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A MATHEMATICAL MODEL TO STUDY THE ACTIVACION PROCESS IN THE CELEBRAL CORTEX

Introduction

The first step requires analysis of neuroscientific models on different scales. Subsequently we will consider a non-linear distributed model on a macroscopic scale, for the interaction of cortical neurons in between which action potentials travel with finite speed of propagation, without taking into account synaptic delays. The model includes several important physiological parameters such as: density of assosciation fibres, density of synaptic contacts, decreasing scales of connections, firing threshold, magnitude of excitatory and inhibitory postsynaptic potentials, etc. The model describes the space-time evolution of stimulated synaptic activity in the presence of a local process of lateral inhibition. A non-linear system of hyperbolic equations is obtained for the excitation–inhibition process, which when applying results from the theory of perturbations can be reduced into one single equation for a new variable activation calling. This model can provide results about the existence of rhythms (stationary waves) and other physiological states (travelling waves), control of the functional activity of the cerebral cortex (control) and reactions from the cortex towards certain stimuli from structures within the brain (periodical solutions).

1. Deduction of the mathematical model

We will begin by stating some basic physiological considerations for the model's construction. The cerebral cortex has a stratified structure made up of six layers of neurons, grouped in units known as columns, which interact amongst each other. The first estimation is that cortical neurons can be divided into two large categories: main neurons which establish cortical connection or distances measuring between one to 20 centimeters, such as neuronal pyramids, and interneurons which only have intracortical neurons and work with a radius of less than a millimeter. The main cells carry out the excitatory synapses while the interneurons carry out the inhibited synapses on the main cells. We suppose that the afferent inputs to the cortex, proceeding from the brain's inferior structures are only excitatory and we will put to one side the synaptic delays which are of no interest for a model of global activity. To simplify the model we will consider a unidimensional band of the cortex, which we will represent by the whole R of real numbers. In this way the model's parameters and variables are the following (signs $+$, $-$ correspond to the excitatory and inhibited activity respectively):

$\lambda_{\pm}^{-1}$ - Longitude scale of connections decrease (cm);

$V_{\pm}$ - Postsynaptic potentials produced by synapses (mV);

$R_{\pm}(x, x', v)$ - Density of corticortical fibers ($+$) and intracortical fibers ($-$) which connect localizations in x in R and $x^{'}$ in R, through which the velocity of propagation of action potentials is v (seg/cm^3);

$F_{\pm}(v)$ - Density of distribution of velocities of propagation of action potentials (seg/cm^3);

$g_0(x, t)$ - Fraction of total of neurons in localization x that are active in instant t (adimensional);

$h_{\pm}(x, t)$ - Lineal density of active synapses in instant t on the neurons located in x ($1/cm$);

$S_{\pm}(x)$ - Lineal density of synapses in localization x ($1/cm$);

$h_0(x, t)$ - Lineal density of excitatory synaptic afferent input to the cortex in localization x in instant t ($1/cm$).

Supposing for simplicity that

$$F_{\pm}(v) = \delta(v - v_{\pm}) ,$$

where δ is the delta of Dirac and $v_{\pm}$ are the characteristic velocities of propagation of the action potentials in the excitatory and inhibitory cells and that besides have the following expression

$$R_{\pm}(x, x', v) = \frac{\lambda_{\pm}}{2} S_{\pm}(x) e^{-\lambda_{\pm}|x-x'|} \delta(v - v_{\pm}) , \tag{1}$$

we obtain the system

$$h_{+}(x, t) = h_0(x, t) + \frac{\lambda_{+}}{2} S_{+}(x) \int_{-\infty}^{\infty} e^{-\lambda_{+}|x-x'|} g(x', t - \frac{|x - x'|}{v_{+}}) dx' , \tag{2}$$

$$h_{-}(x, t) = \frac{\lambda_{-}}{2} S_{-}(x) \int_{x-\varepsilon}^{x+\varepsilon} e^{-\lambda_{-}|x-x'|} g(x', t - \frac{|x - x'|}{v_{-}}) dx' , \tag{3}$$

where the parameter ($\varepsilon > 0$) corresponds to the hypotheses that inhibitory activity is short range.

