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*Rafael E. Saa*

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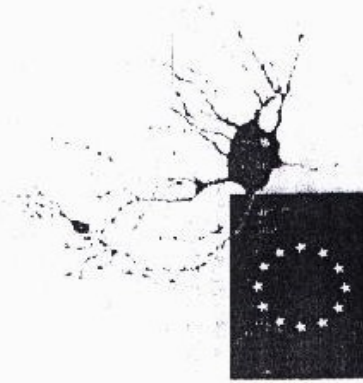
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## CONTENTS

### PREFACE

### PARTICIPANTS

FREQUENCY TUNING IN THE INNER EAR OF VERTEBRATES, <i>L. Robles</i>	1
ORIGIN AND BIOLOGICAL ROLES OF NATURALLY OCCURRING BENZODIAZEPINES, <i>J. H. Medina, I. Izquierdo and A. C. Paladini</i>	15
SEXUAL DIFFERENCES AND EFFECTS OF ESTROGEN ON NEURONAL GROWTH AND DIFFERENTIATION, <i>H. F. Catter, H. Diaz, A. Lorenzo and A. Cáceres</i>	27
MECHANISMS OF ACTIVATION AND CONTROL IN LABYRINTHINE ORGANS, <i>P. Valli</i>	39
STUDIES OF NEURAL PLASTICITY IN THE VESTIBULAR SYSTEM, <i>O. Macadar and A. Pereda</i>	47
SOME CONSIDERATIONS ON THALAMIC AND PONTINE SLEEP MECHANISMS, <i>F. Reinoso-Suárez</i>	59
THERMOREGULATION ACROSS BEHAVIORAL STATES AND THE PRINCIPLE OF HOMEOSTASIS, <i>P. L. Parmeggiani</i>	73
AUDITORY BRAIN STEM UNITARY ACTIVITY IN SLEEP, <i>R. Velluti, M. Pedemonte, J. L. Peña, G. Morales and P. Torterolo</i>	83
ENZYMES AND THEIR INHIBITORS IN RELATION TO AMINERGIC NEUROTRANSMISSION, <i>K. F. Tipton</i>	97



