

Low dimensional dynamics in cardiac tissues. Experiments and theory

Robert F. Gilmour Jr.* ; Mari Watanabe* ; Dante R. Chialvo^{#+}

*Department of Physiology, College of Veterinary Medicine, Cornell University, Ithaca, NY, 14853-6401.

+Computational Neuroscience, SUNY, Syracuse, NY, 13210.

#Santa Fe Institute, Santa Fe , NM 87501.

ABSTRACT

Relevant beat-to-beat measures of local electrical responses during complex cardiac rhythms are interpreted as successive iterates of a low dimensional mapping. That simplified view is supported by previously reported experimental and numerical work. In that approximate theory, low dimensional dynamics (not restricted to chaos) also can be perturbed and controlled, much in the same way as in the Ott et al method for controlling chaos in nonlinear dynamical systems. In the problem at hand, which involves nonlinear waves and spatial degrees of freedom, the task is much more complicated and the phenomena less well understood. Recordings from an *in vitro* model of ventricular fibrillation are analyzed searching for deterministic recurrences in the local period of activation.

1- INTRODUCTION

Controlling complicated patterns of excitation in cardiac tissue during or preceding lethal arrhythmias is a major challenge which can have important clinical implications even if it is only partially successful. The application of strategies derived from the Ott, Grebogi & Yorke (OGY) method¹ to complex *in vitro* cardiac rhythms was first reported by Garfinkel et al². The extension of these initial results to the control of clinically relevant cardiac arrhythmias is hindered by the fact that i) cardiac dynamics evolve in time and space rather than on an isolated point, as in the OGY scenario; and ii) current knowledge of dynamical and electrophysiological aspects of ventricular fibrillation (VF) is incomplete at best. This paper describes in section 2 what is already known of a relatively simpler situation involving complex rhythms in periodically perturbed isolated cardiac tissue. Section 3 discusses the dynamics of certain measures during VF that are relevant for implementing control. The paper closes with a discussion of other "unknowns" that need to be considered in order to apply control in clinically relevant situations.

2- COMPLEX RHYTHMS IN ISOLATED CARDIAC TISSUES

A low dimensional model³ can account for simple and complex patterns of cellular electrical responses in periodically stimulated cardiac tissues. The entire dynamics in the experiments for which this model applies is *local*, the size (about 2-10 mm) of the cardiac tissue is such that no propagation, nor interaction, of waves in space are relevant. The model has a single independent variable: the time from the end of the previous response to the moment of the present stimulation, (the interval d). Three functions of " d " are needed: $t(d)$, the threshold stimulus intensity to produce a tissue response, i.e. an action potential; $a(d)$, the duration of an action potential; and $l(d)$, the delay from the stimulus to the beginning of the action potential.

For a given stimulus period (p) where the stimulus intensity (I_s) is suprathreshold, the next value of d is given by

$$\begin{aligned} d_{i+1} &= p - l_i - a_i \\ \text{for } I_s &\geq t(d_i) \end{aligned} \quad [1]$$

Whereas, if the stimulus intensity fails to elicit a response, then d will be

$$d_{i+1} = d_i + p$$

$$\text{for } Is < t(d_i)$$
[2]

For a given p and Is constant the model reduces to the iteration of a unidimensional map:

$$d_{i+1} = p - l_i - a_i$$

$$= p - g(d_i) \quad \text{for } Is \geq t(d_i),$$

$$= p + d_i \quad \text{for } Is < t(d_i),$$

$$\text{with } g(d) = a(d) + l(d)$$
[3]

The three functions $a(d)$, $t(d)$ and $l(d)$ are measured⁺ by perturbing once the tissue at several different d times. Then it is possible using Eq. 3 to predict all of the important features of the dynamics during repetitive stimulation at various parameter values. As parameters are changed the predicted dynamics includes a wide spectrum of periodic responses, period doubling bifurcations, and chaos. Those predictions agree very well with results obtained from numerical simulations using an ODE ionic model of cardiac cells⁴.

