Dynamics analysis of excitable cells models for myocardial tissue and neuronal networks simulation

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28th January 2007

Abstract

Modelling oscillations is fundamental for the simulation of a large set of biological phenomena such as the heart pulse, polulation cycles, annual blooming of plants and neuronal systems. In this paper we study the dynamics of some well-knonw oscillations models used for biologic systems: the Van der Pol, Fizhugh-Nagumo *and* Aliev-Panfilov *models. We than investigate why these models are so important for the simulation of excitable cells like neurons and myocardiac cells.*

1 Relaxation oscillations

In 1926 *Van der Pol*[3] discovered that triode circuits exibit self-sustained oscillations with an amplitude independent from the initial conditions.

Within a certain range of parameters such systems produce sinusoidal oscillations, while for other ranges the oscillations, called *relaxation oscillations*[2], exibit sudden changes. The main characteristics of this type of phenomena is then the presence of discontinuous jumps (Fig 1) together with the threshold value implicitly shown by the nonlinear system (all-or-none law).

This kind of oscillations, drastically different from sinusoidal and harmonic oscillations, appears to be common in nature and it finds application in many science fields such as physics, chemistry, engineering and in our particular case: biology.

A huge variety of models have been developed to simulate the behavior of these systems, however we will consider only three of the most common models for myocardial (*Van der Pol* model) and neuronal (*Fizhugh-Nagumo* and *Aliev-Panfilov* models) excitable cells.

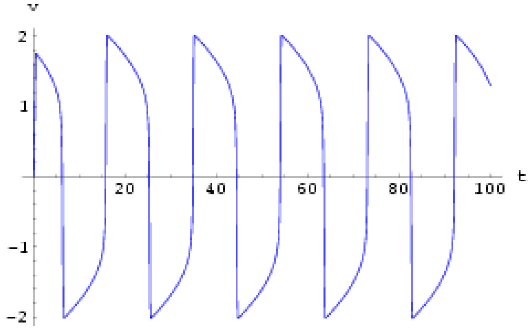

Figure 1. A tipical relaxation oscillation

2 Van der Pol equations

The *Van der Pol* model describes the behavior of electrical circuits employing vacuum tubes under certain system parameters. The same system of equations is also useful on modelling myocardiac tissue and though beat propagation through the heart.

As discussed above they present the tipical *relaxed* oscillatory response and they are described by the following nonlinear system:

$$\begin{aligned}\frac{\partial v}{\partial t} &= f(v,w) = \frac{1}{\epsilon}(w - \frac{v^3}{3} + v)\\ \frac{\partial w}{\partial t} &= g(v) = \epsilon v\end{aligned}$$

Where is usual to assume $0 < \epsilon \ll 1$. As we said the system is non linear, thus we need to perform a qualitative analysis of its dynamics using *Mathematica*.

2.1 Stability

Imposing the conditions:

$$\begin{aligned} f(v,w) &= 0 \\ g(v) &= 0 \end{aligned}$$

The system presents only one equilibrium point in $v = 0$, $w = 0$. The stability is given by the real part of the eigenvalues of the *Jacobian* matrix related to the system. We can though consider an equilibrium point as *stable* only when having negative real parts of every eigenvalues.

Plotting the eigenvalues as function of the parameter ϵ we obtain the plot shown in figure 2.

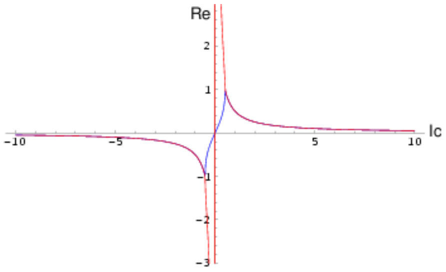

Figure 2. Real part of the eigenvalues in (0, 0)

The graph proves that for positive values of ϵ we have an unstable equilibrium point on (0, 0).

