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 may 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.

$$\frac{\delta u}{\delta t} = u - \frac{1}{3}u^3 - v + D\left(\frac{\delta^2 u}{\delta x^2} + \frac{\delta^2 u}{\delta y^2}\right)$$
$$\frac{\delta v}{\delta t} = \varepsilon(u + \beta + K \iint H(u - u_0)dxdy$$

$u \equiv$ activator (i.e.- $[K^+]_e$)
$v \equiv$ inhibitor
$D \equiv$ the diffusion coefficient

$\varepsilon \equiv$ time scale separation
$\beta \equiv$ threshold
$K \equiv$ mean field coupling
$H \equiv$ Heaviside step function $\left(H(x) = \begin{cases} x < 0 \Rightarrow 0 \\ x = 0 \Rightarrow 0.5 \\ x > 0 \Rightarrow 1 \end{cases} \right)$

Suppose we define c_1 as the velocity of the spreading depression in the x direction and c_2 as the velocity of the spreading depression in the y direction. We can simply the equations by introducing a variable τ:

$$\tau = t + c_1 x + c_2 y$$

This yields the following result:

$$\frac{\delta u}{\delta \tau} = u - \frac{1}{3}u^3 - v + 2D\left(\frac{1}{c_1^2} + \frac{1}{c_2^2}\right)\frac{\delta^2 u}{\delta \tau^2}$$

$$\frac{\delta v}{\delta \tau} = \varepsilon\left(u + \beta + K c_1 c_2 \iint H(u - u_0) d\tau d\tau\right)$$

The value of ε is really small (on the order of 10^{-2}), which means that for small values of τ, $\frac{\delta v}{\delta \tau} = 0$.

This yields the following result:

$$\frac{\delta u}{\delta \tau} \approx u - \frac{1}{3}u^3 + \frac{1}{\alpha}\frac{\delta^2 u}{\delta \tau^2} \left(for\ \tau < \frac{1}{\varepsilon}\ and\ \frac{1}{\alpha} = 2D\left(\frac{1}{c_1^2} + \frac{1}{c_2^2}\right)\right)$$

$$\Rightarrow \frac{\delta^2 u}{\delta \tau^2} = \alpha\left(\frac{\delta u}{\delta \tau} + u\left(\frac{1}{3}u^2 - 1\right)\right)$$

Let $\frac{\delta u}{\delta \tau} = w$:

$$\frac{\delta}{\delta \tau}\begin{bmatrix} u \\ w \end{bmatrix} = \begin{bmatrix} w \\ \alpha\left(w + \frac{1}{3}u^3 - u\right) \end{bmatrix}$$

Thus, the stationary points of this model are at $P_1 = (0,0)$, $P_2 = \left(\sqrt[3]{3}, 0\right)$, $P_3 = \left(-\sqrt[3]{3}, 0\right)$.
The system has the following Jacobian:

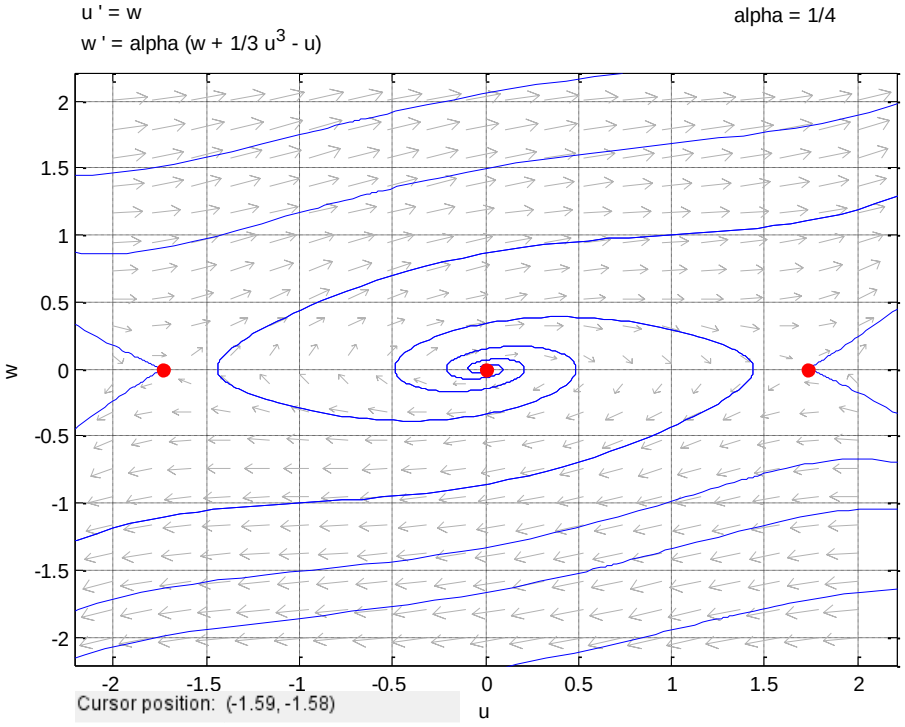
$$J(u,w) = \begin{bmatrix} 0 & 1 \\ \alpha(u^2 + 1) & \alpha \end{bmatrix}$$

