Parameters Analysis of FitzHugh-Nagumo Model for a Reliable Simulation

Binbin Xu, Stéphane Binczak, Sabir Jacquir, Oriol Pont, Hussein Yahia

Parameters Analysis of FitzHugh-Nagumo Model for a Reliable Simulation

Binbin Xu[1,2], Stéphane Binczak[3], Sabir Jacquir[3], Oriol Pont[1,2], Hussein Yahia[1]

1 GEOSTAT, INRIA Bordeaux Sud-Ouest, Talence, France

2 LIRYC, L'Institut de RYthmologie et modélisation Cardiaque, Bordeaux, France

3 CNRS UMR 6306, LE2I Université de Bourgogne, Dijon France

Abstract

Derived from the pioneer ionic Hodgkin-Huxley model and due to its simplicity and richness from a point view of nonlinear dynamics, the FitzHugh-Nagumo model has been one of the most successful neuron / cardiac cell model. It exists many variations of the original FHN model. Though these FHN type models help to enrich the dynamics of the FHN model. The parameters used in these models are often in biased conditions. The related results would be questionable. So, in this study, the aim is to find the parameter thresholds for one of the commonly used FHN model in order to pride a better simulation environment. The results showed at first that inappropriate time step and integration tolerance in numerical solution of FHN model can give some biased results which would make some publications questionable. Then the thresholds of parameters α, γ and ε are presented. α controls the global dynamics of FHN. $\alpha > 0$, the cell is in refractory mode; $\alpha < 0$, the cell is excitable. ε controls the main morphology of the action potential generated and has a relation with the period ($P = 3.065 \times \varepsilon^{-0.8275} + 4.397$). To show oscillations of relaxation with FHN, ε should be smaller than 0.0085. γ influences barely AP, it showed linear relationship with the period and duration of action potential. Globally, when $|\alpha| \geq 0.1$, $\varepsilon < 0.0085$, there is no definite threshold for γ, but smaller values are recommended.

1 Introduction

FitzHugh-Nagumo (FHN) model [1,2] has been since long time one of the basic models to study the cardiac / neuron dynamics, due to its simplicity (2 variables, 3 parameters) and relation to ionic models. It is also the second most cited cardiac / neuron model. The original model respects basically the conditions derived from the Hodgkin-Huxley model [3]. So, it can be considered as physiologically correct in certain

conditions. However, there is nowadays important parameters' diversity in studies with FHN model, which are often considered them as the default / original ones. Unfortunately, this is not always true.

History became legend. Legend became myth. It has been more than 60 years since the publication of FHN model. Today's FHN model is rather than generalized, somehow lost the original conditions of its parameters. The derived models would help to understand FHN model from different aspects. But they act indeed differently. The obtained result could be sometime questionable and even misleading, when inappropriate conditions are applied.

So the aim of this study is to find the parameter thresholds for one of the commonly used FHN model. We track back to the origin of the FHN model in Section 2. In Section 3, we present at first that a problem from numerical solution of FHN model can indeed give some biased results which would make some publications questionable. Different parameter threshold and their relationship with the period of action potential are then presented.

2 Models

2.1 A little history of FitzHugh-Nagumo model

1928, Van der Pol model

The first model to representing the heart's dynamics is the Van der Pol model (BVP) [4]. In 1928, Van der Pol proposed a heartbeat equation based on the concept "relaxation-oscillations" system :

$$\ddot{v} - \alpha\left(1 - v^2\right)\dot{v} + \omega^2 v = 0, \tag{1}$$

where α determines the main dynamics : smaller α makes the system output be more-likely sinusoidal; larger values of α can produce oscillations of relaxation. This equation is then commonly studied as $\ddot{v} - \alpha\left(1 - v^2\right)\dot{v} + v = 0$ by setting $\omega = 1$.

1952, Hodgkin-Huxley model

In 1952, Hodgkin and Huxley presented in their pioneer work a four-dimensional model (V, m, h, n) of ionic mechanisms underlying current conduction and excitation of action potential (AP) in nerve [3] (HH), which opened a door to a new era of electro-physiological studies. Even though it considers only sodium

activation m, sodium inactivation h and potassium activation n, its "gating concept" has become the framework of electro-physiological models. They received the 1963 Nobel Prize in Physiology or Medicine for this work. It is today the most cited physiological model (14695 times, *data from Google Scholar on March 16, 2014*).