2.2 Dynamics of the system, experiments

The next step is to study the direction field of our system in the v-w plane. Drawing the nullclines of our two equations we can have a quite clear idea of the dynamics of the system respect to the time. We don't yet know the solution but we know its derivatives respect to the time.

Therefore, imposing the initial conditions to $v(0) = 1$, $w(0) = 1$ together with the parameter $\epsilon = 0.1$ we can trace an orbit representing one of the particular solutions (fig 3).

On dealing with oscillatory systems one important step is to prove the existence of a limit cycle to which the system converges when the time tends to infinity. Finding the limit cycle is a nontrivial problem, however we can observe that our system has a bounded region *D* on which any entering trajectory cannot leave it.

This annular region around our fixed point contains no equilibrium point. Is however presents one equilibrium point on its focus (our fixed point indeed), proved to be unstable. These conditions are enough to apply the *Poincaré Bendixson Theorem*[8] proving the existence of the limit cycle in the closer orbit of *D*. As a corollary we proved that our system does not present *chaos*[10].

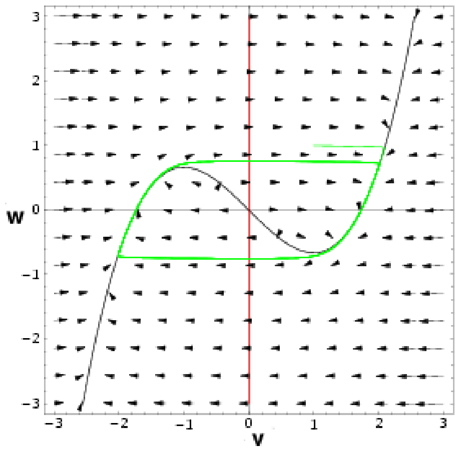

Figure 3. Phase portrait for $v(0) = 1$, $w(0) = 1$, $\epsilon = 0.1$

Finally, to trace the exact solution respect to the initial condition we can use the numerical solver availables on *Mathematica* displaying the orbit and the behavior of the solution $v(t)$ as in figure 4.

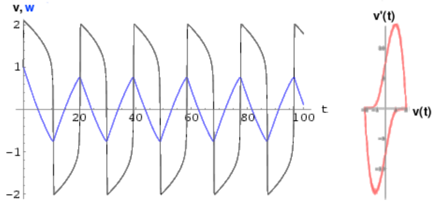

Figure 4. Solution of Van der Pol for $v(0) = 1$, $w(0) = 1$, $\epsilon = 0.1$

2.3 Linearisation

It is obiously possible to write the shown *Van der Pol* equations as a single second order ODE by solving as follows:

$$\begin{aligned} \epsilon\frac{\partial v}{\partial t} - \frac{v^3}{3} + v &= w \\ \frac{\partial w}{\partial t} &= -\epsilon v \\ \epsilon\frac{\partial^2 v}{\partial t} + v^2\frac{\partial v}{\partial t} - \frac{\partial v}{\partial t} &= -\epsilon v \\ \epsilon\frac{\partial^2 v}{\partial t} + (v^2 - 1)\frac{\partial v}{\partial t} + \epsilon v &= 0 \end{aligned}$$

The *Taylor* series imposes that when we have a function, even though non linear f(x), we can approximate it in the neighbourhood of a point v_0 as follows:

$$f(x) \quad = \quad f(x_0) + f'(x_0)(x - x_0) + O(x^2)$$

For $|v| \ll 1$ we can easily linearising the system obtaining:

$$\epsilon \frac{\partial^2 v}{\partial t} - \frac{\partial v}{\partial t} + \epsilon v \quad = \quad 0$$

Comparing the linearized system with the original one we can now evaluate the goodness of our approximation by plotting the linear and non linear solution as in figure 5. We are considering as initial parameters $\epsilon = 0.6$, $v(0) = 0$ and $\frac{\partial v}{\partial t} = 1$ for $t = 0$.