SPECIFICITY OF SYNAPTIC CONNECTIONS, <i>E. L. White</i>	109	TWO PACEMAKERS NEURAL NETWORK, <i>R. Budelli, L. Gómez, J. Torres and E. Catsigeras</i>	215
CORTICAL CELL POTENTIALS AND EEG IN AN <i>IN VITRO</i> TURTLE WHOLE HEMISPHERE, <i>J. C. Velluti, R. E. Russo</i> and <i>E. García-Austt</i>	117	REFLEX VARIABILITY AND PRESYNAPTIC INHIBITION DURING FICTIVE LOCOMOTION IN CRAYFISH, <i>F. Clarac,</i> <i>D. Cattaert</i> and <i>A. El Manira</i>	229
GABA <sub>A</sub> AND GABA <sub>B</sub> -MEDIATED INHIBITORY POSTSYNAPTIC POTENTIALS IN THE DORSAL LATERAL GENICULATE NUCLEUS, <i>D. Jassik-Gerschenfeld</i>	129	MULTIPLE INTRACELLULAR TRANSDUCTION MECHANISMS UNDERLYING NEUROTRANSMITTER-INDUCED ENHANCEMENT OF HIGH-THRESHOLD VOLTAGE-GATED CALCIUM CURRENT IN SNAIL NEURONS, <i>D. Paupardin-Tritsch, C. Hammond,</i> <i>C. De Waele, J.L. Yakel</i> and <i>H.M. Gerschenfeld</i>	245
CENTRAL ASTROGLIA AND PHENOTYPIC EXPRESSION OF ECTOPIC CELLS: IMPLICATIONS FOR CELL TRANSPLANTS, <i>J. A. Colombo</i>	141	COMPLEX INFORMATION PROCESSING IN NEURONES, <i>J. Hounsgaard</i> and <i>O. Kjerulff</i>	259
A NON-CHOLINERGIC ACTION OF AChE IN THE BRAIN: FROM NEURONAL SECRETION TO THE GENERATION OF MOVEMENT, <i>S. A. Greenfield</i>	153	PERIODIC INHIBITION OF PACEMAKER NEURONS, <i>J. P. Segundo</i>	269
SEMANTIC PARAMETERS IN ASSOCIATIVE MEMORIES, <i>E. Mizogji</i>	167	CONDITIONAL DISTRIBUTIONS: A TOOL TO STUDY THE KINETICS OF SINGLE ION CHANNELS, <i>M. Barbi, D. Petracchi,</i> <i>M. Pellegrini, M. Pellegrino</i> and <i>A. Simoni</i>	279
NEURAL OSCILLATORS: SYNAPTIC INTERACTIONS AND MEMBRANE MECHANISMS, <i>W. Buño, L. C. Barrio</i> and <i>A. García-Muñoz</i>	177	CONTRIBUTING AUTHORS	
CELLULAR MECHANISMS OF SENSORY-MOTOR COORDINATION AND THE PLASTICITY OF NEURONAL RESPONSES, STUDIED IN THE ELECTRIC SYSTEM OF MORMYRID FISH, <i>K. Grant</i>	185		
WAVEFORM GENERATION OF THE ELECTRIC ORGAN DISCHARGE IN <i>Gymnotus carapo</i> . I. ANATOMICAL ASPECTS, <i>O. Trujillo-Cenóz, D. Lorenzo</i> and <i>A. Caputi</i>	197		
WAVEFORM GENERATION OF THE ELECTRIC ORGAN DISCHARGE IN <i>Gymnotus carapo</i> . II. PHYSIOLOGICAL STUDIES, <i>D. Lorenzo, F. Sierra</i> and <i>A. Sitba</i>	207		

- Hopkins, C.D. 1980. Evolution of electric communication channels of mormyrids. *Behav. Ecol. Sociobiol.* 7:1-13
- Hopkins, C.D. 1986. Behavior of Mormyridae. In *Electroreception*, ed. T.H. Bullock, W. Heiligenberg, pp. 627-77. New York: John Wiley & Sons
- Lorenzo, D., Sierra, F., Silva, A., Macadar, O. 1990. Spinal mechanisms of electric organ discharge synchronization in *Gymnotus carapo*. *J. Comp. Physiol.* 167:447-452
- Lorenzo, D., Vallati, J.C., Macadar, O. 1988. Electrophysiological properties of abdominal electrocytes in the weakly electric fish *Gymnotus carapo*. *J. Comp. Physiol. A* 162:141-144
- Macadar, O., Lorenzo, D., Vallati, J.C. 1989. Waveform generation of the electric organ discharge in *Gymnotus carapo*. II. Electrophysiological properties of single electrocytes. *J. Comp. Physiol.* 165:353-360
- Szabo, T. 1961a. Quelques observations sur l'innervation de l'organe électrique de *Gymnotus carapo*. *Arch. Anat. Microsc. Morphol. Exp.* 49:89-92
- Szabo, T. 1961b. Anatomophysiologie des centres nerveux de quelques organes électriques. In *Bioelectrogenesis*, ed. C. Chagas, A. Pass de Carvalho, pp. 185-201. Amsterdam: Elsevier
- Trujillo-Cenóz, O., Echagüe, J.A. 1989. Waveform generation of the electric organ discharge in *Gymnotus carapo*. I. Morphology and innervation of the electric organ. *J. Comp. Physiol. A* 165:343-351
- Trujillo-Cenóz, O., Echagüe, J.A., Macadar, O. 1984. Innervation pattern and electric organ discharge waveform in *Gymnotus carapo*. *É. Neurobiol.* 15:273-281