Experimentally, low dimensional chaos consistent with the predictions of Eq. 3 was reported³ under driving periods of 170-200 msec, preceded by at least one period doubling bifurcation. Figure 1 reproduces an example of chaotic dynamics. In this case the consecutive amplitudes (which are also a function of d , see discussion in reference 3-4) of the

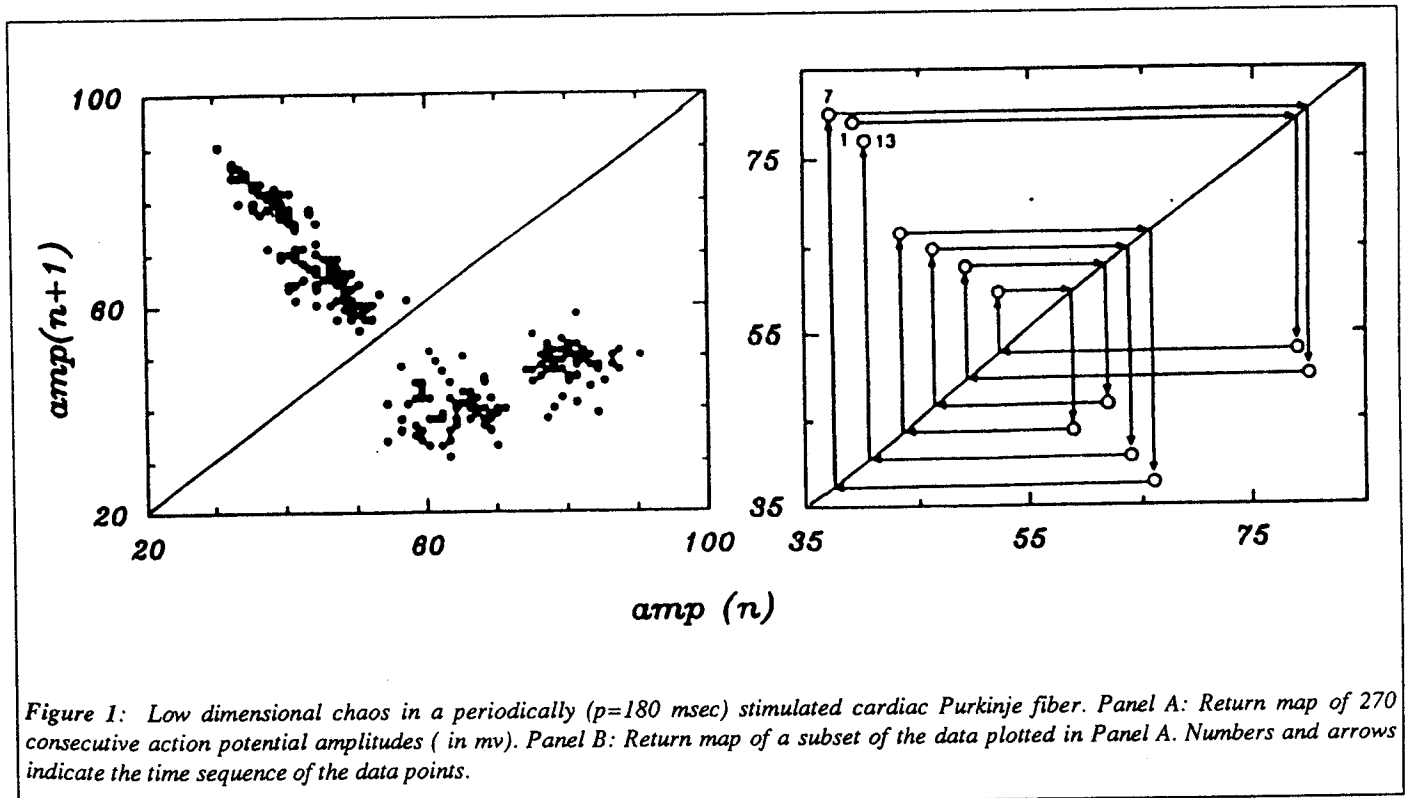


Figure 1: Low dimensional chaos in a periodically ($p=180$ msec) stimulated cardiac Purkinje fiber. Panel A: Return map of 270 consecutive action potential amplitudes (in mv). Panel B: Return map of a subset of the data plotted in Panel A. Numbers and arrows indicate the time sequence of the data points.

