Wave Patterns and Their Application to Migraine

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Migraines are recurrent in many individuals and are characterized by a throbbing pain in the head, normally on one side of the head or the other. These headache attacks are often associated with nausea, vomiting, and sensitivity to light, sound and movement[1]. Individuals suffering migraines often seek dark, quiet places to lessen the effects of the symptoms. This state of a migraine is debilitating and frequently interrupts the sufferers day-to-day activities. Because migraines are so debilitating, migraines are ranked at 0.71 on a disability scale from 0.0-1.0 (1.0 being highly disabled)[2]. In addition, migraines can be classified into two types: migraines with aura (MA) or migraines without aura (MO). In MA, additional neurological symptoms (aura) occur. Such symptoms include visual hallucinations and are caused by spreading depression, which will be discussed later in this paper. The aura phase occurs before the headache phase and lasts for usually less than one hour. It is argued that if SD occurs in MO, the physiological phenomena must remain clinically silent (meaning clinical symptoms not present), and the neurological symptoms must last less than five minutes[1]. Because of the short duration of time, noninvasive imaging is difficult if SD is silent. By creating a mathematical model, scientists maye be able to better understand migraines (particularly the SD phase) without going through the difficulty of imaging an individual experiencing SD.

Migraine aura symptoms are caused by a phenomenon called Spreading Depression (SD). SD is a chemical imbalance in the brain due to seizure-like discharges of neurons, and it usually lasts no longer than an hour. It is not known whether SD is also responsible for the subsequent headache phase of the migraine, and in particular in cases of MO. During SD, there is a significant increase in blood flow to particular regions in the cortex, or hyperemia, that lasts for 2 minutes. Then, the hyperemia is followed by a 2-hour decrease in blood flow, or oligemia. It is not known whether the changes in blood flow are merely something that occurs during SD, or are part of the cause of SD. To determine where SD occurs in the cortex during a migraine episode, measuring the duration and velocity of the hyperemia and oligemia phases were used. In particular, the concentration of certain ions in the blood, such as potassium ions, are used to measure, and subsequently model, the SD. The concentration of potassium ions is known as the activator. The neurons in the area affected by SD are relatively inactive (hence the name). The neurons beyond the area affected by SD have a high-frequency of activity and "increased synaptic noise". The neurons at the edge of the area affected by SD undergo seizure-like discharging. When the neurons at the front of the area affected by SD discharge, this provides an "electrical signal transmission" to other surrounding neurons not affected by SD, which causes hyperemia in the surrounding areas. The hyperemia in the surrounding areas outside the areas affected by SD can cause the estimated area affected by SD to be overestimated when measured. The hyperemia in the neurons not affected by SD can cause the neurons to be less susceptible to SD. This resistance to SD is known as the inhibitor.

The model proposed by Markus A. Dahlem and Thomas M. Isele is a modified version of the FitzHugh-Nagumo equations with diffusion in the activator equation:

$$\frac{\delta u}{\delta t} = u - \frac{1}{3}u^3 - v + D\nabla^2 u$$

$$\frac{\delta v}{\delta t} = \epsilon\left(u + \beta + K\iint H(u - u_0)dxdy\right)$$

where *u* is the activator value, *v* is the inhibitor value, *t* is the value for time, u_{sat} is the activator saturation value, *D* is the diffusion constant ϵ is the time separation constant, and β is the initial inhibitor state. It is important to note that the activator value and the inhibitor values represent *energy states*, and do not actually represent any physiological phenomena explicitly. While this model has its advantages, there are two noteworthy problems that arise from the model. First, *u* has no mechanism that prohibits it from becoming negative, which is not very plausible. Secondly, $\frac{\delta v}{\delta t}$ is always positive, which prevents the value of *v* from every leveling off with respect to time. From the phase diagram if Dahlem's model (Figure 1), it is clear there are two relevant nodes. Without the inhibitor term in the activator equation (Equation 1), these two nodes are stable. However, with the inhibitor term, both of these nodes are transient, and these nodes shift depending on the inhibitor value. While this is desirable for the rightmost node in the phase diagram, this is not desirable for the leftmost node, which must remain at the origin in order to accurately model the phenomena.