## TWO PACEMAKERS NEURAL NETWORK

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Working with neuronal network models which take into account all the established properties of each neuron and its synapses (Mulloney et al. 1981) we realized that there were many sensible networks able of reproducing the results. We therefore became interested in the determination of the repetitive firing patterns that may be produced by a small network of simple neuronal models. Some neural networks with symmetric connections have several attracting states (Hopfield 1982), but other cases may result in limit cycles (Mulloney et al. 1981), bistability (Omata et al. 1988), intermittency and chaos (Sporns et al. 1987). An intensive study of more general neural networks models is therefore mandatory. The behaviour of a single oscillator (i.e., a pacemaker neuron model) with periodic input has been extensively studied (Rescigno et al. 1970; Stein et al. 1972; Knight 1972; Poggio and Torre 1977; Ascoli et al.



1977a, 1977b; Glass and Pérez 1982; Pérez and Glass 1982; Glass et al. 1983; Budelli et al. 1984). The study of the dynamic behavior of two coupled oscillators (which may be interpreted as neuronal pacemakers) has already been undertaken for some particular networks (Peskin 1975; Kawahara 1980; Allen 1983; Babcock and Westervelt 1986, 1987; Wang and Nichols 1987; Sporns et al. 1987; Pérez and Lomnitz-Adler 1988). Our first goal is to continue with the characterization of the behaviour of two interconnected neurons modeled by relaxation oscillators. In this paper we study the behaviour of two pacemakers simulated by relaxation oscillators.

## THE MODEL

The model consists of two pacemaker neurons (hereafter called A and B) reciprocally connected by synapses. Each one was modeled by an integrate-and-fire (Knight 1972) or leaky integrator system (Rescigno 1972). When neuron A fires, the synapse from A to B is activated producing a potential shift in neuron B while that of A resets to 0; and viceversa (Fig. 1). The change in potential of neuron A (when B fires) will be called  $a$ , and that of B (when A fires),  $b$ . Values  $a$  and  $b$  will be negative or positive, depending on whether the interaction is inhibitory or excitatory. If the potential of the postsynaptic neuron reaches threshold immediately after the presynaptic neuron fires, both reset to zero.

Let us call stage to the period between successive discharges. Fig 1 shows 5 stages for the model with a particular set of parameters. In this example,  $v_A = v_B$ , both neurons start the first stage from zero; the asymptotic value of the potential of neuron B (B) is larger than that of A (A); and both synapses are excitatory ( $a > 0, b > 0$ ). By convenience, we assume the threshold is 1. In this case the first neuron to reach the threshold is B; then, the action of the synapsis increase the potential of A in  $a$  and that of B goes to 0, finishing the first stage and beginning the second one. After stages 2 and 3, the forth one finishes when B reaches the threshold, and then the increase in the potential of A

produces its discharge. Then, the fifth stage reproduces the first one, and so on. Consequently, if the neurons fire once synchronously, the firing pattern composed by the stages 1, 2, 3, 4, will repeat thereafter. In this case, B will fire 3 times for every 2 discharges of A: we will say there is a 3/2 phase-locking. In general, when B fires  $m$  times every  $n$  discharges of A, we will say there is a  $m/n$  phase-locking. It is worth to note that this pattern is stable, as required by the phase-locking concept: a small change in the state of the network will be preserved until the next simultaneous firing and afterwards the original pattern will repeat again.