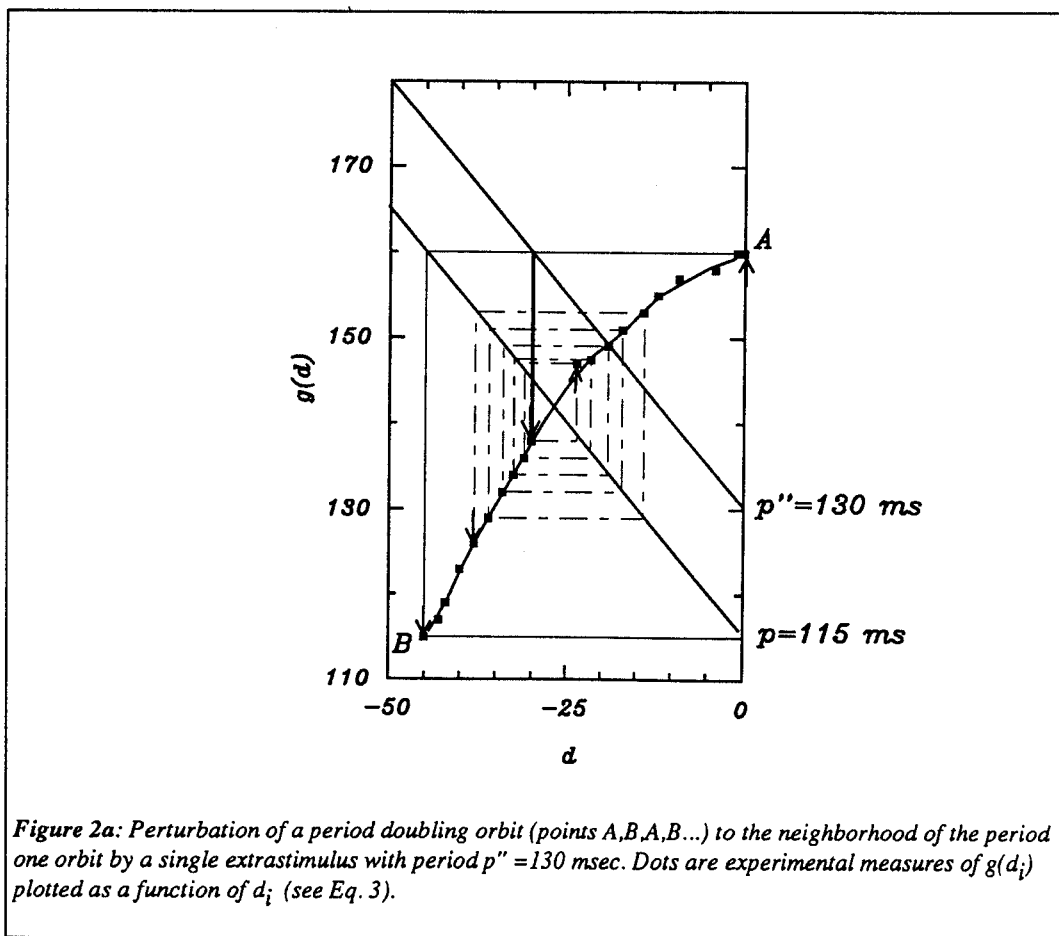
⁺ Measurement of these functions is straightforward, see examples in references 3-4