1961, FitzHugh model

In a series of studies of 1950's, FitzHugh found that BVP model can serves as a simple representative of a class of excitable-oscillatory systems including the HH model. In 1961, using BVP model and the Lienard transformation $y = \dot{x}/c + x^3/3 - x$ [5], he proposed a two-dimensional model [1] of the electrical activities of nerve membrane (x corresponding to v in Eq. (1)) :

$$\dot{x} = c\left(y + x - x^3/3 + z\right), \quad \dot{y} = -\left(x - a + by\right), \tag{2}$$

where $1 - 2b/3 < a < 1$, $0 < b < 1$, $b < c^2$.

1962, Nagumo's electrical circuit and Nagumo's equation

In 1962, Nagumo et al. confirmed this model (Eq. (2)) with experimental evidence from an electrical circuit model [2]. In this work, they proposed also a mathematical models of the nerve axon (z : normalized potential) :

$$\frac{\partial^3 z}{\partial t \partial x^2} = \frac{\partial^2 z}{\partial t^2} + \mu(1 - z + \epsilon z^2)\frac{\partial z}{\partial t} + z, \tag{3}$$

where $\mu > 0$, $\frac{3}{16} > \epsilon > 0$. In fact, this transmission line simulator of nerve axon can be found in another work of theirs in 1961 [6], same time as FitzHugh's work. Later in 1965, Nagumo et al. [7] proposed a more general active transmission equation in neuron :

$$\frac{\partial^2 u}{\partial x^2} = \frac{\partial u}{\partial t} + (u + 1)(u - m)(u - 1), \tag{4}$$

where $0 \geqslant m > -1$. It is known as *Nagumo's equation*. Due to their equal contribution, the Eq. (2) is thereby named as FitzHugh-Nagumo model (FHN).

2.2 Today's FitzHugh-Nagumo model

The success of FHN model is not only due to its mathematical simplicity and its richness from a point of view of system dynamics, but also because of its correlation to HH model. In fact, the four-dimensional HH model could divided into two subsystems: (V, m) corresponds to v in FHN, fast dynamics representing excitability; (h, n) corresponds to w, slow dynamics representing accommodation and refractoriness. In consequence, the result obtained with FHN model can be qualitatively interpreted as other ionic models. For these reasons, FHN model becomes thus one of the most studied models in analytical neuroscience / electrocardiology.

Many variations of FitzHugh-Nagumo model have been derived from the original one. One of the most used is :

$$\dot{v} = v(v-\alpha)(1-v) - w, \quad \dot{w} = \varepsilon(v - \gamma w), \tag{5}$$

where α is considered playing a dominant role in the fast dynamics (sodium currant) of the FHN model. The condition of α is commonly chosen as $\alpha > 0$ (either $0 < \alpha < 0.5$ or $0 < \alpha < 1$) to keep its qualitative electro-physiological meaning. However it is in contradiction to the one in Nagumo's equation.

2.3 So, what is the real condition for α ?

Eq. (5) is in fact a variation of the combination of FitzHugh's model (Eq. (2)) and Nagumo's equation (Eq. (4)). This model takes advantages of both models : global dynamics from FitzHugh's model and more generalized cubic function from Nagumo's equation. The cubic functions from Eq. (2) and Eq. (5) can be represented respectively :

$$f(x) = x - \frac{x^3}{3} = -\frac{x}{3}\left(x + \sqrt{3}\right)\left(x - \sqrt{3}\right), \tag{6a}$$

$$f(v) = v(v-\alpha)(1-v) = -v\,(v-\alpha)\,(v-1)\,. \tag{6b}$$

Eq. (6) implies in a intuitive way that, to ensure that the model could produce electrical wave pulse (in other wards, *excitable*), α in Eq. (5) should be negative. However, this does not mean that positive α is wrong. In fact, $\alpha > 0$ in Eq. (5) means that the cell simulated with FHN model is in refractory mode. In this period, external stimulation cannot provoke action potential.