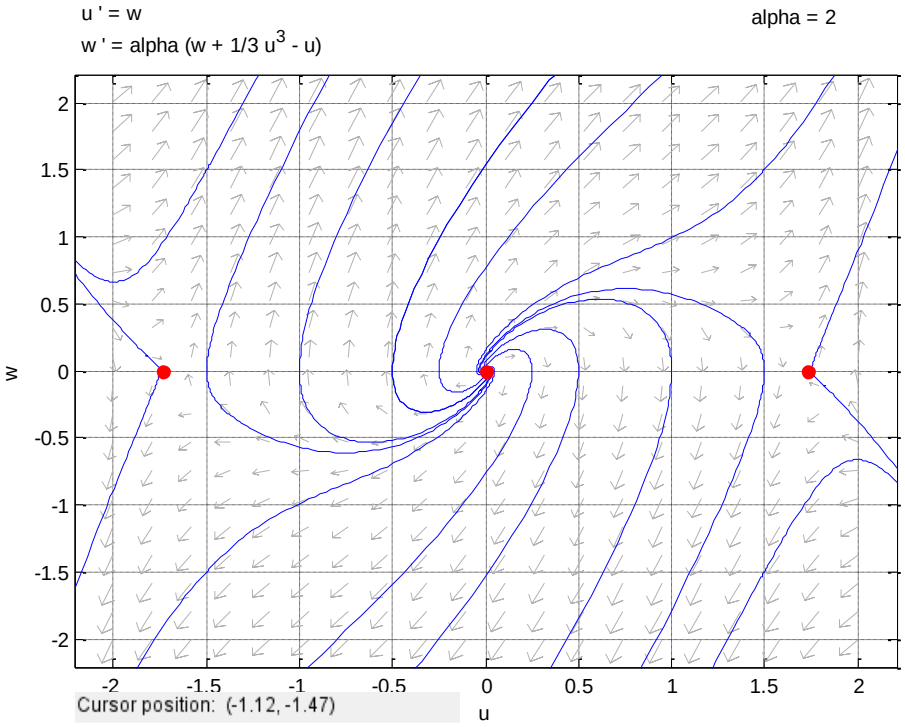
$J(0,0) = \begin{bmatrix} 0 & 1 \\ \alpha & \alpha \end{bmatrix} \Rightarrow \lambda = \pm 1 \Rightarrow$ P_1 is a saddle point.

$J\left(\sqrt[3]{3}, 0\right) = \begin{bmatrix} 0 & 1 \\ \alpha\left(\left(\sqrt[3]{3}\right)^2 + 1\right) & \alpha \end{bmatrix} \Rightarrow \lambda = \pm\sqrt{\left(\left(\sqrt[3]{3}\right)^2 + 1\right)} \Rightarrow$ P_2 is a saddle point.

$J\left(-\sqrt[3]{3}, 0\right) = \begin{bmatrix} 0 & 1 \\ \alpha\left(\left(-\sqrt[3]{3}\right)^2 + 1\right) & \alpha \end{bmatrix} \Rightarrow \lambda = \pm\sqrt{\left(\left(\sqrt[3]{3}\right)^2 + 1\right)} \Rightarrow$ P_3 is a saddle point.

Note that $\alpha \neq 0$ because $D \neq \infty$, which made the above operations valid. Further, $\alpha > 0$ because $D > 0$, $c_1 > 0$, and $c_2 > 0$.





There are many theories of cause of migraines. The paper mainly investigated the migraine generator and the spreading depression theory. The author collected the data of transient cortical wave patterns and built the canonical reaction-diffusion model. The model verified that waves of cortical spreading depression have a causal relationship with the headache phase in migraine, so SD occurs not only in migraine with aura (MA), but also in migraine without aura (MO). Both theories can be validly maintained, therefore, they are not mutually exclusive. We do not know if MO and MA have same pathophysiological mechanisms, but the author thinks it is likely. The result of maximal instantaneous affected cortical area is uncorrelated to both SD duration and total affected cortical area which explained why the headache is less severe in MA than in MO. This study analyzed the model of the cause of migraine.

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