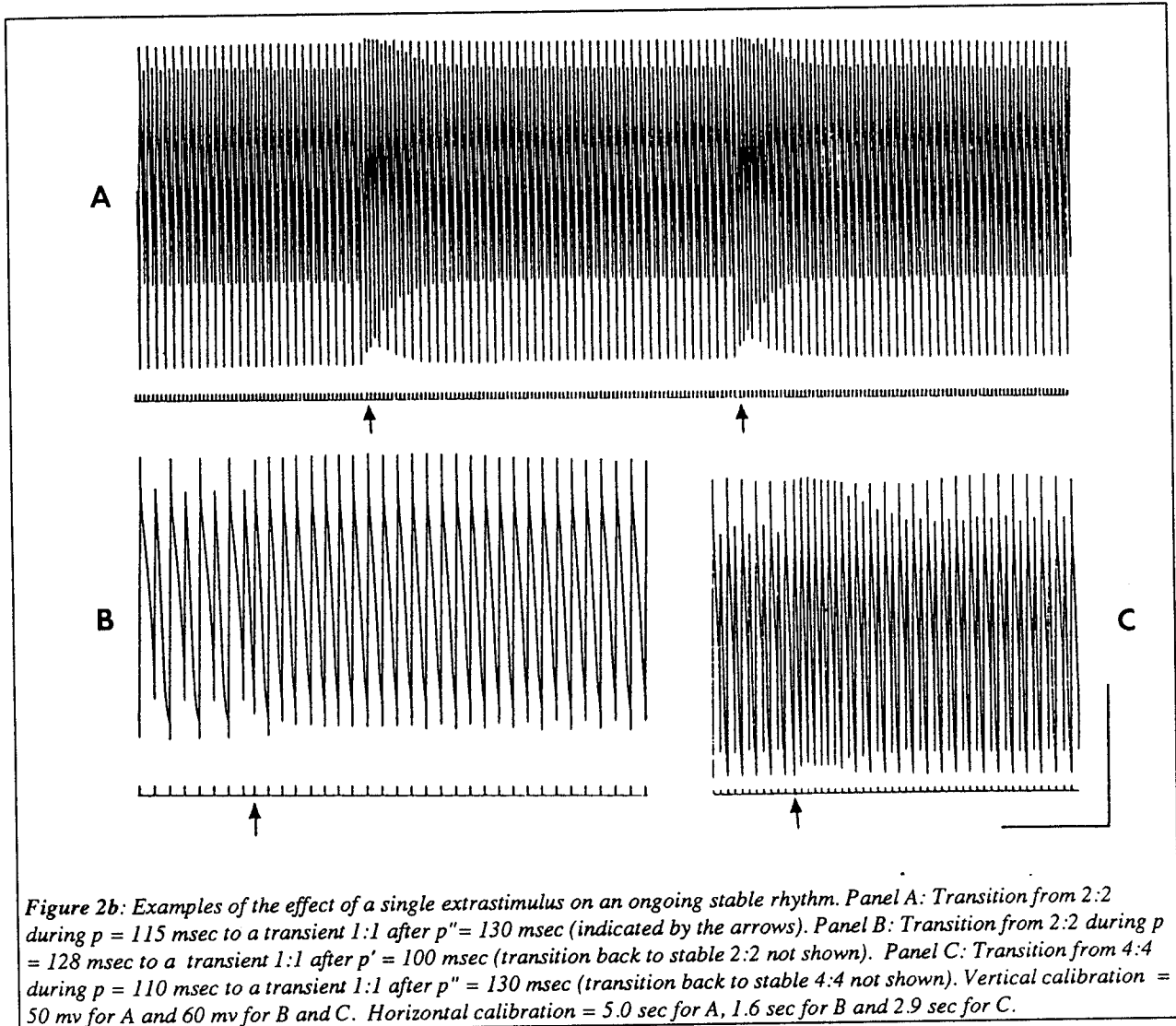
responses is plotted. Notice that during aperiodic activity the consecutive amplitudes follow a sequence compatible with the iteration of a unimodal map with sensitive dependence on initial conditions.

During driving at a constant p , the resulting period doubling or chaotic dynamics can be altered by the insertion of a single premature or postmature pulse (i.e., shorter or longer than p , respectively) at certain times. Consider the simple case of a period 2 cycle that results from $p = 115$ msec plotted in Figure 2. In this figure experimental measures of g on the i^{th} beat are plotted versus its respective d (on the same i^{th} beat). By plotting the data in this way (instead of as a return map of consecutive $g(d)$) one can solve graphically Eq. 3 for any p : the identity line in this graph crosses both abscissa and ordinate at the p value.