3 Results

3.1 Integration tolerance and time step

Many studies showed that FHN model can be used to study chaotic phenomena in neuron system. However, they are mostly based on discrete Euler method. As a first-order method, the local error of Euler method is proportional to the square of the step size. Its global error is proportional to the step size. To obtain relatively reliable results with Euler method for nonlinear stiff ODE systems like FHN, very small integration step size is only the basic condition. Even this condition is satisfied, the stability cannot be fully guaranteed. For these reasons, Euler method is not recommended for practical use [8].

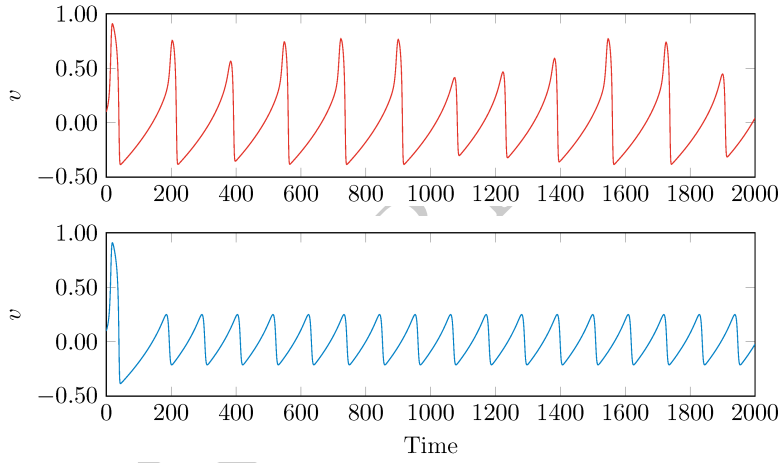

Figure 1. Different v due to numerical integration tolerance error, fourth-order Runge-Kutta method. Upper figure with RelTol: 1e-3 and AbsTol: 1e-6; lower figure with RelTol: 1e-7 and AbsTol: 1e-10. Parameters : $\alpha = 0.008$ (upper figure), $\alpha = -0.008$ (lower figure), $\gamma = 0.008$, $\varepsilon = 0.01$; initial conditions : $v_{\text{ini}} = 0.1$, $w_{\text{ini}} = 0$; adaptive time step.

Taking the same parameters and initial conditions, the first simulation is performed with larger tolerance (RelTol: 1e-3 and AbsTol: 1e-6), we obtained a arrhythmia-type v (Fig. 1, upper) which is misleading. Since the true result should be regular (Fig. 1, lower. smaller tolerance : RelTol: 1e-7 and AbsTol: 1e-10). It showed that if the stability condition is not satisfied, small numerical integration tolerance could "distort" the final results (even with high order integration methods). Especially in case of reaction-diffusion equations, the false new result could serve as *stimulation* to the system. If this stimulation happened in excitable mode, an action potential can be provoked. Since the *new stimulations* are not constant; the amplitude of newly provoked action potentials would be therefore irregular. In this way, a *cardiac arrhythmia* with FHN model can be generated. This phenomenon is in fact a course of

different stimulation to the cell, instead of one real *cardiac arrhythmia*. The results are thus questionable. In consequence, all other simulations presented in this study are performed with smaller error tolerance.

3.2 $\alpha > 0$ vs $\alpha < 0$

If $\alpha = 0$, the cubic function in Eq. (5) will be $f(v) = v^2(1 - v)$. This is a special case of FHN model and lost the generality of the model. So, only $\alpha \neq 0$ is studied. Two cases are considered : single cell and tissue (cells grid).

Single cell

All other parameters in this section are the same except for α. As shown in Fig. 2, when $\alpha > 0$, since the membrane is in refractory period, external stimulation (initial condition serves as a single stimulation) cannot induce an AP in the membrane. So the potential v decreases exponentially to resting state. However, if $\alpha < 0$, the membrane is in excitable period. Even a small initial stimulation ($v_{\text{ini}} = 0.1$) can