Due to the previously-mentioned flaws with Dahlem's model, a new model was proposed:

$$\frac{\delta u}{\delta t} = u\left(\frac{u_{sat}}{1+v} - u\right) + D\nabla^2 u$$

$$\frac{\delta v}{\delta t} = \epsilon(u - \alpha v + \beta)$$

where *u* is the activator value, *v* is the inhibitor value, *t* is the value for time, u_{sat} is the activator saturation value, *D* is the diffusion constant ϵ is the time separation constant, α is the inhibitor scaling coefficient, and β is the initial inhibitor state. In this model *u* has a mechanism which prevents it from becoming negative: the $\frac{u_{sat}}{1+v}$ term. Furthermore, with the addition of the $-\alpha v$ term in the inhibitor equation (Equation 4), *v* can now level out. Lastly, from the phase diagram of the new model (Figure 2), you can see that, as with the previous model, there are two nodes. Different from the previous model, however, is that the leftmost node is stable irrespective of the value of *v*, which is desired behavior.

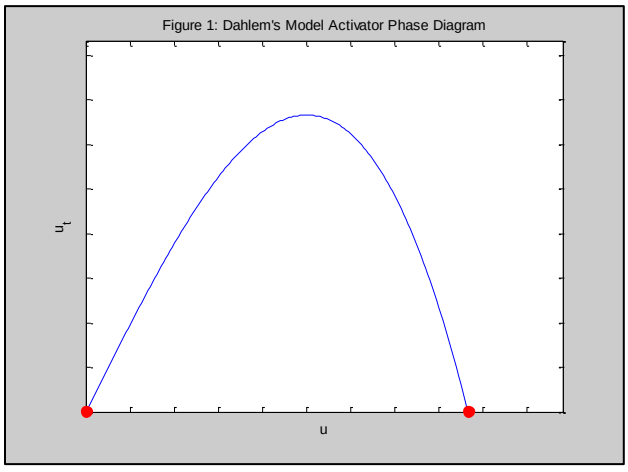

Figure 1: Dahlem's Model Activator Phase Diagram

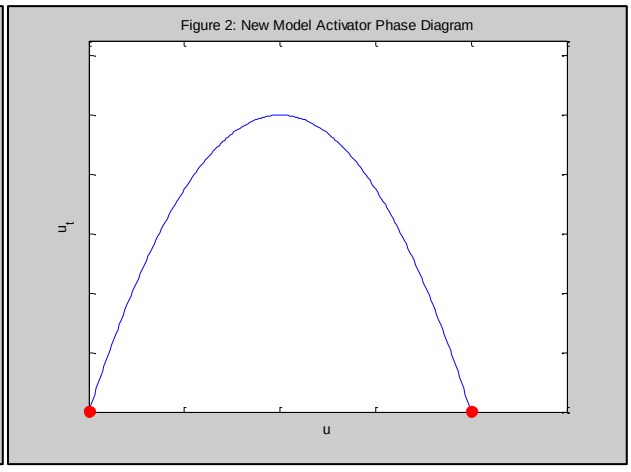

Figure 2: New Model Activator Phase Diagram

The inhibitor equation in the new model (Equation 4) is a linear, first order differential equation, which is solvable. Assuming an initial condition of $v(0) = 0$, solving the inhibitor equation for $v(t)$ gives the following equation:

$$v(t) = \frac{\beta}{\alpha}(1 - e^{-\epsilon\alpha t}) + \epsilon e^{-\epsilon\alpha t}\int u(t)e^{\epsilon\alpha t}dt$$

In conjunction with simplifications in activator equation for the new model, described later in the paper, this equation can be analyzed numerically (Figure 5). This is further evidence that $v(t)$

has the potential to level out, but does not have the potential to become negative, which is reasonable and expected. There are a couple of noteworthy features of the equation. For starters, the equation can be divided into 2 parts: a part that is dependent on the u, and a part that is independent of u. Initially, the part that is independent of u is very small, which means the part that is dependent on u will dominate the part that is independent on u. Additionally, each part has its own unique coefficient: for the part that is independent on u, the coefficient is $\frac{\beta}{\alpha}$, and for the part that is dependent on u, this coefficient is ϵ (which is expected given that ϵ is the time scaling factor). Lastly, there are many exponential terms in the equation for $v(t)$, each with an exponential growth/decay constant of $\pm\epsilon\alpha$. This means the equation for $v(t)$ can be altered to use 3 parameters: $\frac{\beta}{\alpha}$, ϵ, and $\epsilon\alpha$.

