

Integrate-and-Fire Neurons and Circle Maps

HUMBERTO CARRILLO

Laboratorio de Dinámica no Lineal

Facultad de Ciencias, Universidad Nacional Autónoma de México

MIGUEL ANGEL MENDOZA REYES

Universidad de la Ciudad de México

FERNANDO ONGAY LARIOS

Universidad Autónoma del Estado de México

<http://www.dynamics.unam.edu/>

Abstract: - Integrate-and-fire ($I+F$) systems are ubiquitous in nature and neurons constitute a conspicuous example. The interaction of nerve cells in a neural network frequently involves the transmission of periodic signals. On the other hand, the investigation of the dynamics of a periodically stimulated $I+F$ system is a difficult and classical problem of nonlinear oscillation theory, of interest not only to Neurophysiology but to many others fields of science and engineering. In this paper, we present a simple mechanical integrate-and-fire system that mimics the process of periodic stimulation of a neural pacemaker; we use it to illustrate the application of the mathematical theory of circle maps when investigating this "mechanical cell's" response to external stimulation. In particular, we discuss the importance of some regularity properties —continuity and injectivity— of the system's firing circle maps, in helping to understand the synchronization phenomena that manifest themselves in this scenario.

Key-Words: - Neuron models, Integrate-and-fire systems, Forced oscillators, Synchronization, Relaxation oscillations, Circle maps, Rotation interval, Phase locking, Multistability.

1 Integrate and Fire Neurons

In the second half of the past century, interest in integrate-and-fire ($I+F$) systems arose in connection with Balthazar van der Pol's studies of non linear oscillation phenomena in electronics and physiology [1,2,3]. Originally $I+F$ systems were called "relaxation oscillators" because they exhibit certain kind of periodic behavior in which a slow phase of charge is followed by a sudden discharge that "relaxes" the system towards a lower energy rest state. Later, as a consequence of the work of A.L. Hodgkin, A.F. Huxley, and R. FitzHugh in the 1960's, the connection of this relaxation-oscillation phenomenon to excitability processes which are fundamental for the physiology of nerve cells, was made clear [4,5].

Today, the class of $I+F$ systems is understood to be constituted by systems in which a characteristic mechanism of charge (integration) and discharge (firing) gives place not only to the relaxation process and the consequent nonlinear oscillations investigated by van der Pol, but also to the distinctive features of the excitability phenomenon: the existence of a firing threshold, an "all or none" response and a refractory period. Accordingly, nerve cells constitute a paradigmatic case of $I+F$ behavior in which the accumulation of ionic charge, that

brings the cell membrane potential above threshold and causes the nerve impulses (action potentials), follows the integration of afferent signals.

A combination of causes of biophysical nature underlies the dynamics of the action potential across the cell membrane. Active channels that selectively allow ionic flow through the membrane have been identified as being responsible for the variation of membrane permeability and the time dependency of the ionic currents across it. After Hodgkin and Huxley's pioneer work, the dynamics of these currents and the voltage across the cell membrane have been successfully modeled in terms of differential equation systems. Hodgkin and Huxley's famous model, used a set of four differential equations, but more equations were required to model other phenomena that were discovered afterwards. The mathematical complexity of the models, determined by the high dimension and nonlinearity of the equations, presents major difficulties in carrying out their analysis and motivates the design of simplified models. For instance, the two dimensional FitzHugh-Nagumo model (simpler than Hodgkin and Huxley's model) [6,7] although sacrificing a good deal of biophysical meaning, has enough dynamic complexity to explain the basic aspects of excitable behavior. Similarly,

modeling more complex phenomena, like the parabolic bursting oscillations observed in the abdominal ganglion of aplysia, requires models with more than four differential equations [8,9], although their basic dynamic features has been captured with simpler three dimensional models which clearly show the main mechanisms responsible for the observed phenomenon [10].