2. Reduction and simplification of the system (2), (3)

If in (**??**) and (**??**) we divide both sides by $S_+(x)$ and $S_-(x)$ respectively and we apply the operator $\frac{\partial^2}{\partial x^2}$, then for the new unknown functions

$$H_\pm(x,t) = \frac{h_\pm(x,t)}{S_\pm(x)}$$

the equivalent system of differential equations is obtained

$$\frac{\partial^2 H_+}{\partial t^2} + 2\lambda_+ v_+ \frac{\partial H_+}{\partial t} + \lambda_+^2 v_+^2 H_+ - v_+^2 \frac{\partial^2 H_+}{\partial x^2} = F_0(x,t) + \lambda_+^2 v_+^2 g_0(x,t) + \lambda_+ v_+ \frac{\partial g_0}{\partial t}(x,t)\,, \tag{4}$$

$$\frac{\partial^2 H_-}{\partial t^2} + 2\lambda_- v_- \frac{\partial H_-}{\partial t} + \lambda_-^2 v_-^2 H_- - v_-^2 \frac{\partial^2 H_-}{\partial x^2} = G_0(x,t,\varepsilon)\,, \tag{5}$$

where

$$F_0(x,t) = \frac{\partial^2 H_0}{\partial t^2} + 2\lambda_+ v_+ \frac{\partial H_0}{\partial t} + \lambda_+^2 v_+^2 H_0 - v_+^2 \frac{\partial^2 H_0}{\partial x^2}\,,$$

$$H_0(x,t) = \frac{h_0(x,t)}{S_+(x)}\,,$$

$$\begin{aligned} G_0(x,t,\varepsilon) &= \lambda_-^2 v_-^2 g_0(x,t) + \lambda_- v_- \frac{\partial g_0}{\partial t}(x,t) \\ &-\frac{1}{2}\lambda_- v_- e^{-\lambda_-\varepsilon}\left\{\lambda_- v_- \left[g_0\left(x+\varepsilon, t-\frac{\varepsilon}{v_-}\right) + \frac{\partial g_0}{\partial t}\left(x+\varepsilon, t-\frac{\varepsilon}{v_-}\right)\right] + \right. \\ &\left. \left[g_0\left(x-\varepsilon, t-\frac{\varepsilon}{v_-}\right) + \frac{\partial g_0}{\partial t}\left(x-\varepsilon, t-\frac{\varepsilon}{v_-}\right)\right]\right\} - \\ &\frac{1}{2}\lambda_- v_-^2 e^{-\lambda_-\varepsilon}\left\{\frac{\partial g_0}{\partial x}\left(x+\varepsilon, t-\frac{\varepsilon}{v_-}\right) - \frac{\partial g_0}{\partial x}\left(x-\varepsilon, t-\frac{\varepsilon}{v_-}\right)\right\}. \end{aligned}$$

If we suppose that g_0 and $grad(g_0)$ are continuous functions, then $G_0(x,t,\varepsilon)$ converge when $\varepsilon \to 0$, uniformly at zero on compacts sets of R^2. From this it can be concluded that the solution of Cauchy's problem associated to the equation (**??**) converges uniformly on compacts sets of R^2 to solution the corresponding Cauchy problem when (**??**) is substituted $G_0(x,t,\varepsilon)$ by zero. With this in mind and moving on to adimensional variables

$$\tau = \lambda_+ v_+ t\,, \quad y = \lambda_+ x$$

starting from (??) and (??) we obtain the following simplified model

$$\begin{aligned}\frac{\partial^2 u}{\partial \tau^2}+2\frac{\partial u}{\partial \tau}+u-\frac{\partial^2 u}{\partial y^2} &= V_+\left[g(y,u)+\frac{\partial g}{\partial u}(y,u)\frac{\partial u}{\partial \tau}\right] \\ &\quad +f_0(y,\tau)+C_0(y,\tau)\end{aligned} \tag{6}$$

for the new variable

$$u(y,\tau)=V_+H_+(y,\tau)-V_-H_-(y,\tau),$$

which we will call the activation variable. In (??) we have considered that $g_0(x,t)=g(y,u)$ where function g, which is associated to neuronal activity for a determined physiological state is for each y fixed a sigmoid function of the activation variable. Besides the term