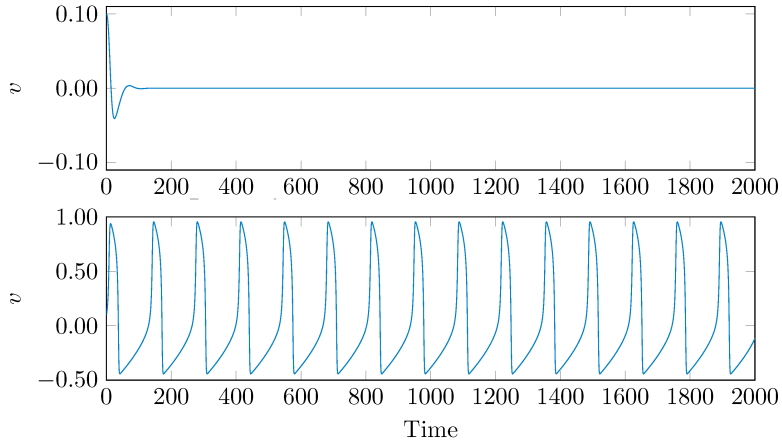

Figure 2. Comparaison of $\alpha = 0.1$ (upper) and $\alpha = -0.1$ (lower) in FHN model (Eq. (5)). Parameters : $\gamma = 0.008$, $\varepsilon = 0.01$; initial conditions : $v_{\text{ini}} = 0.1$, $w_{\text{ini}} = 0$; adaptive time step.

provoke a pulse train with full amplitude.

Tissue

two-dimensional cells grid. Eq. (5) becomes in this case :

$$\dot{v} = \mathrm{D}\Delta v + v(v - \alpha)(1 - v) - w, \quad \dot{w} = \varepsilon(v - \gamma w),$$

where D is the diffusion parameter and Δ is the Laplace operator (4 points scheme in this study). The following simulations are based on isotropic cells grid 200×200, $\mathrm{D}_x = \mathrm{D}_y = 0.1$. The parameters are respectively: $\alpha = 0.1$ ($\alpha = -0.1$), $\gamma = 1\mathrm{e}-4$ and $\varepsilon = 0.005$.

One of the common illustrations of FHN model is to simulate the plane wave propagation. As shown in Fig. 3, if the tissue is initiated with border non-null condition. Plane wave can be provoked. $\alpha < 0$ in excitable mode. When $\alpha > 0$, only one plane wave is generated; if $\alpha < 0$, this initial condition became a

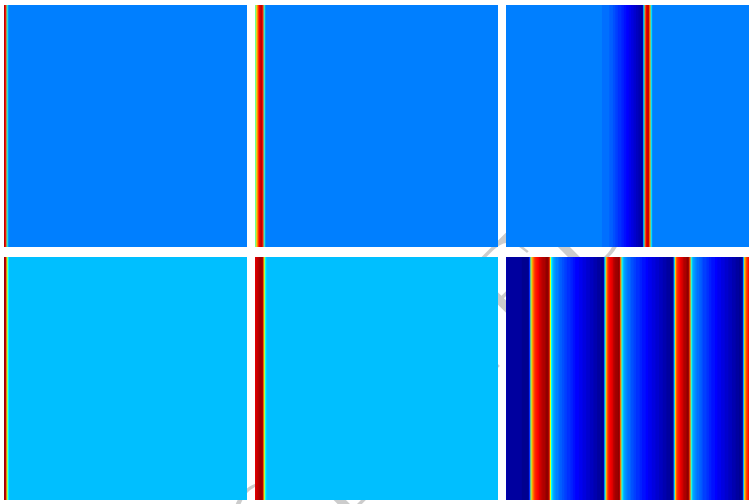

Figure 3. $\alpha = 0.1$ (upper) and $\alpha = -0.1$ (lower), border initiation : $v_{\mathrm{ini}}(1, 1:200) = 1$, zeros for other cells; $w_{\mathrm{ini}}(1:200, 1:200) = 0$.

wave source. These two results implied same conclusion as in Fig. 2 : $\alpha > 0$ in refractory period.