Efforts to simplify the mathematical structure of the models, while conserving enough richness to produce and study the phenomena of interest, have also been applied to the analysis of an old and fundamental problem in the theory of oscillations which is the main subject of this paper: the periodic forcing of an $I+F$ oscillator. The neurobiological context poses some issues of interest in relation with this problem. One of these is to ascertain whether the integrate-and-fire neuron will have some sort of synchronization (with respect to the afferent periodic signal) or if its response will be asynchronous (disordered). Again, because of their mathematical complexity, these problems cannot be fully approached analytically. Even the analysis of the periodic stimulation of the simple two dimensional model of FitzHugh-Nagumo poses great difficulty and only limited results have been obtained (mainly computational) [11-14]. Nonetheless, an important step forward in the understanding of the synchronization problem has been taken by developing even simpler models in which the dynamics of the voltage across the cell membrane obeys just one differential equation [15,16] or in which the model is constructed without a differential equation but rather with a plain geometrical rule [17]. The importance of these models is that they allow the study of the dynamics of the forced oscillator in terms of the iteration of a circle map. These models of forced $I+F$ systems are called *differential*, or *geometrical one dimensional models*, respectively.

2 Circle Maps and Synchronization

Since all the action potentials (spikes) that are fired by a particular neuron are identical, the long run behavior of the stimulated cell can be accounted for by the specification of a sequence of firing times $\{t_n\}$. This firing sequence completely describes the activity of the stimulated cell (Fig.1).

We want to analyze the response (the firing sequences) of a neural pacemaker that is receiving a periodic stimulation, of period T_0 . For this objective it will be also convenient to monitor the *phases* of the firing times.

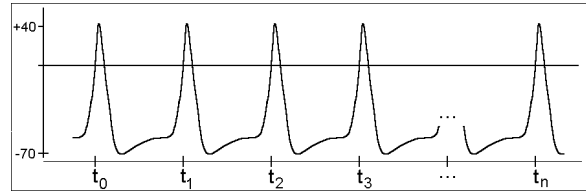


Fig.1 Action potentials train of a neural pacemaker

Each instantaneous event (spike) will occur at a certain time t_n which in turn occurs at certain phase x_n of the stimulating cycle ($0 \leq x_n \leq T_0$), called the *firing phase*. The sequence $\{x_n\}$ can be plotted in the circumference of length T_0 and it is called the *firing phase sequence* of the forced oscillator (Fig.2). Firing phases (x_n) and firing times (t_n) are related by the equation: $x_n = t_n \bmod T_0$, where T_0 is the period of the stimulating signal and $t_n \bmod T_0$ denotes the remainder of the division t_n / T_0 .

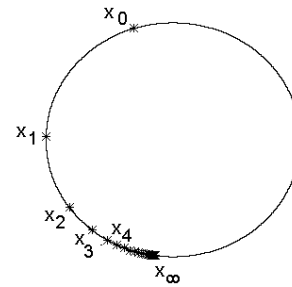


Fig.2 Firing phases in the circumference converging to the phase x_∞ .

When the cell is responding to the stimulation with a simple 1:1 synchronization mode (the cell fires once per each stimulation cycle), the corresponding firing time sequence is given recursively by the equation $t_{n+1} = t_n + T_0$. More general modes of synchronization ($q:p$), with q and p positive integers, involve more complex “periodic sequences”, $\{t_n\}$, in which a temporarily structured set (rhythm), of q spikes and duration interval pT_0 , periodically repeats: $t_{n+q} = t_n + pT_0, \forall n \in \mathbb{N}$ (the cell fires q spikes during p stimulation cycles). When this *rational synchronization* condition is not satisfied, the response of the stimulated system is classified as irregular or asynchronous.