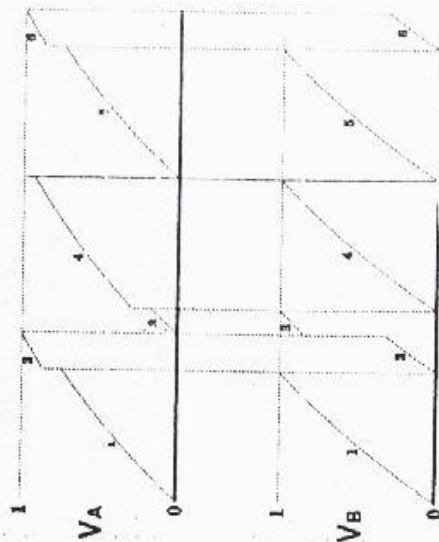


Figure 1.- The model. The membrane potentials ( $V_A$  and  $V_B$ ) from two neurons (A and B) evolve exponentially with time from a reference value (0) up to one of them (B in this case) reach a threshold value ( $T=1$ , by convenience). Then, it fires, its potential resets to 0 and the potential of the other neuron increases in a fixed amount ( $a$  in this case). The values between successive discharges are called stages and are numbered (from 1 to 5) at bottom.

We may represent these trajectories in the plane of the phases (the space of the pairs  $(V_A, V_B)$ , Fig. 2). Each stage from Fig. 1 is identified in Fig. 2 by the corresponding number. After the fourth segment hits the phase locking corner the plot starts again from the origin (see Budelli et al. 1991, for a more detailed description).



There are several advantages of working in the space of phases: we reduce the number of variables since the time disappears, both time constants collapse in only one parameter and the trajectories belong to a given family (straight lines or paraboles through  $(A, B)$ ).

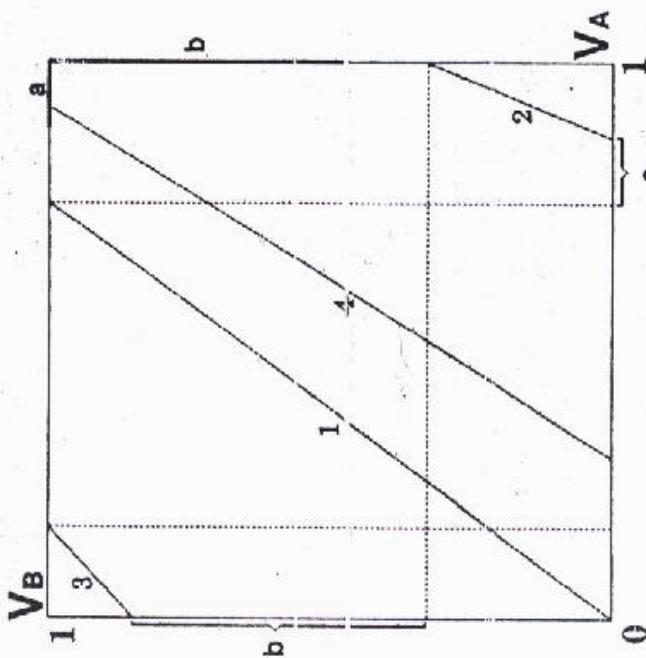


Figure 2: Trajectory representation in the phase space. Representation of the pairs  $(V_A, V_B)$  from Figure 1. Curves corresponding to the different siges are identified by the number used in Figure 1. Segments  $(V_A, V_B)$ :  $V_A = 1, 1-b < V_B < 1$ , and  $1-b < V_A < 1, V_B = 1$  are in thick lines.

## RESULTS

In this section we present first theoretical results and, afterwards, those obtained by simulation using an IBM PC AT compatible computer.

## Patterns of Discharge

Different patterns of discharge will appear. We describe (Catsigeras and Budelli 1991) the possible patterns of discharge, when we model the neurons by a general class of relaxation oscillators. Besides, we prove that most of them appear when we simulate the neurons by leaky integrators, a particular case of the oscillators just mentioned.

### Only one neuron fires

Lets assume neuron A is inhibitory and its effect on B is large enough to preclude the firing of B. When both ipsaps are large enough, two stable patterns of firing are possible: either neuron A or B fires and the other remains silent.

### Phase-locking with simultaneous firing

This pattern occurs when at least one neuron is excitatory (Fig. 1). In this case starting from  $V_A = 0, V_B = 0$ , and after eventual discharges, both neurons fire synchronously. Catsigeras and Budelli (1991) show that this is the behavior when both neurons are excitatory ( $a > 0$  and  $b > 0$ ).