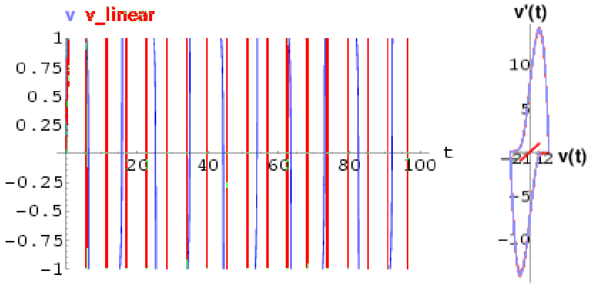

Figure 5. Comparison between linear (red) and non linear (blue) systems

Furthermore, the phase portrait (direction field together with the nullclines and the orbit) gives us a more detailed interpretation of the dynamics of the linearised model (fig. 7).

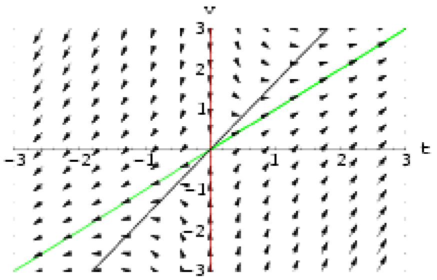

Figure 6. Phase portrait of the linear system

Analysing the system for $t \to \infty$ we obtain the behavior shown in figure 7. In this case the system seems to diverge to $-\infty$.

We can clearly observe that the linearised system is a quite raw approximation of our initial model. However the linearised system seems to describe fairly well the fast-process of the oscillation while it represents very badly the slow-process. We in fact imposed the approximation to be computed around the point v_0, during the fast-process of our solution. Only in this narrow range therefore, the linearised system solution tends to overlap the nonlinear one, showing a quite good approximation.

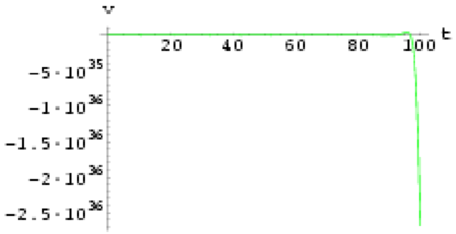

Figure 7. Limit for $t \to \infty$ of the linear solution

3 Fitzhugh-Nagumo equations

The *Fitzhugh-Nagumo*[4][5] model describes a prototype of an excitable cell such as a neuron. It consists on a simplified version of the *Hodgkin-Huxley* model.

Contrary to the *Hodgkin-Huxley*[7], the electro-chemical behavior of the cell membrane due to the sodium and potassium ions is not modeled in the *Fitzhugh-Nagumo* model where that features are captured by the parameters I, a, γ and ϵ. The equations for the dynamical system read:

$$\begin{aligned} \frac{\partial v}{\partial t} &= f(v,w) = I - v(v-a)(v-1) - w \\ \frac{\partial w}{\partial t} &= g(v,w) = \epsilon(v - \gamma w) \end{aligned}$$

As the *Van der Pol* model, this model produces relaxation oscillations. In particular for a=0 and γ=0 the system behaves exactly as a *Van der Pol* oscillator. The above equations actually models a current pulse injected into an axon of a neuron which can then generate a response defined as *action potential* under certain circumstances.

3.1 Stability

We start studying the fixed points and their stability for the parameters $\epsilon = 0.008$, a = 0.139 and $\gamma = 2.54$. For these values we have a single real solution for the system which corresponds to a single equilibrium point. Plotting the eigenvalus curves we obtain the graph in figure 8.

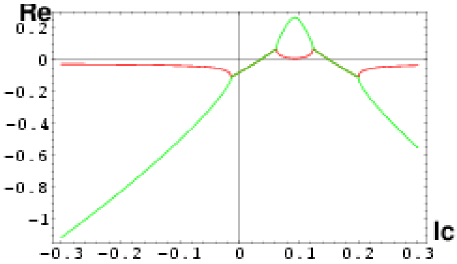

Figure 8. Real part of the two eigenvalues for the single fixed point

It appears clearly that the system remains in a stable state, called *excitable* state, until we inject a certain amount of current I_c.