General natural systems and nerve cells in particular, involve various physical parameters. An important research objective is to find out for a given forced $I+F$ model, what forms of synchronization are permissible and what parameter conditions determine them. The simple one dimensional models that we consider in this paper (either geometrical or differential), determine a

firing map, $a: R \rightarrow R$, whose iterations generate the firing sequences in the line, that is to say:

$$t_n = a^n(t_0), \quad n \in \mathbb{N}.$$

It is a remarkable fact that (because of the periodicity of the stimulus) this firing map has the following property: $a(t + T_0) = a(t) + T_0$, for all t . This means that $a(t)$ represents (is a lift of) a map from the circle onto itself. This circle map, $a(x)$, encodes the phase response of the $I+F$ system to the periodic stimulation and is called the *firing phase map*. The firing phase sequences are the orbits of the semi-dynamical system in the circumference (of length T_0) generated by $a(x)$:

$$x_n = a^n(x_0), \quad n \in \mathbb{N}.$$

Therefore, if the firing phase map has a periodic attractor of period q and winding number p , the $I+F$ system exhibits $(q:p)$ -synchronization.

The attractor in the circle is constituted by a finite sequence of firing phases (periodic orbit): x_0, \dots, x_{q-1} at which the system cyclically fires. The cycle is completed after the system has circled p times around the circumference, (of length T_0), and again reaches the initial phase x_0 .

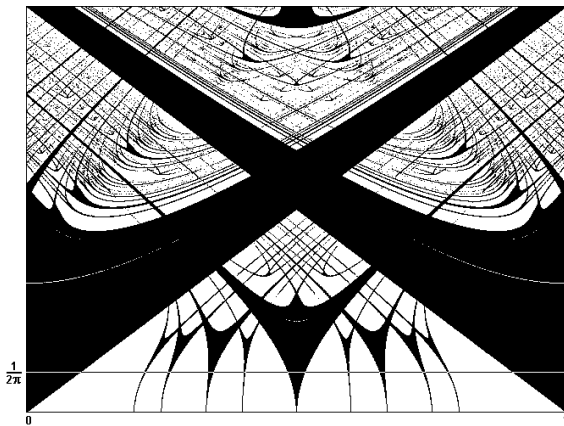


Fig.3 Rational synchronization regions in the classical bifurcation diagram.

In general, the synchronization mode of a forced parameter-dependant $I+F$ system will change with the parameters values; the regions in the parameter space where the system has the same type $(q:p)$ of synchronization, are known as *synchronization regions* or *Arnold's tongues*. The set of synchronization regions in the parameter space constitute a *bifurcation diagram* (Fig.3) that encodes the synchronization properties of the $I+F$ system. The *rotation theory* of circle maps that we review below, gives us elements to calculate these synchronization regions. This theory relates the notion of *rotation number*, originally formulated by H. Poincaré, with the existence of *periodic*

attractors of the circle map, and has evolved today to constitute a convenient framework to describe and investigate the synchronization phenomena that manifest in forced one dimensional $I+F$ systems. We will see below, how it follows from rotation theory that some relevant features of the geometrical structure of the array of tongues in the parameter space depend upon the regularity properties of the system's firing maps.

3 A Mechanical Neuron Analog

In Fig.(4A) we see an ancient device known as the "*see-saw oscillator*". As the water falls from the pipe, the container fills up until it reaches a threshold weight (w_0) that displaces the system away from equilibrium. In doing, so the water in the container (membrane voltage $v(t)$) falls down and the system recovers the initial equilibrium state with a certain amount of water $v_R < w$. If the container receives only a sub-threshold amount of water, the see-saw just suffers a slight deviation from equilibrium and recovers without discharging any water at all. Like a neural pacemaker, when this mechanical analog receives a constant flow of water, it responds with a periodic train of discharges (spikes) that creates a saw-tooth pattern (Fig.4B).

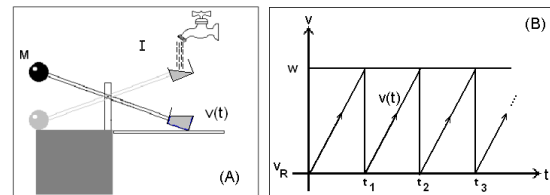


Fig.4 (A) Mechanical neuron. (B) Saw-tooth oscillations

As would be expected, the inter-spike period, $T(I)$, is a decreasing function of the flow intensity, I : $T(I) = (w - v_R)/I$. The firing sequence is obtained recursively with the equation: $t_{n+1} = t_n + T(I)$.

