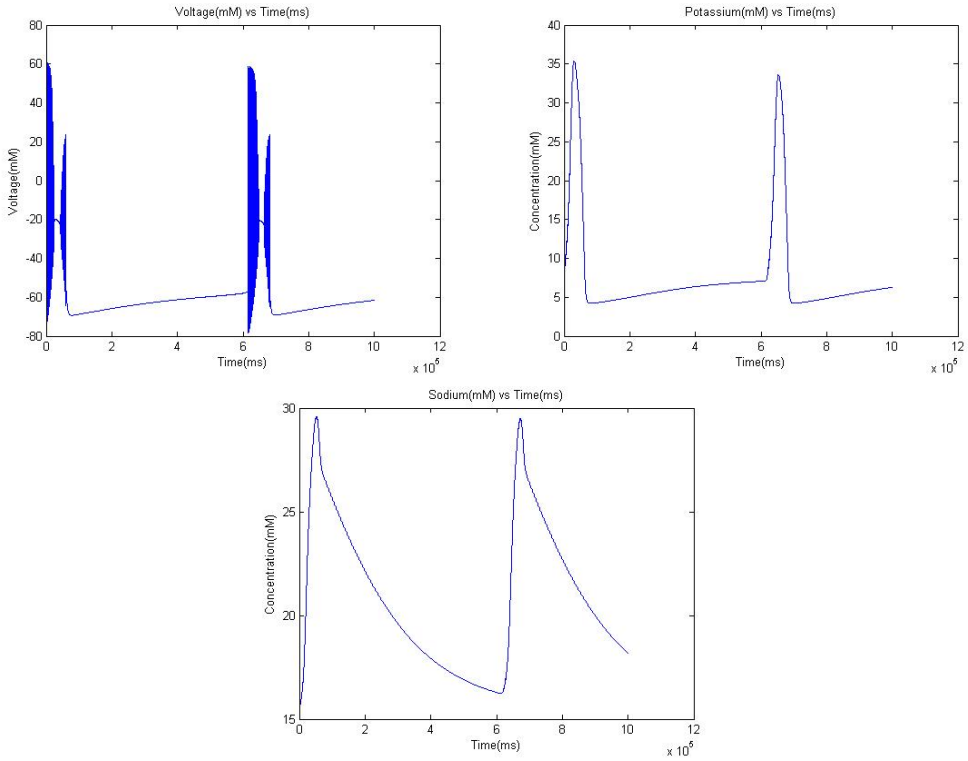

Figure 9: Replicated results of Figure 4b. ϵ is multiplied by 0.2. G_{glia} is multiplied by 0.4.

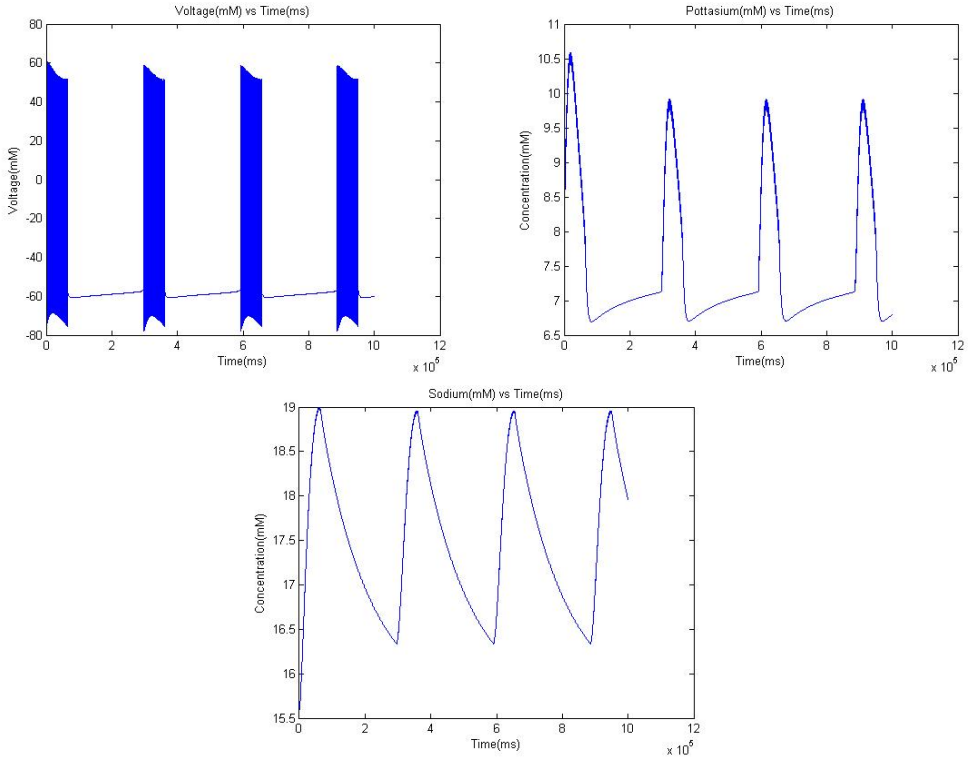

Figure 10: Replicated results of Figure 4c.