Without diffusion, the activator equation for the new model can be analyzed (Figure 3). The figure produced by this analysis is revealing because it shows a cross-section produced by the activator equation, or, in other words, it shows the general shape of the wave of the spreading depression. As expected, there is a very quick and very large increase in the activator value initially, which nicely illustrates the hyperemia phase of the spreading depression, followed by a very slow and very gradual decrease in the activator value, which illustrates the oligemia phase of the spreading depression. Unfortunately, due to a lack of available data, the behavior of the oligemia phase cannot be verified. Authenticating this behavior is something that will have to be done in future work.

The activator equation for the new model (Equation 3) WITH diffusion is unsolvable, which means certain assumptions must be made in order to model it. For this paper, radial symmetry was assumed, which simplified the activator equation:

$$\frac{\delta u}{\delta t} = u\left(\frac{u_{sat}}{1+v} - u\right) + D\left(\frac{1}{r^2}\frac{\delta}{\delta r}\left(r^2\frac{\delta u}{\delta r}\right)\right)$$

The above equation can be solved numerically (Figure 4). There are a couple crucial features of the figure generated that are important to observe. Firstly, it is important to note the significance of the boundary condition for the boundary at $r \approx 0$. This boundary condition, a simple Gaussian bell curve shown below, represents an initial environment factor that *triggers* the migraine:

$$u(r,0) = a_0 e^{-2r^2}$$

where a_0 is an arbitrary coefficient. This boundary condition demonstrates how environmental factors affect the migraine: the environmental factor creates a sudden spike in the potassium ion concentration level in the blood, which subsequently triggers the migraine aura.

Other important features of the figure relate to the shape and behavior of the activator wave. The wave created by the activator grows linearly with respect to the radial distance over time. This indicates the total volume of the brain affected by the spreading depression increases cubically. Furthermore, there is a subtle decrease in the slope of the wave with respect to time, which indicates, after a certain point in time, there is a global (but not necessarily uniform) decrease in the activator level of the volume of brain affected by the spreading depression. Suppose there is a certain activator threshold in which activator values that exceed this threshold will result in in pain. Thus, what the model shows is that the volume of the brain that is affected by pain will initially increase cubically, but will gradually fade away over time.

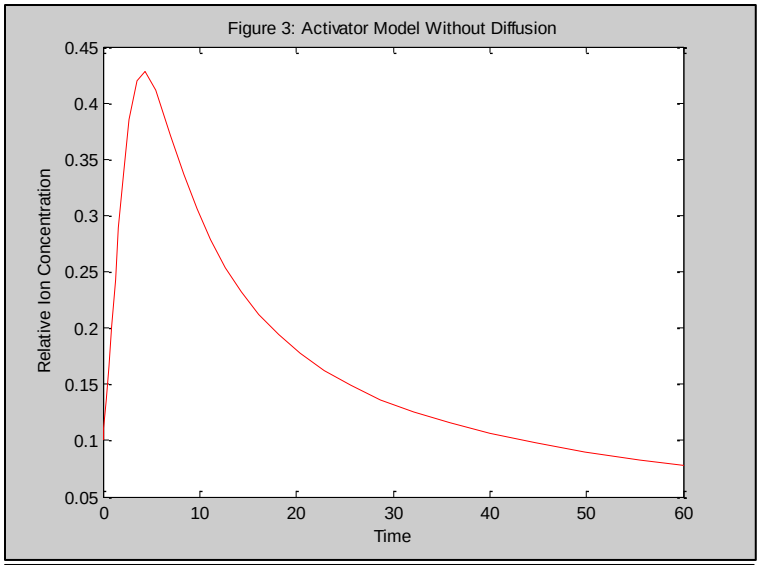
Figure 3: Activator Model Without Diffusion
Relative Ion Concentration
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
10
20
30
40
50
60
Time