The stable pattern is an alternans between responses of 160 msec and 115 msec (points labeled A and B respectively in the figure). In the intersection between the identity line labeled $p = 115$ and the function $g(d)$ lies one of the unstable fixed points, which corresponds to 1:1 activation (i.e., one response of about 140 msec duration following each stimulus). As shown by the thick downward arrow, a single extrastimulus with $p'' = 130$ msec sets the system near the fixed point of period 1. Afterward, since the stability of the new orbit is marginal (at best), consecutive responses (dots connected by dotted lines) diverge towards the stable period 2 fixed point.

Figure 2b shows the intracellular recording obtained in an actual experiment of the type described in Figure 2a. The tissue is being driven at a constant period (marks at the bottom of each trace). The basic rhythm corresponds to period doubling bifurcations (2:2 panels A and B and 4:4 in panel C) which precede the chaos illustrated in Figure 1. In each case an instantaneous change from p to p'' (indicated by the arrows) results in a (transient) period 1 that eventually evolves to the basic stable rhythm, as discussed above.





3- SEARCHING FOR DETERMINISTIC RECURRENCES IN VENTRICULAR FIBRILLATION

In the preceding section dynamical control of various response patterns was predicted from a simple but basic knowledge of the electrophysiological mechanisms. It was sufficient to know the nonlinear response of g vs d and p to correctly interpolate a single extrastimulus and set the desired pattern. In principle, application of a similar strategy to the control of VF requires: i) a *deterministic low dimensional* recurrence of spontaneously occurring p during VF and ii) a good understanding of how spatial degrees of freedom contribute to the dynamics being recorded at a single point.

To determine whether a decipherable pattern of cycle lengths exists during VF, action potentials were recorded from isolated pieces of canine left ventricle (approximately 30 cm^2 and 1 cm thick) during perfusion of the left coronary artery with normal Tyrode solution at $32\text{-}36^\circ\text{C}$. With low frequency external stimulation this experimental preparation shows "normal" traveling waves. Using a short train of rapid stimulation, a self-sustained complicated spatiotemporal activation develops that approximates *in vivo* VF. This experimental setup has the additional advantage of providing a relatively stable environment

during the arrhythmia (as opposed to the *in vivo* VF preparation that degrades very rapidly). An example of an action potential recording obtained during such an experiment is shown in Figure 3.

To infer spatial information based solely on the data recorded at a single point is not straightforward. However, from first principles of nonlinear excitable waves some information can be extracted from the data. Relatively large amplitude upward deflections (and of relatively long duration; for example, the first three at the beginning of the recording) on the traces in Fig. 3 indicate that a wavefront has propagated through the point of recording. On the other hand, the smaller upward deflections (which are frequent during VF and absent during normal rhythm) are an indication that either: a) a wavefront has approached but not crossed the recording site, or b) a wavefront is being initiated at the site (to become, as it propagates, a larger deflection a few mm away). The interval between upward deflections is sometimes referred to as cycle length (equivalent to p or period of activation here)

During VF new wavefronts are being continuously 1) generated, 2) propagated, and 3) subsequently extinguished by collision. New wavefront/s can be generated from the residual wavelets of the collision. The lifetime of this 1-2-3 cycle can be estimated by the rate of occurrence of the small amplitude, short duration action potentials, since they reflect either