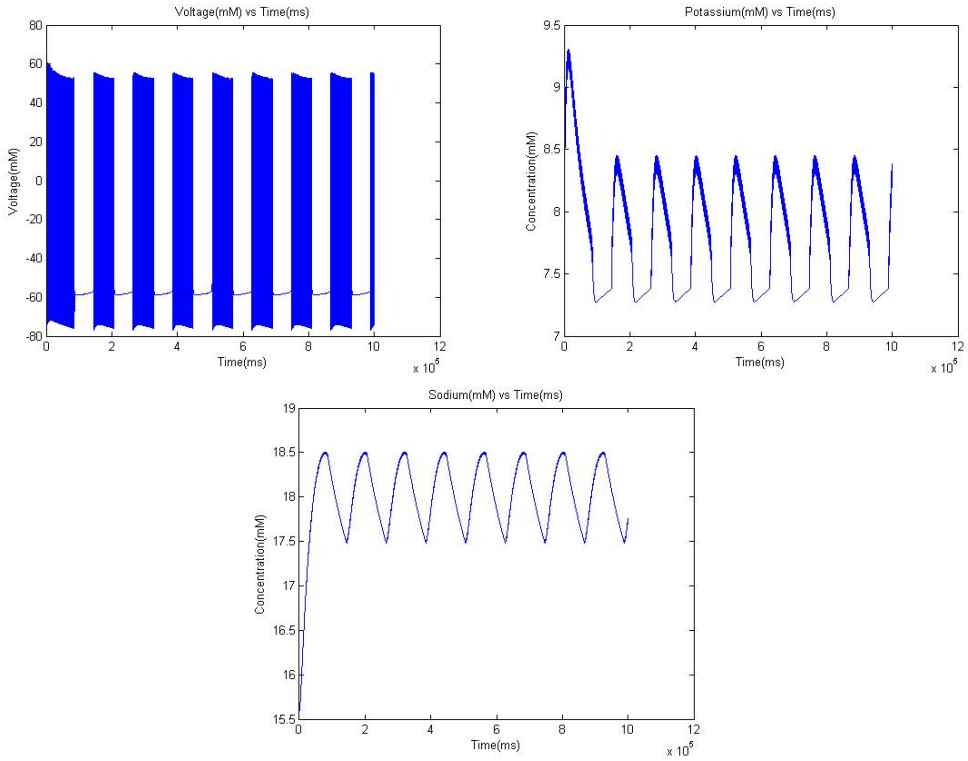

Figure 11: Replicated results of Figure 4d. ϵ is multiplied by 2.0.