$$f_0(y,\tau)=\frac{V_+}{\lambda_+^2 v_+^2}F_0\left(\frac{y}{\lambda_+},\frac{\tau}{\lambda_+ v_+}\right)$$

corresponds to the excitatory input produced by the brain's interior structures and

$$C_0(y,\tau)=-V_-\left[\frac{\partial}{\partial \tau^2}+2\frac{\partial}{\partial \tau}+1-\frac{\partial^2}{\partial y^2}\right]H_-\left(\frac{y}{\lambda_+},\frac{\tau}{\lambda_+ v_+}\right)$$

is the control produced by the inhibitory activity. It must be noted that on considering

$$G_0(x,\tau,\varepsilon)\equiv 0$$

on the right hand side of (??) , inhibitory control $C_0(y,\tau)$ depends uniquely on the initial state of inhibition.

3. Some results obtained from model (??)

Firstly we will suppose that $f_0(y,\tau)+C_0(y,\tau)\equiv 0$, $g(y,u)=g(u)$ in (??) and then study the existence of travelling waves

$$u(y,\tau)=\varphi(y-c\tau)$$

in the resulting model and that they travel at speed c. In this case placing

$$y-c\tau=\xi\,,\quad \varphi'(\xi)=\psi(\xi)\,,$$

equation (??) is reduced to system

$$\frac{d}{d\tau}\begin{pmatrix}\varphi\\ \psi\end{pmatrix}=\begin{pmatrix}0 & 1\\ \frac{1}{1-c^2} & \frac{-2c}{1-c^2}\end{pmatrix}\begin{pmatrix}\varphi\\ \psi\end{pmatrix}+\frac{V_+}{1-c^2}\begin{pmatrix}0\\ cg'(\varphi)\psi-g(\varphi)\end{pmatrix}. \tag{7}$$

The existence of travelling waves of (**??**) is equivalent to the existence of bounded solutions of (**??**) differing to the stationary solution.

Theorem 1. *We consider that in (**??**) is*

$$g = g(u) = \left(1 + e^{-\alpha u+\beta}\right)^{-1}, \quad \alpha\,,:\beta > 0,$$

and also

$$f_0(y,\tau) + C_0(y,\tau) \equiv 0.$$

We suppose that $2V_+\alpha < 1$ *and also in this case* $\varphi_0 > 0$*, the only constant solution of the equation (**??**). Then for each* $\rho > \max(\varphi_0, \frac{1}{2\alpha})$ *exist numbers* $0 < c_1(\rho) < c_2(\rho) < 1$ *so that* $c_1(\rho) \to 0$ *and* $c_2(\rho) \to 1$ *when* $\rho \to \infty$ *and satisfy the following properties: if* $0 < c < c_1(\rho)$ *the only bounded solution of (**??**) contained in*

$$|\varphi|^2 + |\psi|^2 \leq \rho^2$$

is the stationary solution $\begin{pmatrix} \varphi_0 \\ 0 \end{pmatrix}$*, and if*

$$c_1(\rho) \leq c \leq c_2(\rho)\,,$$

*then homoclinical solutions exist of (**??**) contained in*

$$|\varphi|^2 + |\psi|^2 \leq \rho^2$$

with asymptotic value φ_0*, when* $\varepsilon \to \pm\infty$ *, and that correspond to travelling waves of (**??**) with speed* c*.*

Proof. If $G(\tau, c)$ denotes the main Green principle that corresponds to the matrix

$$\begin{pmatrix} 0 & 1 \\ \\ \frac{1}{1-c^2} & -\frac{2c}{1-c^2} \end{pmatrix},$$

then the bounded solutions of (**??**) coincide [1, page 81] with the solutions of the non-linear integral equation

$$\begin{pmatrix} \varphi(\xi) \\ \\ \psi(\xi) \end{pmatrix} = \frac{V_+}{1-c^2}\int_{-\infty}^{\infty} G(\xi-\tau, c) \begin{pmatrix} 0 \\ \\ cg'(\varphi(\tau))\psi(\tau) - g(\varphi(\tau)) \end{pmatrix} d\tau. \qquad (8)$$