However, the reason of the plane wave generation in last figure when $\alpha > 0$ is that border initiation is a special case of two-dimensional simulation. It is in fact due to the boundary condition of discrete Δ. Applying a center initiation to the tissue (Fig. 4), $\alpha > 0$ cannot indeed provoke a wave as in Fig. 3. For negative α, multiple circular waves are generated, which confirmed once more previous conclusion. To generate wave in case of $\alpha > 0$, continuous stimulation is needed:

$$\dot{v} = \mathrm{D}\Delta v + v(v-\alpha)(1-v) - w + I_{\mathrm{stim}}$$

As shown in Fig. 5, a single circular wave is provoked in the tissue. The tissue is nevertheless in a refractory period. For these reasons, no other waves are generated.

This result is also important in clinical applications, for example the defibrillation by sub-threshold stimulation. To terminate fibrillation using multiple sites simulation of small amplitude, it is necessary

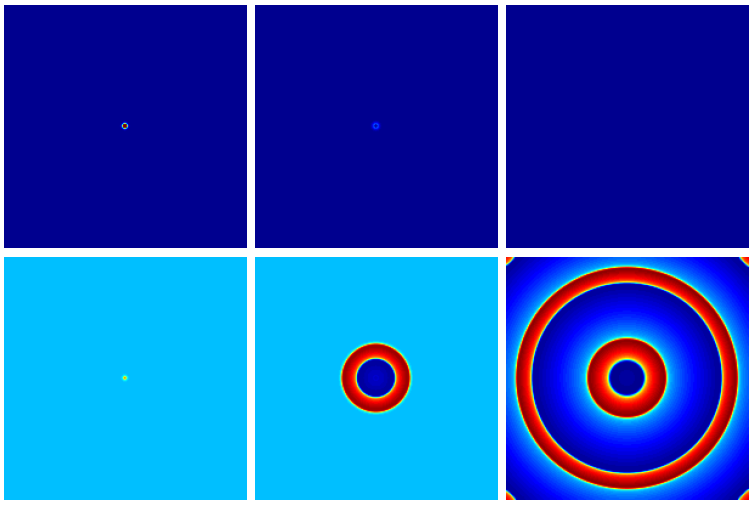

Figure 4. $\alpha = 0.1$ (upper) and $\alpha = -0.1$ (lower), center initiation : $v_{\text{ini}}(100, 100) = 1$, zeros for other cells; $w_{\text{ini}}(1 : 200, 1 : 200) = 0$.

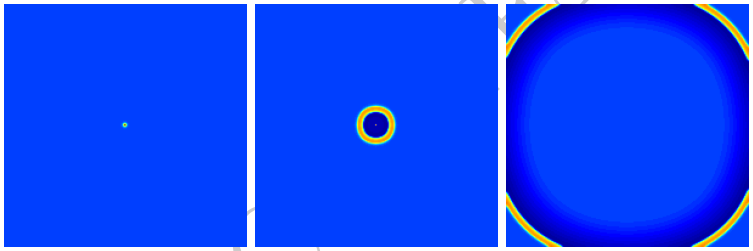

Figure 5. $\alpha = -0.1$ (upper) : center stimulation, $I_{\text{stim}}(100, 100) = 1$

to reduce firstly tissue's excitability, otherwise the defibrillation cannot be achieved [9]. Results in this section confirmed that if the tissue is in excitable mode ($\alpha < 0$), external stimulation will become an ectopic focus. In realistic situation, collision of new waves will generate spiral wave which makes the defibrillation be unsuccessful or even worse.

3.3 Parameters' thresholds

In this section, the aim is to determine the influence of the three parameters α, γ and ε on the action potential's cycle length (period) and duration APD90 (Action Potential Duration at 90%). So some reasonable thresholds could be obtained. After the preliminary study, the final testing ranges for γ and ε are $0.001 : 0.0025 : 0.25$, α is in $-0.25 : 0.0025 : -0.001$. In total, 10^6 simulations have been performed.