### Phase-locking without simultaneous discharges

When the neurons are modelled by leaky integrator models they may phase-lock without simultaneous discharges, in opposition to what happen with integrate and fire models. We proved that, in this case, the rotation number (or phase-locking relationship,  $m/n$ ) is independent of the initial phase, and consequently, there exist two values  $m$  and  $n$  such that all the possible phase-lockings are  $m/n$ . Furthermore, we proved that the sequence of neuron discharges only depends on the value of the phase-locking relationship. For leaky integrators models of neuron we prove that: there is at most one phase-locking cycle without simultaneous firing.



## Non trivial compact attractor

When both synapses are inhibitory, either: the discharges phase-lock or all the orbits tends to a non trivial compact attracting set. Furthermore, using results by Keener (1980), we prove that phase-lock occurs for almost any set of parameters.

## Bistability

We have shown that when both neurons are inhibitory and intensive enough, the first in discharging preclude the discharge of the other one; and, consequently, bistability turns out. There is another possibility of bistability, when for a given set of parameters phase-locking with and without synchrony may occur, depending on the initial conditions.

## Bifurcation Diagrams

Simulation results will be obtained calculating for several values of  $p$  the values of  $a$  and  $b$  leading to  $m/n$  phase-locking. We will present in a plane plot the values  $(a, b)$  leading to each  $m/n$  phase-locking: the bifurcation diagrams (Arnold 1980; Glass and Pérez 1982; Pérez and Glass 1982; Budelli et al. 1984, 1991). Figures 4, and 5 show the bifurcation diagrams for different sets of parameters  $(A, B, \tau_A, \tau_B)$ . Those regions where phase-locking occurs with synchrony are shown in white with black limits; those where it occurs without synchrony are black with white limits, and those where both kinds of phase-locking occur are also shown in black.

Figure 4 show the bifurcation diagrams for  $A=3, B=3.01$  and  $\tau_A=\tau_B$ . In this case, for  $a < -1$  when neuron B discharges, preclude the discharge of neuron A; then, only neuron B will discharge. Reciprocally, when  $b < -1$ , if A discharges, it will discharge thereafter. Consequently, when  $a < -1$  and  $b < -1$  either neuron A or B will discharge alone; which one will discharge depends on the initial conditions.

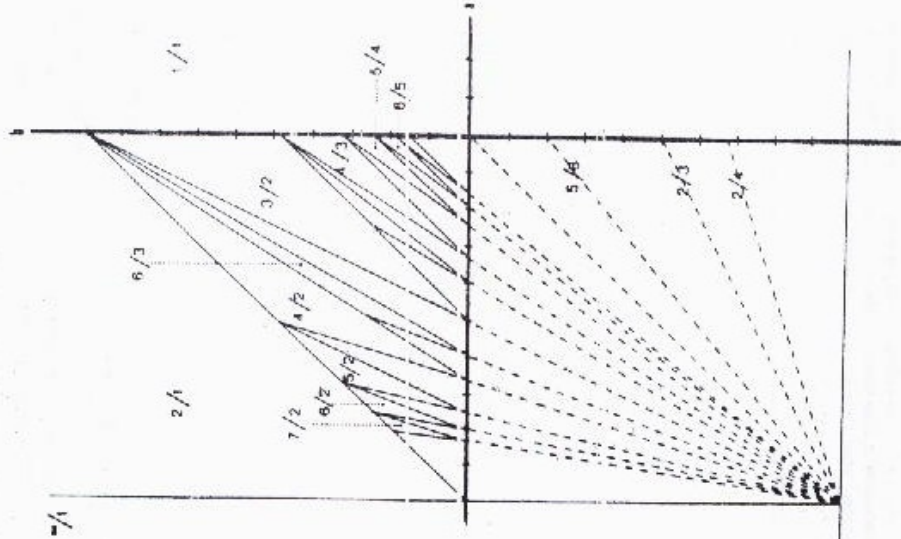


Figure 3.- Bifurcation diagrams of the integrator and fire model for  $p$  very close to and larger than 1.