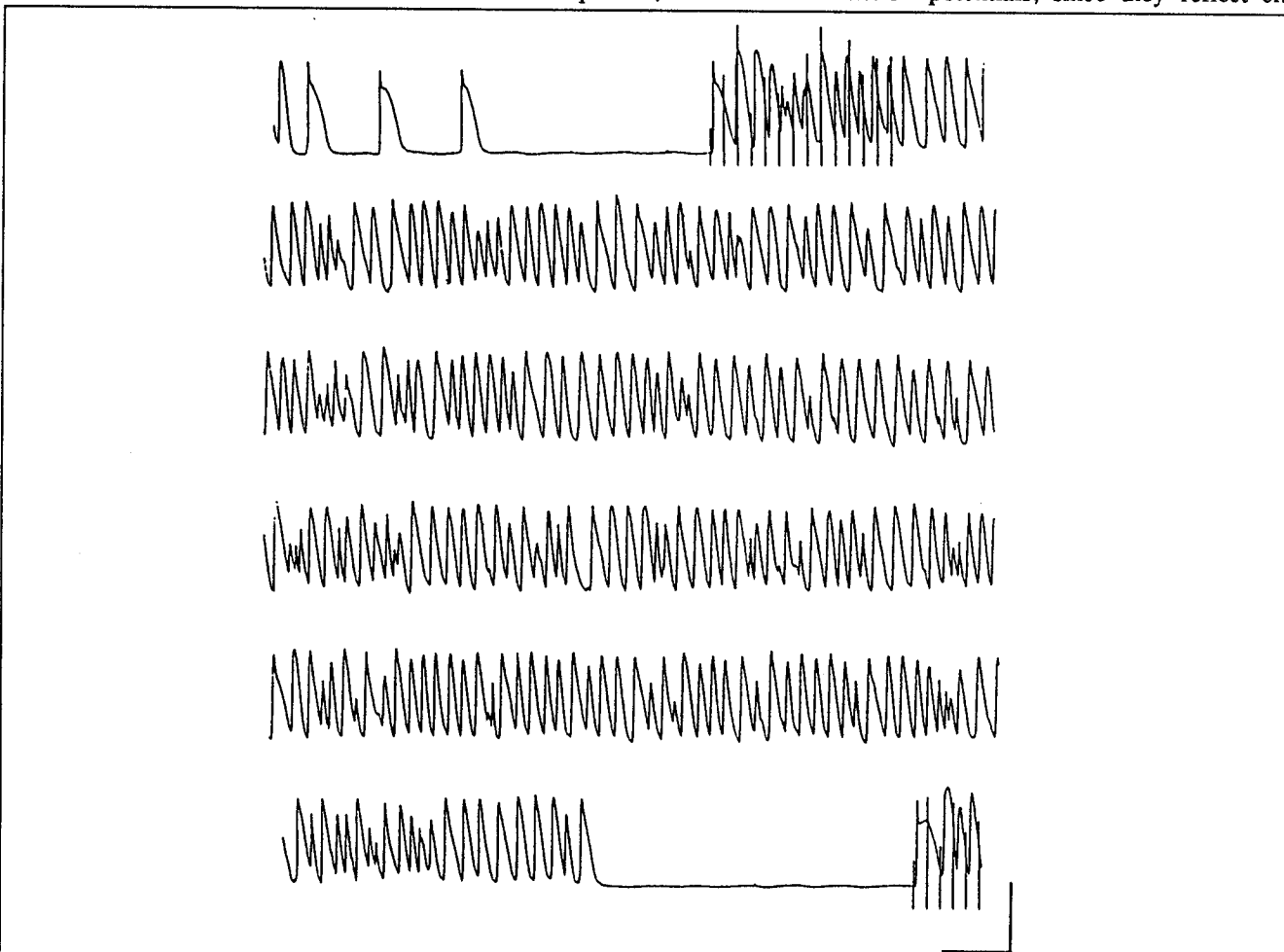


Figure 3: Intracellular membrane potential recording from an isolated perfused section of canine left ventricle. Traces are continuous. After a period of quiescence, VF was induced using a train of 14 stimuli delivered at a cycle length of 100 msec (upper right). VF terminated spontaneously and was reinitiated after a period of quiescence (lower right). Vertical calibration = 80 mv. Horizontal calibration = 0.5 sec.

origination or termination of a wavefront. In other words the small events recorded at any given site should have a mean rate related with this process of creation-destruction of waves. An attractive conjecture is whether the "stability" of VF (and the possibility of spontaneous or induced termination of the arrhythmia) can be characterized on these terms.

How significant are the patterns (if any) of activation during VF? Is there any deterministic recurrence that can be detected? A simple testable null hypothesis is that the activation intervals measured from the recording in Fig. 3 occur randomly. Surrogate time series⁵ (realizations of the null hypothesis) are constructed by reordering at random the raw intervals such that first order statistics are preserved while higher orders are destroyed. Then a given statistic is measured in both raw and surrogate data sets. Finally, the significance at which the null hypothesis can be rejected is calculated. For the specific concern here, which is to detect recurrences in the activation intervals, the point spectra⁶ is calculated in raw and surrogate data sets.