For very high values of current however, the system returns to a stable state probably due to the oscillator saturation. Therefore, injecting current with a value between the described range, we can excite the neuron switching the system to the *oscillatory* state and causing a *firing* of the neuron directed to the neighbours through its dendrites. The entire phenomena is known as *charge-fire-rest* process[8] and can be easily understood from the figure 9.

3.2 Bifurcations

In order to understand the dynamic of the fixed points of the system on varying the injected current we have to study its bifurcations. As we said previously, our system presents a single fixed point (for the imposed parameters) which looses stability with an *Hopf* bifurcation (the w-nullcline slope is larger than 1).

Changing the parameters in order to produce a w-nullcline slope smaller than 1 however, results on a bistable system (with 2 stable and 1 unstable fixed point) where no oscillations occur.

3.3 Dynamics of the system, experiments with constant current

We now study the orbit of the solution for constant values of I: first we impose I=0.1 and then I=0.01, both with initial conditions v(0)=0.5 w(0)=0.1. The resulting phase portraits are shown in figures 9 and 10.

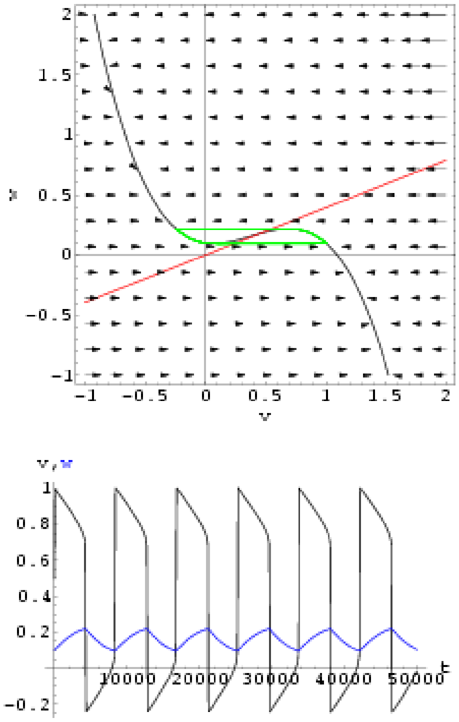

Figure 9. Phase portrait and solution of the system for I=0.1

As we expected, in the first case we are able to destabilize the system injecting enough current. Contrary in the second case we have no oscillatory response and the system falls into its stable equilibrium point according to the capacitor discharge law $e^{-t/\tau}$.

As shown above though, we have an oscillatory system which is quite similar to the one described by the *Van der Pol* model: destabilizing the fixed point we switch between a excitable state to a limit cycle, producing relaxation oscillations.

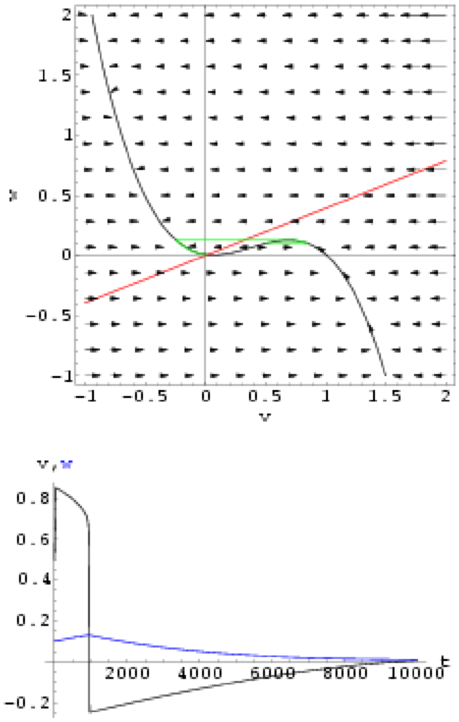

Figure 10. Phase portrait and solution of the system for I=0.01

3.4 Dynamics of the system, experiments with non constant current

The next step is to analyze the system for non constant injected currents. We want to study in fact the reaction of the neuron to an external stimulus induced in the reality by another neuron connected to its axon.