Phase-locking regions with simultaneous discharges are similar for integrate and fire (Fig. 3) and leaky integrator pacemaker models (Budelli et al. 1991). For  $b > 0$  and  $a < -1$  phase-

locking  $1/1$  occurs. In the square  $-1 < b < 0$  y  $0 < a < 1$  regions corresponding to the Farey's serie between  $2/1$  and  $1/1$  are found, together with some other ones (for example:  $4/2$ ).

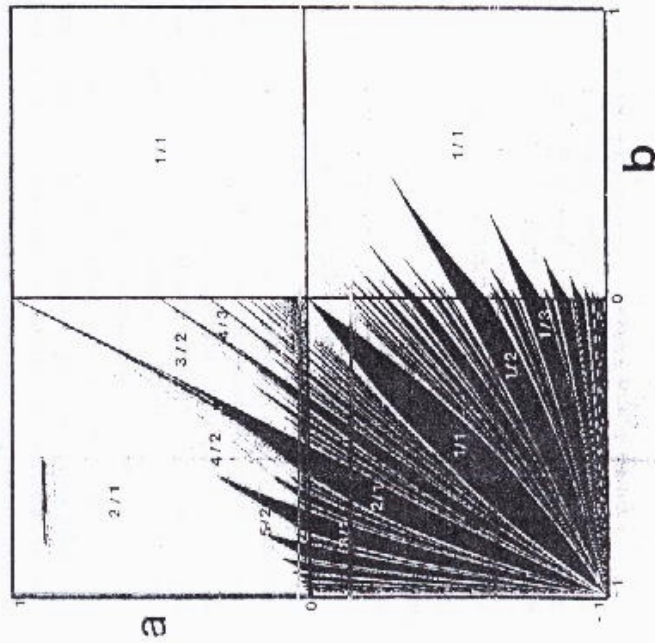
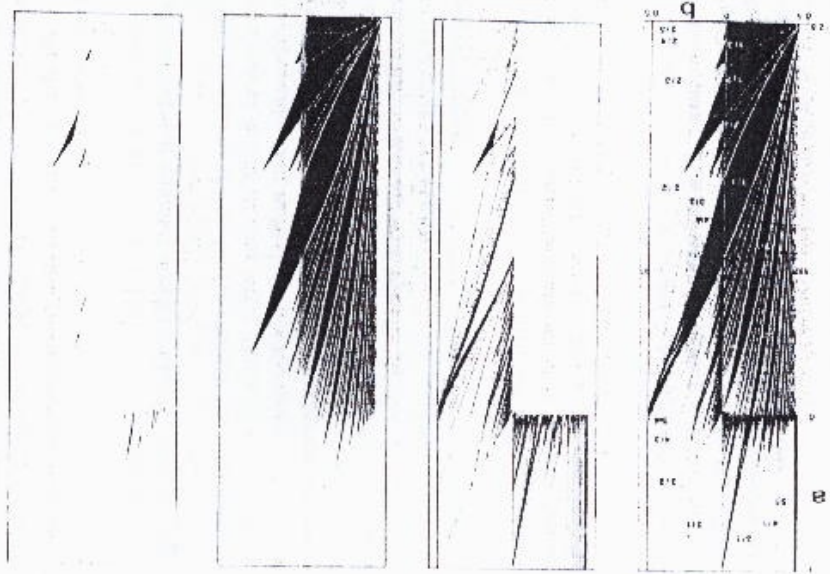


Figure 4 - Bifurcation diagrams for  $A=3$ ,  $B=3.01$  and  $1, 2, 3$ . Phase locking regions with simultaneous discharges are shown in white with black limits and those without simultaneity are shown in black with white limits. Black regions for  $b > 0$  present bistability; for some initial values phase-locking  $1/1$  with synchrony occurs and for others phase-locking without synchrony with  $m/n$  relations indicated.