If

$$\frac{V_+}{1-c^2}\,|cg'(\varphi_1)\psi_1 - g(\psi_1)| \leq M$$

and

$$\frac{V_+}{1-c^2}\left|(cg'(\varphi_1)\psi_1 - g(\varphi_1)) - (cg'(\varphi_2)\psi_2 - g(\varphi_2))\right| \leq$$
$$q(|\varphi_1-\varphi_2|^2 + |\psi_1-\psi_2|^2)^{1/2}$$

for

$$|\varphi_i|^2 + |\psi_i|^2 \leq \rho^2 :, \quad i = 1\,,\,2,$$

and besides

$$\| G(\tau, c) \| \leq N e^{-\nu|\tau|},$$

then the condition for the integral operator in (**??**) is contracting in

$$B_\rho = \left\{ \begin{pmatrix} \varphi(\xi) \\ \\ \psi(\xi) \end{pmatrix} : \mathbf{R} \to \mathbf{R}^2 \text{ continues } |\varphi(\xi)|^2 + |\psi(\xi)|^2 \leq \rho^2 \right\}$$

is that satisfies the inequalities

$$M \leq \frac{\rho\nu}{2N}, \quad q < \frac{\nu}{2N}. \tag{9}$$

The inequations system (**??**) are satisfied for $0 < c < c_1(\rho)$ and in this case the only bounded solution of (**??**) is the stationary solution $\begin{pmatrix} \varphi_0 \\ 0 \end{pmatrix}$. To prove the second part of the theorem we denote by $K\left(\begin{matrix} \varphi \\ \psi \end{matrix}, c\right)$ the integral operator in (**??**). Then, there is $c_2(\rho) > c_1(\rho)$ such that for $0 < c \leq c_2(\rho)$, K is an operator of B_ρ in B_ρ, and their differential

$$D_{\binom{\varphi}{\psi}} K\left(\binom{\varphi_0}{0}, c\right)$$

has a norm less than 1 when

$$c_1(\rho) \leq c \leq c_2(\rho).$$

Applying the theorem of the implicit function to operator K in B_ρ it can be obtained for each $\tilde{c}$ in a neighborhood of c

$$(c_1(\rho) \leq c \leq c_2(\rho)),$$

that there is a bounded solution

$$\begin{pmatrix} \varphi(\xi, \tilde{c}) \\ \\ \psi(\xi, \tilde{c}) \end{pmatrix}$$

of (??) different to $\begin{pmatrix} \varphi_0 \\ 0 \end{pmatrix}$, which corresponds to a homoclinical solution of (??) and therefore, defines a travelling wave of (??) with speed $\tilde{c}$. We will consider in what follows a small portion of cortex where we can suppose that there is no spatial variation of the activation function. Then from (??) we obtain for $u = u(\tau)$ the following Lienard equation

$$\frac{d^2u}{d\tau^2} + (2 - V_+ g'(u))\frac{du}{d\tau} + (u - V_+ g(u)) = f_0(\tau) + c_0(\tau). \tag{10}$$

Note that on eliminating the dependence of the spatial variable y, one has to

$$c_0(\tau) = -V_-\left(\frac{\lambda_- v_-}{\lambda_+ v_+} - 1\right) e^{-\frac{\lambda_- v_-}{\lambda_+ v_+}\tau}\left[\left(\frac{a}{\lambda_+ v_+}\tau + b\right)\left(\frac{\lambda_- v_-}{\lambda_+ v_+} - 1\right) - \frac{2a}{\lambda_+ v_+}\right], \tag{11}$$

where a and b are parameters of control that depend on the initial conditions of inhibition.

Lemma 1. *The solution of the equation (??) which satisfies the initial conditions $u(0) = u_0$, $u'(0) = u_0'$, coincides with the solution of the equation of first order*

$$\frac{du}{d\tau} + u - V_+ g(u) = (f(\tau) + c(\tau) + K)e^{-\tau}, \tag{12}$$

which satisfies the initial condition $u(0) = u_0$ where

$$f(\tau) = \int_0^\tau f_0(t)e^t dt\,, \quad c(\tau) = \int_0^\tau c_0(t)e^t dt\,,$$

$$K = u_0' + u_0 - V_+ g(u_0)\,.$$

The previous lemma allows us to prove the following theorem.