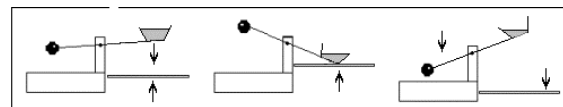


Fig.5 Periodically stimulated mechanical neuron.

In order to mimic the process of periodic stimulation of the cell (that we assume has a period T_0), we let the see-saw to collide and discharge over the surface of an accessory elevator that periodically moves up and down (Fig.5). Since the elevator will collide with the see-saw at different heights, the

amount of water discharged will also be variable; therefore, after each discharge the container will reach the equilibrium position with different levels of water. Consequently, the elapsed time between discharges $t_{n+1} - t_n$ will be not only a function of the current intensity I , but will also depend on the initial phase of the movement. For a given initial time t_0 , the corresponding time sequence $\{t_n\}$ may be synchronized with the stimulating agent ($t_{n+q} = t_n + pT_0$, " $n \hat{I} N$) or, in the opposite case, it will be distributed in an asynchronous fashion with respect to the forcing rhythm.

Being a classical mechanical system, the dynamics of the forced see-saw oscillator is governed by a system of two ordinary differential equations whose analysis is complicated because they are not linear and have discontinuous coefficients. In the search of a simpler one dimensional geometrical model, we take into account the following: if the intensity of the water current is not too large, the time of discharge will be fast compared with the charge process, therefore, in a first approximation we can assume that the discharge occurs instantly. Consequently the temporal course of $v(t)$, the weight of the water contained in the tank at time t , follows the sawtooth graph presented in Fig.6. In it we see that after each discharge (action potential) the system relaxes to a "periodic floor" whose height is determined by the amount of water left in the container after each discharge.

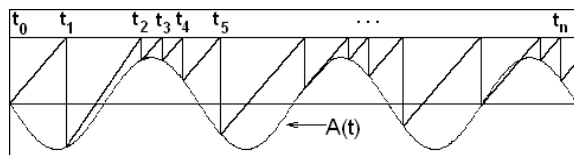


Fig.6 Geometrical model.

For convenience, we assume here that the forcing period is $T_0 = 1$ and that the weight of the water left after a discharge at time t , is given by the function:

$$A(t) = -H \sin(2\pi t).$$

The associated firing phase map, a , of the mechanical neuron depends on the values of the system parameters (H, I, w) , where I is the intensity of the current and w is the counterweight of the see-saw. Two remarkable facts arise:

(1) The dynamics of this one dimensional geometrical model of the periodically stimulated neuron is governed by the classic family of circle maps [18]:

$$a(t) = a + t + b \sin(2\pi t) \bmod 1,$$

where $a = w/I$ and $b = H/I$.

2) This parametric family of circle map reproduces qualitatively the dynamics of the two dimensional system of differential equations that governs the mechanical neuron analog [19].

It is well known that the maps of the classic family may have periodic orbits of all periods q and winding number p . Therefore we predict that it is possible to make the mechanical neuron to exhibit any type $(q:p)$ of synchronization, choosing appropriate values for the parameters (a, b) . Using Poincaré's rotation number and other concepts of modern circle maps rotation theory [20], it is possible to calculate the synchronization regions in parameter space depicted in Fig.3.

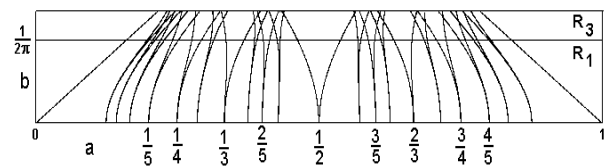


Fig.7 Regions R_1 and R_3 for the mechanical neuron. (close-up of Fig.3)

Each region in this bifurcation diagram, represents the set of parameters values (a, b) that configure the system to produce a specific type of synchronization. As we cross the boundaries of these synchronization regions, the response of the neuron to the external stimulation changes from one type $q:p$ of synchronization, to another type $q':p'$. A peculiar property of this classical bifurcation diagram is that the system responds with synchronization $q:p$ at the tongue that is rooted at the point $(a, b) = (p/q, 0)$ of the parameter space (Fig.7).