We already investigate the oscillatory behavior of this type of excitable cell and we know the response under certain constant stimuli. Under these assumptions we now perform a set of experiments with pulsing injected currents by starting from a single pulse with tunable intensity and period as in figure 11.

We discovered that for every experiment the system does not switch to oscillatory. We of course obtain the first firing due to the charging of the neuron but no continuous oscillations appear.

In this second case instead, we modeled square wave of pulses with tunable period, intensity and duty-cycle, simulatating a *PWM* control. The results are very interesting as shown in figure 12.

As depicted in the second graph it seems the neuron needs a particular continuous stimulus to switch to an oscillatory state.

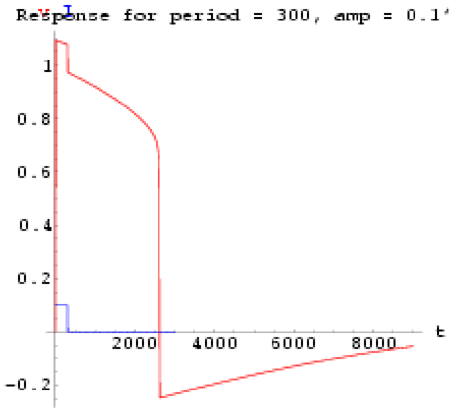

Figure 11. Solution for a single pulse of current with period=300s and amplitude=0.1mV

In particular it is triggered from those stimuli that appear to form a coherent object. Unrelated stimuli cause no oscillations. These results are coherent with the *temporal correlation* theory which describes the pattern perception of the brain depending on the temporal correlation among the firing activities of the neurons.

Under certain contidions of coherence of the input signal the neuron is though able to *carry* it further, resulting in the creation of groups of neurons which act as a single oscillator.

A synchronization among a group of neurons produces in the large scale the perception of a pattern. Multiple synchronized oscillators desynchronized between each others permit to represent a set of patterns, such different objects of a scene.

The main application of this issue are the *LEGION* (Locally Excitatory Globally Inhibitory Oscillator Networks) networks[8] where the neurons are connected to the immediate neighbours.

The original descripion used *Termal-Wang* oscillators on which was applyed a gaussian noise to test robustness and assist desynchronization. A global inhibitor acts as a feedback for the system and a constant sync-desync process results in the capacity of the network to recognize patterns. A tipical usage of such type of neuronal network is for example *image segmentation*. Further information about LEGION networks can be found on [8].

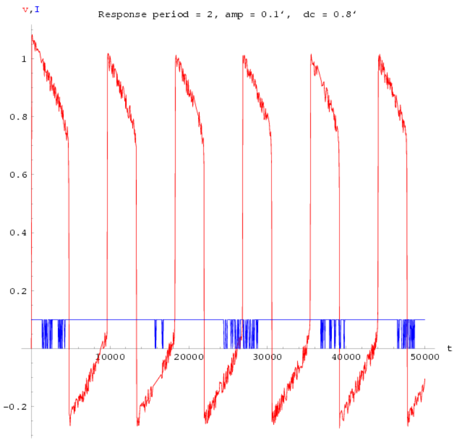

Figure 12. Solution for a pulse wave with period=2s, amplitude=0.1mV, duty-cycle=80%

4 Aliev-Panfilov model

The *Aliev-Panfilov model*[6] is a modification of the *Fitzhugh-Nagumo* model developed to describe adequately the dynamics of myocardial pulse propagation. Comparing the following two equation of this model for the fast and slow processes:

$$\begin{aligned}\frac{\partial v}{\partial t} &= \frac{\partial d_{i,j}}{\partial x_i}\frac{\partial v}{\partial x_j} - kv(v-a)(v-1) - vw \\ \frac{\partial w}{\partial t} &= \epsilon(v,w)(-w - kv(-w - kv(v-a-1))\end{aligned}$$

where $\epsilon(v,w) = \epsilon_0 + \frac{\mu_1 w}{(v+\mu_2)}$, k = 8, a = 0.15, ϵ_0 = 0.002 and $d_{i,j}$ represents the conductivity of the system. The model is very similar to the *Fitzhugh-Nagumo*, however the last term of the first equation is in this case *uv* instead of only *v*. This improves the description of the shape of the action potential, much more important on modelling myocardial tissue.