In this square Phase-locking regions without simultaneous discharges also appear, corresponding to Farey's serie for values larger than  $1/1$ . These regions alternate with the other ones in a rather tangled order. We always found phase-locking with or without simultaneity, but never bistability.

Figure 5 - Bifurcation diagrams for  $A=3$ ,  $B=3.01$  and  $1, 2, 3$ . From left to right: 1) the same as in preceding figures, 2) contours of phase-locking with synchrony zones, regions with bistability are shown in black, 3) zones of phase-locking without synchrony, 4) bistability zones.





Inside  $0 < b < 1$  and  $-1 < a < 0$ , apart from  $1/1$  phase-locking with simultaneous discharges, we found phase-locking without simultaneity ordered according to Farey's series between  $1/1$  and  $0/1$ . In these regions bistability occurs.

Inside the square  $-1 < a < 0$ ,  $-1 < b < 0$  phase-locking regions without simultaneity turn out showing a fan-shaped structure, centered in  $(-1, -1)$ . We may call such a shape: a devil's winder stair. We did not find regions corresponding to a non trivial compact attractor.

According to Catsigeras and Budelli (1991) results, we do not find phase-locking without simultaneity for  $a > 0$ ,  $b > 0$ .

Figure 5 shows at the left the bifurcation diagram for the same values of A and B as in Fig. 4, but with  $\tau_a = 2\tau_b$ . The second graphic from the left, only presents the contours of the regions where phase-locking with simultaneous discharges occurs, and in black the regions of bistability. The third one shows, in black, the regions of phase-locking with synchrony. On the right only the bistability zones are shown.

## DISCUSSION

In this paper we only discuss differences with the integrate and fire model and we refer the readers to the discussion of our first paper in this field for a more general view (Budelli et al. 1991).

This model presents a behaviour richer and more intricate than the others. Phase-locking regions without simultaneity are ordered following the Farey's serie (Allen 1983; Pérez and Lomitz 1988). They interlock with phase-locking with simultaneity regions in a rather arbitrary order.

Recording pacemakers from the subesophageal ganglia from the *Helix aspersa*, Cervantes (1989) obtained patterns of firing with relationships  $2/1$  and  $3/2$  with simultaneity. It seems we are in the presence of a circuit similar to those studied in this paper.

With integrate and fire models we only found phase-locking with simultaneity (Budelli et al. 1991). Conversely, with leaky integrators (Gómez et al., in preparation) and more general pacemaker models (Catsigeras and Budelli 1991) we found both phase-locking with and without simultaneity, opening the possibility for a new type of bistability. In this situation phase-locking appear also for two inhibitory neurons, as occurs in many experimental situations (Selverston and Moulins 1985; Mulloney et al. 1981). Hartline and Gassie (1982) reciprocally coupled a pair of crayfish stretch receptors by artificial connections. Synapsis on these neurons are inhibitory, and consequently they do not discharge simultaneously. As predicted by the present model  $1/1$  phase locking without simultaneous firing is easy to obtain. It would be very interesting to know if other types of phase locking may be obtained with this preparation. Lamentably, they only produce a communication to the Neuroscience Meeting and not a full paper.

We never found chaos, although there are points where regions of phase-locking with quite different rotation numbers join. This situation may be difficult to distinguish experimentally from chaos.

Among three papers (Budelli et al. 1991; Catsigeras and Budelli 1991; Gómez et al., in preparation) we were able to give a relatively general description of the behavior of two neurons reciprocally connected.