4 Differential Models (1-D)

Periodically stimulated $I+F$ neurons are also modeled [16,21,22] with just a first order differential equation

$$\dot{v} = F(t, v, \mathbf{I}), \quad (1)$$

periodic in t , of period T_0 , and subjected to a firing condition:

$$v(t) = v_R \text{ if } \lim_{t \rightarrow t^-} v(t) = v_T \quad (2)$$

(left lateral limit), where v_R and v_T are fixed constants corresponding to the rest and threshold membrane electric potential values and \mathbf{I} is a vector of parameters. At any given time t , the system's firing map, $a(t)$, is then defined as (Fig.8):

$$a(t) = \min \{t > t : v(t) = v_T\}.$$

If for some time t this set is empty, the function $a(t)$ is not defined in t , and it is said that "the neuron does not fire from the time t ". When there are such points, t , outside of the domain (D_a) of the firing map and $a(D_a) \not\subset D_a$, some firing sequences will end in finite time; this situation is known as the "oscillator's death". It follows from this remark that the knowledge of D_a is fundamental to determine the extent of the life domain of the oscillator. In general, since the firing function a is not analytically accessible, there are some difficulties to calculate D_a : it would be necessary to find out the general solution of the nonlinear differential equation, for which there are no formulas or general methods of solution. However, there are general results about the extent and topological structure of the set D_a that apply in the case in which the state variable (voltage) of the $I+F$ system grows linearly, that is, when $F(t, v, I)$ is a linear function of the variable v [23]. The general nonlinear case still remains to be investigated.

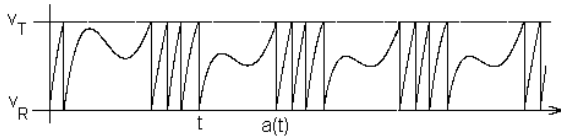


Fig.8 Sawtooth oscillations of a differential model.

It should be observed that, in this context, the fact that this firing map a is a circle map is a direct consequence of the periodicity of the differential equation.

5 Rotation Intervals

For a continuous circle map a , the rotation number of the orbit with starting time $t_0 = t$, is defined as:

$$r(a, t) = \lim_{n \rightarrow \infty} \left(\frac{a^n(t)}{n} \right) \bmod 1$$

if this limit exists. If the rotation number is a rational number p/q , then the orbit converges to a periodic attractor of period q , and winding number p , which means a $(q:p)$ synchronization from the initial condition $t_0 = t$. Generally, the limit value and the synchronization type will depend on the value t of this initial condition. However, when the firing map $a(t)$ is continuous and injective, the limit exists and does not depend upon t . In this case, assuming that the rotation number is p/q , it can be proved that almost all the orbits converge to a periodic attractor of the same period q and winding number p .

Consequently, the theory predicts that the $I+F$ system will exhibit an observable synchronized response, $(q:p)$, to the periodic stimulus. This type of synchronization will be observed for almost all initial conditions. On the other hand, when the firing map is not injective, the set of rotation numbers may be a non trivial closed interval $[a, b]$. For every rational number p/q in this rotation interval, there will be a periodic orbit of the circle map with period q and winding number p . But not all of these periodic orbits will cause an observable $q:p$ -synchronization; this is due to the fact that all, but a finite number of these orbits are unstable.

The dynamics of periodically stimulated neurons that are encoded by non injective maps has a rich complexity and may exhibit multistability and even chaotic behavior. In contrast, the dynamics of the neurons that have associated continuous and injective maps is simpler; it is restricted to express synchronization of a unique $q:p$ type, for each parameter configuration. A brief review of rotation theory can be found in [18].