Figure 5 shows that there are two significant frequency components in the activation interval fluctuations. One high frequency (of about 10-11 Hz), which corresponds to the mean interval, and the second at low frequency (around 1 Hz) which probably corresponds to the mean time of revolution of the loop already suspected from inspection of the return map.

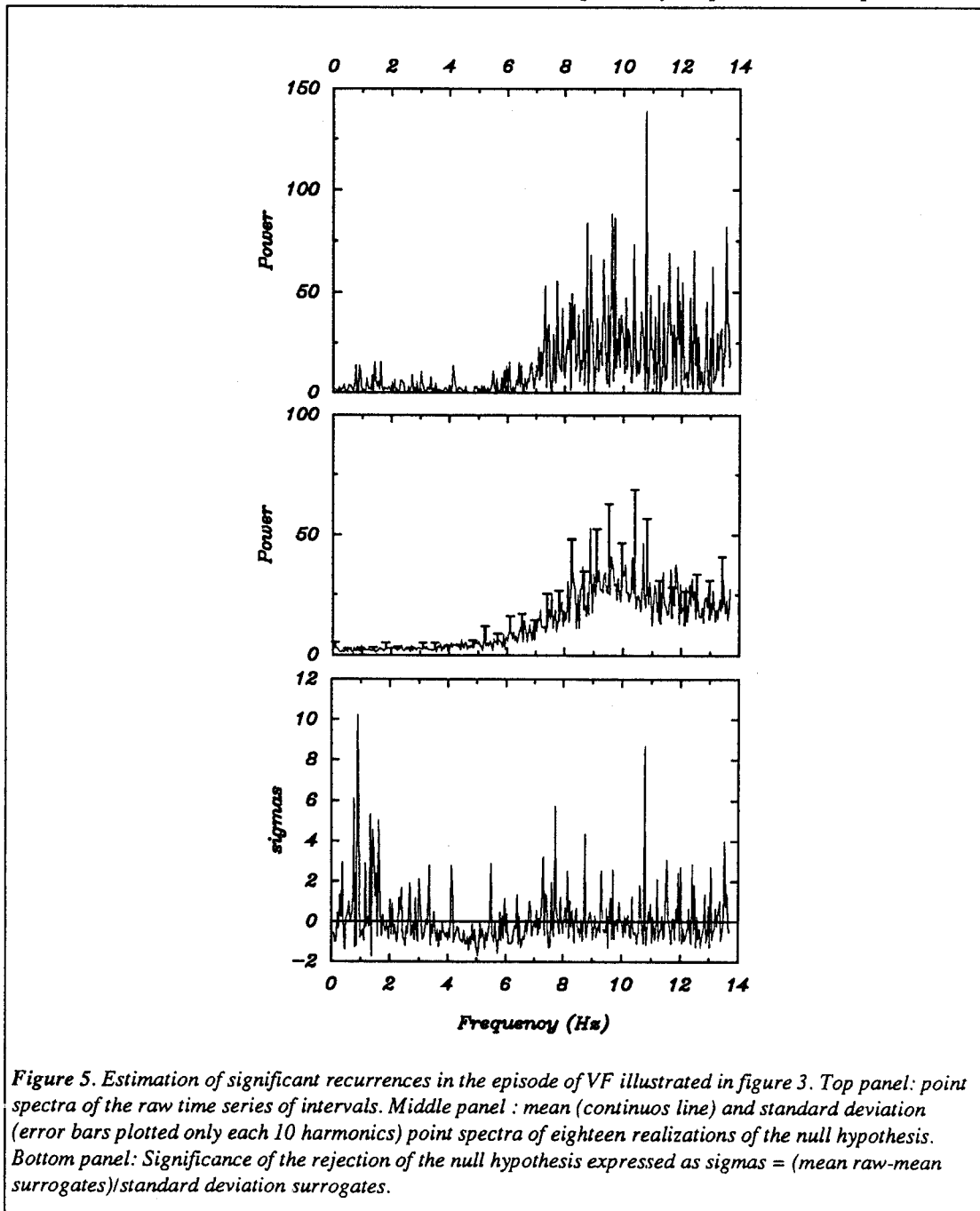


Fig. 4. The low frequency fluctuation could be associated with the process of creation-destruction of new waves mentioned before, probably due to shifts and interactions in space of multiple reentrant vortices, as postulated by Winfree⁷ and demonstrated experimentally by Johnson et al⁸.