As shown in Fig. 6, ε influences dramatically the period of AP. Since ε controls the recovery current in FHN model, so larger ε means larger w, so v will thus be reduced. In fact, ε has a power function

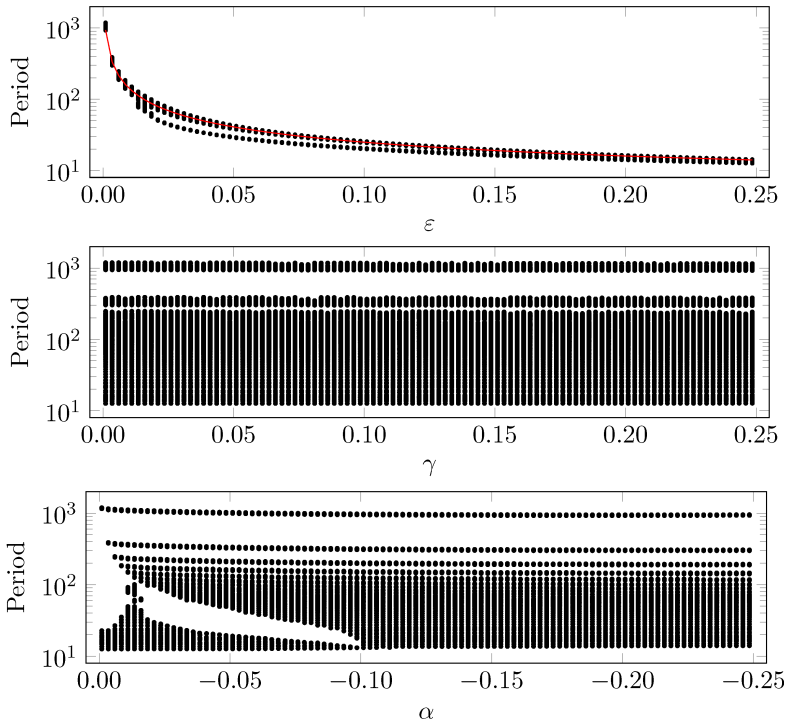

Figure 6. Parameters' influence on period of AP in FHN. Red curve in first sub-figure is the fitted curve : Period $= 3.065 \times {\varepsilon_{\alpha,\gamma}}^{-0.8275} + 4.397$. (*discontinuity in third sub-figure means no valid AP generated.*)

relationship with period P :

$$\mathrm{P} = 3.065 \times {\varepsilon_{\alpha,\gamma}}^{-0.8275} + 4.397, \tag{7}$$

which is shown in the first sub-figure of Fig. 6. Fixing ε and α, γ is linear to the period. This relationship reflects the property of first order of w from Eq. (5). As discussed previously, α should be negative in order to produce an AP train. However, this is just one of the conditions. Even $\alpha < 0$, FHN cannot always produce valid action potential (3^{rd} sub-figure in Fig. 6). It depends also on ε and γ. When $\alpha > -0.1$, there exists a region where no valid AP is provoked. If $\alpha < -0.1$, α and period of AP have practically a linear relationship.