6 Regularity of the Firing Maps

The following theorems establish computable conditions to determine the parametric configurations of the model that will render a continuous and/or injective firing map [24].

These regularity theorems apply to a general differential $I+F$ model like the one given by the equations (1) and (2). Consequently, F stands for the function referred in those equations and D_a denotes the domain of the $I+F$ system's firing map.

Injectivity theorem. The firing map $a(t)$ is injective in $\text{int}(D_a)$ if and only if $F(t, v_R, I) \geq 0$ for all $t \in \text{int}(D_a)$.

Continuity theorem. The firing map $a(t)$ is continuous in $\text{int}(D_a)$ if and only if $F(t, v_T, I) \geq 0$ for all $t \in \text{int}(D_a)$.

The force of these theorems resides in the fact that they do not require any knowledge about the solutions of the differential equations: all the information required to validate the hypothesis is in the function $F(t, v, I)$ that defines the model. In fact, if we define the functions $S_R(I) = F(t, v_R, I)$ and $S_T(I) = F(t, v_T, I)$, it follows from these regularity theorems that the two hyper-surfaces (manifolds) defined in the parameter space by the equations:

$$S_R(I) = 0$$

$$S_T(I) = 0,$$

are the boundaries of the continuity and injectivity regions of the system.

These hyper-surfaces may divide the parameter space in many different ways and (in the more general case) will determine all the following regularity regions for the firing map:

(R_1). Where the map is one to one and continuous;

(R_2). Where the map is one to one but not continuous;

(R_3). Where the map is continuous but not injective;

(R_4). The complement of the previous. (where the map is neither continuous nor injective).

Each point in the parameter space represents a parameter configuration of the system and has an associated firing map to which it corresponds, a unique rotation interval. Nevertheless, the rotation intervals of two different maps (corresponding to different parameter configurations) may intersect and foster the coexistence of periodic attractors with different periods and winding numbers (multistability phenomenon). This situation provides a theoretical explanation of the synchronization jumps that has been observed in these forced $I+F$ systems as we perturb the initial conditions (with a fixed parameter configuration).

Rotation theory predicts that the rotation intervals of the firing maps of an $I+F$ system with parametric configuration in the region R_1 can not have non trivial intersections: in this region the rotation interval reduces to a single point. Therefore, in this region all the periodic orbits ought to have the same period q and winding number p and hence the system cannot suffer synchronization jumps.

For some $I+F$ systems the number of regularity regions may be smaller. We can observe this fact in the bifurcation diagram of the mechanical neuron (Fig.3). Since for this particular example we have an explicit analytical expression for the bi-parametric family of firing maps, it is easy to check that the circle maps of the family are continuous for all parameter values and they are injective only when $b=1/(2\pi)$. Thus, the parameter space of the mechanical neuron is the union of only two regularity regions: R_1 and R_3 . It is clear from the close-up of Fig.7 that the synchronization regions do not intersect with each other when they are contained in the regularity region R_1 , but intersect pair wise as they extend into the regularity region R_3 . It is in this region where the bi-stability phenomenon and the consequent jumps of synchronization emerge.

As we have seen, the system's circle firing map is charged with useful information about the dynamics of the forced oscillator. In general we will not be

able to obtain an explicit analytic formula for this map as we have done for the mechanical neuron. However, in virtue of the regularity theorems, for a general differential $I+F$ model we can calculate the boundary of these regions using the above defined hyper-surfaces $S_R(I)$ and $S_T(I)$.

6 Acknowledgements

This research was partially supported by the grants: DGAPA (IN-101700, EN-104203) and CONACyT (J200.644/2003), for H. Carrillo and UAEM (2004-02), for F. Ongay.