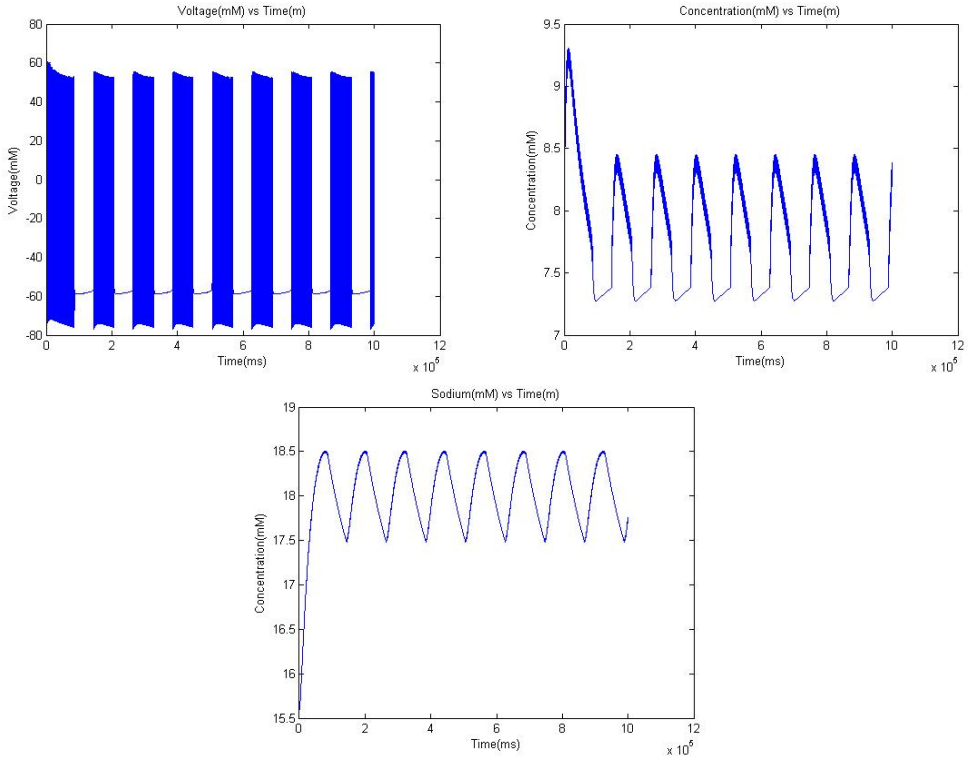

Figure 12: Replicated results of Figure 4e. ϵ is multiplied by 2.0. G_{glia} is multiplied by 1.75.

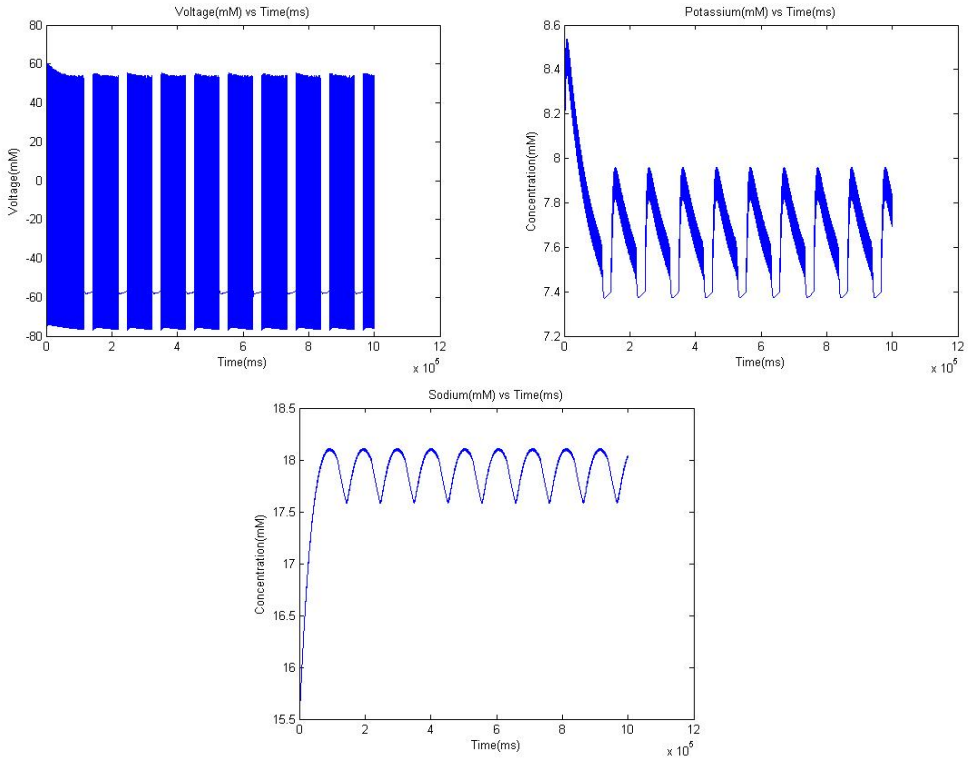

Figure 13: Replicated results of Figure 4f. ϵ is multiplied by 3. G_{glia} is multiplied by 1.75.

References

[1] Cressman, et al *The influence of sodium and potassium dynamics on excitability, seizures, and the stability of persistent states: I. Single neuron dynamics*

[2] Ullah, et al *The influence of sodium and potassium dynamics on excitability, seizures, and the stability of persistent states: II. Network and glial dynamics*

[3] Beatrijs van der Hout-van der Jagt, et al *A mathematical model for simulation of early decelerations the cardiotocogram during labor*

[4] Beatrijs van der Hout-van der Jagt, et al *Insight into variabel fetal heart rate declarations from a amathematical model*