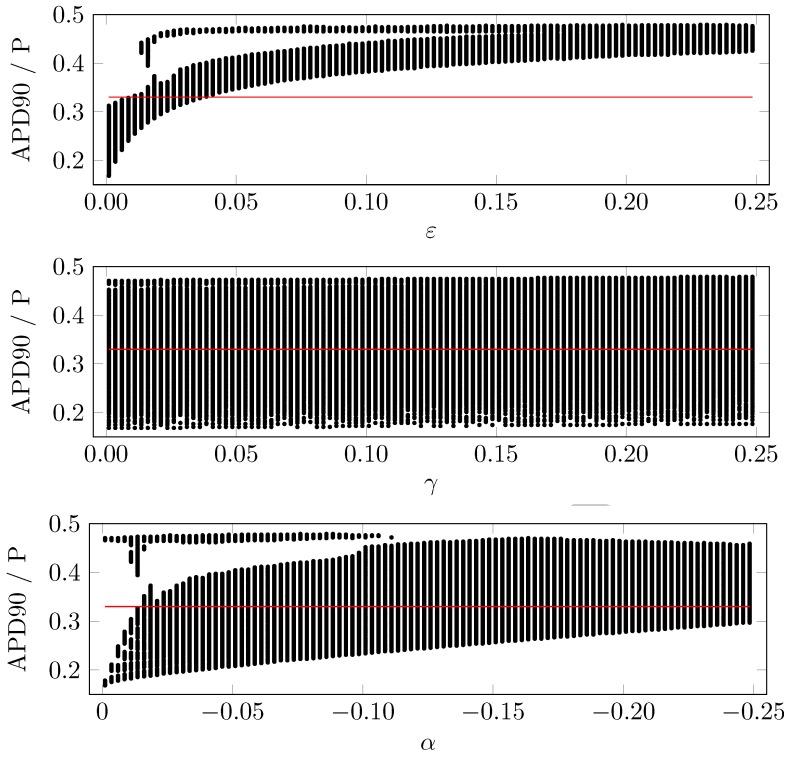

Figure 7. Ratio of Period/Duration. Red line is the ratio threshold at 0.33

The relationships between the duration of AP and these three parameters are almost the same as those for period. To determine their thresholds, we introduce the ratio R_{DP} between the AP period and its duration (Fig. 7). We found if $R_{\mathrm{DP}} > 0.33$, only sinusoidal signal are observed. In this case, the FHN lost its essential *oscillations of relaxation* property that it is designed for. To respect this property, it should be $R_{\mathrm{DP}} \leq 0.33$. In consequence, the strict condition for ε should be $\varepsilon \leq 0.0085$ to generate oscillations of relaxation. Under this condition of ε, then α and γ can be chosen properly. It is advisable to avoid the interval $-0.1 < \alpha < 0$ due to the constraint shown in Fig. 6. As for γ, no absolute threshold exists. So small values are recommended, as conventionally did.

4 Conclusion

In this article, we studied the parameters ε, γ and α in FitzHugh-Nagumo model. It is clear now that α controls the global dynamics of FHN. $\alpha > 0$, the cell is in refractory mode and does not respond to external stimulation; if $\alpha < 0$, the cell is excitable. ε controls the main morphology of the action potential

generated and has a relation with the period ($P = 3.065 \times {\varepsilon_{\alpha,\gamma}}^{-0.8275} + 4.397$). When $\varepsilon > 0.0085$, the obtained curves are more likely to be sinusoidal. To show oscillations of relaxation with FHN, ε should be smaller than 0.0085. γ influences barely AP, it showed linear relationship with the period and duration of AP. When $\alpha \leq 0.1$ and $\varepsilon < 0.0085$, γ can be freely chosen for excitable cell, but smaller values are recommended. Another issue in numerical studies of FHN model is the error tolerance and the order of integration method. It is better to avoid using low order integration methods; otherwise, the integration stability error would alter the results and lead to questionable conclusion.

References

1. R. Fitzhugh, "Impulses and physiological states in theoretical models of nerve membrane," *Biophysical Journal*, vol. 1, no. 6, pp. 445–466, 1961.

2. J. Nagumo, S. Arimoto, and S. Yoshizawa, "An active pulse transmission line simulating nerve axon," *Proceedings of the IRE*, vol. 50, no. 10, pp. 2061–2070, 1962.

3. A. Hodgkin and A. Huxley, "A quantitative description of membrane current and its application to conduction and excitation in nerve," *The Journal of physiology*, vol. 117, no. 4, p. 500, 1952.

4. B. van der Pol and J. van der Mark, "The heartbeat considered as a relaxation oscillation, and an electrical model of the heart," in *Philosophical Magazine Series 7*, vol. 6, pp. 763–775, Nov. 1928.

5. N. Minorsky, *Introduction to non-linear mechanics: topological methods, analytical methods, nonlinear resonance, relaxation oscillations*. J.W. Edwards, 1947.

6. J. Nagumo and M. Shimura, "Self-oscillation in a transmission line with a tunnel diode," *Proceedings of the IRE*, vol. 49, no. 8, pp. 1281–1291, 1961.

7. J. Nagumo, S. Yoshizawa, and S. Arimoto, "Bistable transmission lines," *Circuit Theory, IEEE Transactions on*, vol. 12, no. 3, pp. 400–412, 1965.

8. W. H. Press, S. A. Teukolsky, W. T. Vetterling, and B. P. Flannery, "Integration of ordinary differential equations," in *Numerical Recipes : The Art of Scientific Computing*, ch. 17, pp. 899–954, Cambridge University Press, 2007.

9. B. Xu, S. Jacquir, G. Laurent, *et al.*, "A hybrid stimulation strategy for suppression of spiral waves in cardiac tissue," *Chaos, Solitons & Fractals*, vol. 44, pp. 633–639, aug 2011.