References:

- [1] B. van der Pol. On relaxation oscillations. *Philos. Mag.* (7) 2 (11) (1926) 978.
- [2] B. van der Pol. Biological rhythms considered as relaxation oscillations. *Acta Med. Scand. Suppl. CVIII* (108) (1940) 76.
- [3] B. van der Pol, van der Mark. The heartbeat considered as a relaxation oscillation and an electrical model of the heart. *Philos. Mag.* 6 (1928).
- [4] A.L. Hodgkin, A.F. Huxley, A quantitative description of membrane current and its application to conduction and excitation in nerve. (1952) *J. Physiol.* (London) 117. 500-544.
- [5] R. FitzHugh (1961) Impulses and physiological states in models of nerve membrane, *Biophys. J* 1, 445-466.
- [6] R. FitzHugh, H.P. Schwan. *Biological Engineering*. Cap. I. McGraw-Hill, New York, 1969
- [7] J.S. Nagumo, S. Arimoto, S. Yoshizawa, An active pulse transmission line simulating nerve axon, (1962) *Proc. IRE* 50, 2061-2070.
- [8] Plant RE. Bifurcation and resonance in a model for bursting nerve cells. *J Math Biol*, 1981, 11: 15-32.
- [9] J. Rinzel, Y.S. Lee, Dissection of a model for neuronal parabolic bursting. *J Math Biol*, 1987, 25: 653-675.
- [10] S. M. Baer, J. Rinzel, H. Carrillo. Analysis of an Autonomous Phase Model for Neuronal Parabolic Bursting. *Journal of Mathematical Biology*, Vol. 33 1995, pp 309-333.
- [11] M. L. Cartwright, Non-linear vibrations: a chapter in mathematical history, *Math. Gazette*, 36 (1952) 80-88.
- [12] J. Flaherty, F. Hoppensteadt, *Studies in Appl. Math.* 58(1978), 5-15.
- [13] M. Levi, *Qualitative Analysis of the Periodically Forced Relaxation Oscillations*, Mem. AMS 244, 1981.

- [14] J. Grasman, *Asymptotic Methods for Relaxation Oscillations and Applications*, S-Verlag, 1987.
- [15] A. Rescigno, R.B. Stein, R.L. Purple, R.E. Poppele. A Neuronal Model for the Discharge Patterns Produced by Cyclic Inputs. *Bulletin of Mathematical Biophysics*. Vol. 32, 1970.
- [16] J.P. Keener, F.C. Hoppensteadt, J. Rinzel. Integrate-and-Fire Models of Nerve Membrane Response to Oscillatory Input. *SIAM J. APPL. Math.* Vol. 41, No. 3, 1981.
- [17] R. Pérez, L. Glass. Bistability, period doubling, bifurcations and chaos in a periodically forced oscillator. *Physics Letters* 90A, 441- 443, 1982.
- [18] I. E. Díaz Bobadilla. *Análisis de las Propiedades de Sincronización de un Modelo Mecánico de Neurona*. Master Thesis, Facultad de Ciencias, Universidad Nacional Autónoma de México. Marzo de 2002. (www.dynamics.unam.edu)
- [19] C. Barriga, H. Carrillo, Synchronization properties of a mechanical neuron analog (in preparation).
- [20] J. R. Guzmán, H. Carrillo, F. Ongay Larios. Dinámica de las Iteraciones de la Función de Arnold. *Aportaciones Matemáticas, Serie Comunicaciones, Sociedad Matemática Mexicana*. 14 (1994) 405-414.
- [21] S. Coombes. Liapunov exponents and mode-locked solutions for integrate-and-fire dynamical systems. *Physics Letters A* 255 (1999) 49-57.
- [22] S. Coombes, P.C. Bressloff. Mode locking and Arnold tongues in integrate-and-fire neural oscillators. *Physical Review E* (60) 2. August 1999.
- [23] M. A. Mendoza Reyes. *Análisis de Modelos de Neuronas de Integración y Disparo con Acumulación Lineal*. Master Thesis, Facultad de Ciencias, Universidad Nacional Autónoma de México,. 2001. (www.dynamics.unam.edu).
- [24] H. Carrillo, F. A. Ongay-Larios. On the Firing Maps of a General Class of Forced Integrate and Fire Neurons. *Mathematical Biosciences* 172. 2001. 33-53.