4- WHAT ELSE (IS UNKNOWN TO US)?

Theoretical studies on VF are heavily based on an understanding of periodic solutions in extended excitable media. As such, the theory of spiral waves seems crucial for explaining the very beginning of VF^{7,8}. However, it appears that once established, VF is not built upon a linear sum of a few of these periodic solutions. The view followed here is that VF is a dynamical "monster" that needs to be understood *de novo*. Its relevant dynamical components, stability in parameter space and so on are completely unknown, despite many years of research⁹⁻¹¹ (most of the time in random directions).

It seems obvious to first characterize what is going on during VF, rather than to force the available theory of spiral waves to accommodate the experimental observations. If VF is composed of a *very large* number of interacting spirals (which probably is correct, considering recent data⁸), then attempting to understand the dynamical scenario from bottom-up (i.e., from one to several spirals) could be as unproductive as to study fluid turbulence from a particle physics viewpoint. Rather, it may be more productive to build a first order theory for the dynamical scenario of VF by quantifying relevant deterministic components in simple *in vitro* models of VF, and their fluctuations, for instance the mean lifetime of waves, their relation with electrophysiological variables and variation under external forcing or control in a relatively small area. Oversimplified numerical models of VF¹² already have shown that many of the dynamical properties seen in the experimental preparation can be understood in these terms.

5- ACKNOWLEDGMENTS

Partially supported by NIMH grants MH 47184 and MH 50064 (DRC) and by NIH grant HL-40800 (RFG). MW is a Howard Hughes Medical Institute Predoctoral Fellow.

6- REFERENCES

1. Ott E, Grebogi C, Yorke JA: Controlling chaos. *Phys. Rev. Letters*: 64:1196-1199, 1991
2. Garfinkel A, Spano M, Ditto WL, Weiss GN: Controlling cardiac chaos. *Science* 257: 1230-1235, 1992.
3. Chialvo DR, Gilmour RF Jr, Jalife J: Low dimensional chaos in cardiac tissue. *Nature* 343:653-657, 1990.
4. Vinet A, Chialvo DR, Michaels D, Jalife J: Nonlinear dynamics of rate-dependent activation in models of single cardiac cells. *Circulation Research* 67: 1510-1524, 1990.
5. Theiler J, Eubank S, Longtin A, Gladrikian B, Farmer JD: Testing for nonlinearity in time series: the method of surrogate data. *Physica D* 58:77-98, 1992.
6. Cox DR, Lewis PA: *Point processes*. Chapman and Hill 1966
7. Winfree AT: *When Time Breaks Down, The Three Dimensional Dynamics of Electrochemical Waves and Cardiac Arrhythmias*, Princeton University Press, 1987.
8. Johnson EE, Rollins DL, Wolf PD, Smith WM, Ideker RE: Mechanism of ventricular fibrillation as mapped with 524 closely spaced simultaneously recorded epicardial electrodes. *Circulation* 86:I-820, 1992.
9. Watanabe Y, Toda H, Uchida H: Electrophysiological mechanisms for the initiation and maintenance of ventricular fibrillation in non-ischemic rabbit hearts. *Heart and Vessels* suppl 2:69-87, 1987.
10. Witkowski FX, Penkoske PA: Activation patterns during ventricular fibrillation. *Annals of the New York Academy of Sciences* 591:219-231, 1990.
11. Kirchhof C, Chorro F, Scheffer G-J, Brugada J, Allesie M: The effects of rapid pacing on atrial fibrillation studied by high resolution mapping. *Circulation* 84:II-503, 1991.
12. Chialvo DR, Gilmour RF Jr.: Searching for deterministic recurrences in an in vitro model of ventricular fibrillation. *Proceedings of NATO ARW*, Leeds, UK, 1993.