Theorem 2. *If $(f(\tau) + c(\tau) + k)e^{-\tau}$ is a periodic function (something which occurs if the afferent input $f_0(\tau)$ is asymptotically periodic) and also $V_+ g'(u) < 1 : (u \in \mathbf{R}) :$, then for any value $K \in \mathbf{R}$ there is a unique periodic solution of (??) with the same previous period whose initial conditions satisfy the equality*

$$K = u_0' + u_0 - V_+ g(u_0).$$

Proof. Equation (??) is proved to have bounded solutions for which Banach's theorem of fixed point is used whose application requires condition $V_+ g'(u) < 1$. Therefore from the periodicity of $(f(\tau) + c(\tau) + k)e^{-\tau}$ [3, page 116] the existence of and unicity of periodic solution is deduced for (??) and from lemma 1 the affirmation of the theorem is concluded.

Theorem 3. *Equation (??) is controllable regards parameters a and b, that is to say for any instant $T > 0$, initial conditions u_0 :,: u'_0 and final conditions u_T and u'_T, exist parameters a and b :*

$$a = a(u_0, u'_0, u_T, u'_T, T)\,, \quad b = b(u_0, u'_0, u_T, u'_T, T)$$

for which the solution $u(\tau)$ of (??) which

$$u(0) = u_0 \ \ and \quad u'(0) = u'_0$$

executes also satisfies

$$u(T) = u_T \ and \quad u'(T) = u'_T.$$

Proof. If the solution of (??) satisfying initial conditions

$$u(0) = u_0\,, \quad u'(0) = u'_0$$

is denoted for $u(\tau, a, b)$, and we consider the transformation

$$U : \mathbf{R}^2 \to \mathbf{R}^2;$$

$$U\,\binom{a}{b} = \begin{pmatrix} u(T; a, b) \\ \\ \frac{du}{d\tau}(T; a, b) \end{pmatrix};$$

then the Jacobean matrix DU has a determinant different from the zero of the whole $\mathbf{R}^2$. From this we can conclude that the image of U is a non-empty open subset $\mathbf{R}^2$. On the other hand, if the sucesion

$$\begin{pmatrix} u(T; a_n, b_n) \\ \\ \frac{du}{d\tau}(T; a_n, b_n) \end{pmatrix}$$

is convergent of the continuous dependency of the solution of (??) regards the parameters a and b we can conclude that the limit belongs to the image of U. With this we conclude that the image of U is whole $\mathbf{R}^2$, from which we obtain equation (??) which is controllable.

4. Conclusions

Theorem 1 corresponds to the existence of physiological states which propagates itself on the cortex with a velocity lower than that of the propagation of the excitatory action potentials, just as seems to occur with rhythms of cortical activity [5], [6].

Theorem 2 tells us that cortical activity of a piece of cortex can join with that of the sustained periodic afferent input as has been obtained experimentally ([3], [4]). In [2] we also conclude the controlling role, of the inhibitory activity in the cortex, which is confirmed in *theorem* 3.

References

[1] **Daleckii Ju.L., Krein M.G.** Stability of solutions of differential equations in Banach space. American Mathematical Society, Providence, Rhode Island. 1974.

[2] **Dickson C.T., Alonso A.** Muscarinic induction of Synchronous population activity in the entorhinal cortex // Journal of Neuroscience. 1997. V.17. P.6729–6744.

[3] **Hale J. and Kocak H.** Dynamics and Bifurcations. Springer Verlag, New York. 1991.

[4] **Lukatch H.S. and Mac Iver B.** Physiology, Pharmacology and Topography of cholinergic neocortical oscillations in vitro // Journal of Neuroscience. 1997. P.2427–2444.

[5] **Nuñez, P. L. and Katznelson, R. D.** Electric Fields on the Brain, the Neurophysics of EEG. Oxford University Press, New York. 1981.

[6] **Nuñez, P. L.** Neocortical Dynamics and Human EEG Rythms. Oxford University Press. 1995.