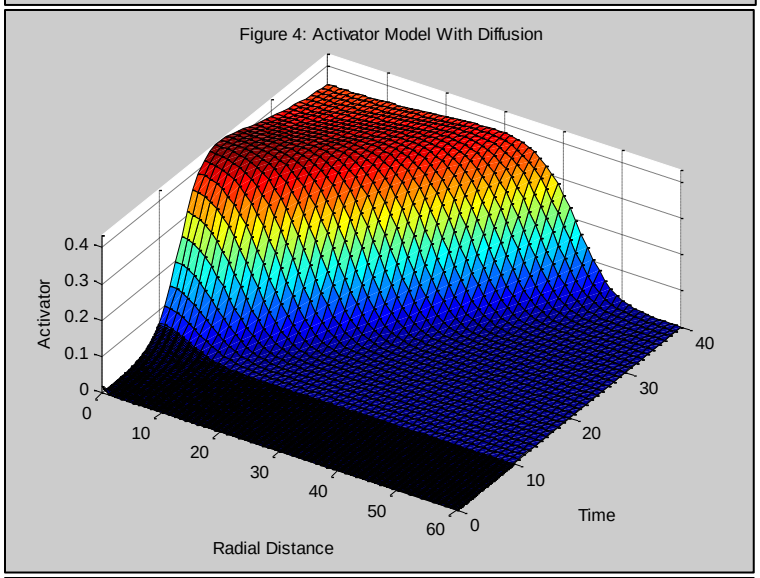
Figure 4: Activator Model With Diffusion
Activator
0.4
0.3
0.2
0.1
0
0
10
20
30
40
50
60
Radial Distance
0
10
20
30
40
Time

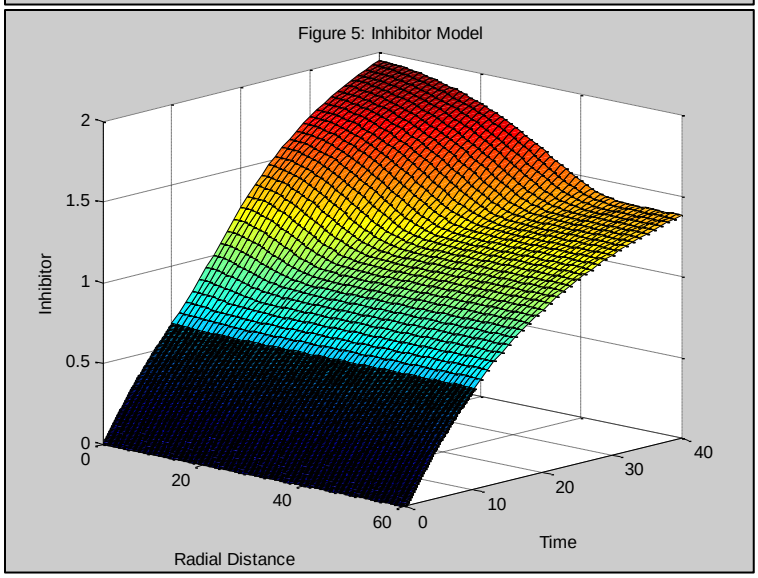
Figure 5: Inhibitor Model
Inhibitor
2
1.5
1
0.5
0
0
20
40
60
Radial Distance
0
10
20
30
40
Time

Though there are many theories as to the cause of migraines, the papers by Dahlem mainly investigated the migraine generator and the spreading depression theory. In his papers, Dahlem collected the data of transient cortical wave patterns and built the canonical reaction-diffusion model. However, his model is not sufficient to explain the behavior of Spreading Depression because of the possibility for the activator to become negative and the ever increasing inhibitor. In this paper, we improved the model of the SD based on information gathered from Dahlem's papers because due to limitations in technology, it is difficult to collect raw data. Currently, MRI is used to measure changes in behavior of SD. Because SD lasts for such a short period of time, it is difficult to image a patient experiencing migraine aura. It is also difficult to measure SD when the aura remains clinically silent because there are no signs of the incident occurring. For future work, the model could be modified to account for multiple starting points in SD as opposed to the current single starting point. In our model, we also assume the edge of SD is radially symmetric from the starting point. Though it is uncertain if MO and MA have same pathophysiological mechanisms, Dahlem thinks it is likely. If this theory is correct, there would only be the need to find one treatment for MA and MO.

References

1. Markus A. Dahlem · Thomas M. Isele, Transient Localized Wave Patterns and Their Application to Migraine, Journal of Mathematical Neuroscience (2013) 3:7 DOI 10.1186/2190-8567-3-7; 2)
2. Markus A. Dahlem, Migraine generator network and spreading depression dynamics as neuromodulation targets in episodic migraine, Chaos: An Interdisciplinary Journal of Nonlinear Science 23, 046101 (2013); doi: 10.1063/1.4813815 View online: http://dx.doi.org/10.1063/1.4813815