Studying the nullclines of the system depicted in figure 13, we can observe that the cubic curve referring to the *u-nullcline* has a lower slope respect to the same nullcline in the *Fitzhugh-Nagumo* model.

This characteristic prevents the system from becoming *super-repolarized*, feature which is modeled by the FHN equations but does never occurs on real myocardium. Some adaptations had been performed also for the *w-nullcline*, which in this case is no more linear but cubic as well as the *v-nullcline* in order to fit more appropriately the real cell behavior. Our results from the stimulation of the system with single and multiple current pulses are shown in figure 14 and 15. Here as in the previous experiments with multiple pulses we can capture the synchronization process that is taking place.

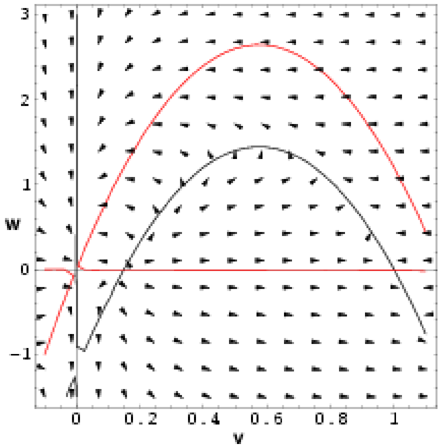

Figure 13. Phase portrait of the nullclines of the system

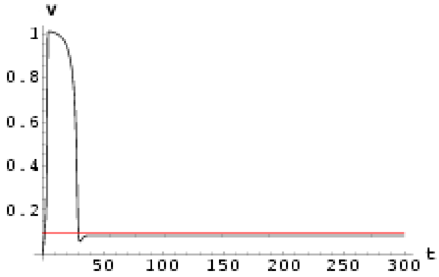

Figure 14. Solution for a single pulse of current

Using this model, together with a geometric model of the heart, becomes possible to study the propagation of the heart pulse on partially damaged tissue. This kind of simulation permits to study and also predict arrythmia and then cardiac attack phenomena.

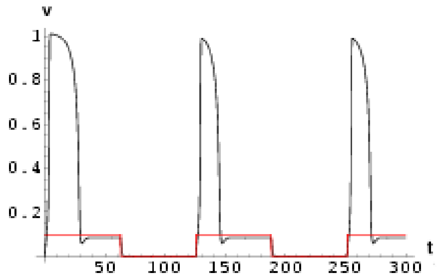

Figure 15. Solution for a pulse wave with period=0.1s, amplitude=0.1mV and duty-cycle=50%

5 Conclusions

The models discussed in this paper find applications in many scientific fields. In particular, regarding the simulation of excitable cells, for the *Van der Pol* and *Aliev-Panfilov* models we discussed about arrythmias predictions. In the same way the *Fitzhugh-Nagumo* model is used for LEGION networks discussed previously.

From a wider point of view, we deal with the nontrivial problem of passing from the real system to the simulation. The objective of this process is to create a simple, correct and computable mathematical representation of the reality. This means we have to be able to zoom out from the local atomic/molecular behavior to the global behavior, going through several factors of scale.

Each approximation of the model has to be verified experimentally needing a huge effort; however once we have a description of the model with the discussed properties we can go further on study the real system from a higher point of view.

Concluding, this process involves several tasks: from the experimental observation, through the mathematical analysis of the problem and its validation, reaching the final simulation. Each single step has to be performed using a coherent and precise approach exploiting the feedback response of correctness from the other rings ot the process chain.

6 References

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