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## REFERENCES

- Allen, T. 1983. On the arithmetic of phase-locking: coupled neurons as a lattice on  $R^2$ . *Physica* 6D:306-320
- Arnold, V. 1980. *Chapitres supplémentaires de la théorie des équations différentielles ordinaires*. Editions Mir, Moscou
- Ascoli, C., Barbi, M., Chillemi, S., Petracchi, D. 1977. Phase-locked responses in the *Limulus* lateral eye. *Biophys. J.* 19:219-240
- Ascoli, C., Barbi, M., Frediani, C., Ghelardini, G., Petracchi, D. 1977. Rectification and spike synchronization in the *Limulus* lateral eye. *Kybernetik* 14:165-190
- Babcock, K., Westervelt, R. 1986. Stability and dynamics of simple electronic neural networks with added inertia. *Physica* 23D:464-489
- Babcock, K., Westervelt, R. 1987. Dynamics of simple electronic networks. *Physica* 26D:305-316
- Budelli, R., Soto, E., González-Estrada, Macadar, O. 1984. A spike-generator mechanism model stimulates utricular responses to sinusoidal vibrations. *Biol. Cybern.*
- Budelli, R., Torres, J., Catsigeras, E., Enricht, H. 1991. Two neurons network. *Integrato-rod-firo-pecomaster-modelo-Biol. Cybern.* in press
- Cervantes, A. 1989. Modulación de la descarga repetitiva ante pulsos externos en neuronas del círculo *Hélix aspersa*. Master Thesis. Universidad Autónoma de Puebla. Puebla, Pue. México
- Glass, L., Guevara, M., Shrier, A., Pérez, R. 1983. Bifurcation and Chaos in a periodically stimulated cardiac oscillator. *Physica* 7D:89-103
- Glass, L., Pérez, R. 1982. Fine structure of phase-locking. *Phys. Rev. Lett.* 48:1772-1775
- Hartline, D.K., Gassie, D.V. 1982. Artificially cross-coupled tonic neurons produce alternating bursts. *Soc. Neurosci. (Abstr.)* 8:739
- Kawahara, T. 1980. Coupled Van der Pol oscillators-A model of excitatory and inhibitory neural interactions. *Biol. Cybern.* 39:37-43
- Knight, B. 1972. Dynamics of encoding in a population of neurons. *J. gen. Physiol.* 58:734-766
- Mulloney, B., Perkel, D., Budelli, R. 1981. Motor-pattern production: interaction of chemical and electrical synapses. *Brain Res.* 229:25-33
- Omata, S., Yamaguchi, Y., Shimizu, H. 1988. Entrainment among coupled limit cycle oscillators with frustration. *Physica* 31D:397-408
- Pérez R., Glass, L. 1982. Bistability, period doubling bifurcations and chaos in a periodic forced oscillator. *Phys. Lett.* 90A:441-443
- Perez, R., Lomnitz-Adler, J. 1988. Coupled relaxation oscillators and circle maps. *Physica* 30D:61-82
- Peakin, C.S. 1975. *Mathematical aspects of heart physiology*. Courant Institute of Mathematical Sciences. New York University
- Poggio, T., Torres, V. 1977. A Volterra representation for some neuron models. *Biol. Cybern.* 27:113-124
- Rescigno, A., Stein, R., Purpale, R., Poppele, R. 1970. A neuronal model for the discharge patterns produced by cyclic inputs. *Bull. Math. Biophys.* 32:337-353
- Selverston, A., Moulins, M. 1966. Oscillatory neural networks. *Ann. Rev. Physiol.* 47:29-48
- Sporns, O., Roth, S., Seelig, F. 1987. Chaotic dynamics of two coupled oscillators. *Physica* 26D:216-224
- Stein, R., French, A., Holden, A. 1972. The frequency response, coherence and information capacity of two neuronal models. *Biophys. J.* 12:295-322
- Wang, X.J., Nicolis, G. 1987. Bifurcation phenomena in coupled chemical oscillators: normal form analysis and numerical simulations. *Physica* 26D:140-155