



OBSERVATION OF A PERIOD DOUBLING BIFURCATION DURING ONSET OF HUMAN VENTRICULAR FIBRILLATION

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We find evidence of a period doubling bifurcation and transition from pseudo-periodic chaos to a stable limit cycle during onset of ventricular fibrillation (VF) in humans. Novel radial basis modeling techniques are applied to time series of spontaneous VF to estimate time dependent changes in the dynamics. Furthermore, we show that the spectral power content may be used as a surrogate for the underlying bifurcation parameter. With this spectral power measure we demonstrate a characteristic transition from pseudo-periodic chaos to a second pseudo-periodic chaotic regime. The methods described in this paper are generic and applicable to any time series data.

Keywords: Ventricular fibrillation; period doubling; radial basis modeling.

1. Introduction

Ventricular fibrillation (VF) is a rapidly lethal cardiac arrhythmia and a common cause of death in the industrialized world. However, the mechanism underlying onset of VF and successful treatment via electrical defibrillation is poorly understood.

Experimental observations in humans and animals have shown that the cardiac system is inherently nonlinear and that significant nonlinear deterministic structure can be extracted from ECG time series recordings [Small *et al.*, 2000c; Small *et al.*, 2000b; Ravelli & Antolini, 1992]. Experimental preparations of cardiac cells have been shown to exhibit phase locking, period doubling and onset of chaos [Guevara *et al.*, 1981; Chialvo & Jalife, 1990; Savino *et al.*, 1989; Karagueuzian *et al.*, 1993].

However, these experiments consist of externally driven isolated cellular preparations. Theoretical models of the atrio-ventricular (AV) junction and periodically forced cardiac cells predict phase locking and period doubling bifurcation [West *et al.*, 1985]. Period doubling, from period 1 to period 2 (known in the medical literature as *alternans*), can be occasionally observed in the diseased heart (see, e.g. [Goldberger *et al.*, 1985]) and has recently been shown to precede ventricular fibrillation in theoretical models [Hastings *et al.*, 2000]. Cohen and colleagues have demonstrated period doubling (up to five times the base period) in the canine heart [Ritzenberg *et al.*, 1984] and have more recently shown that T-wave alternans is a significant predictor of arrhythmia [Klingenstein *et al.*, 2000].

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Although alternans is indicative of a period doubling bifurcation, a period doubling bifurcation route to chaos may not necessarily manifest itself as alternans. Alternans is defined as a doubling of the underlying *period* of a time series (see Fig. 3), a period doubling bifurcation occurs when the *order* of the periodic behavior doubles — typically to two periods very close to one another, i.e. Alternans is sufficient but not necessary. Many authors have speculated that a period doubling bifurcation may provide a route to chaos during ventricular arrhythmia in humans [Goldberger *et al.*, 1988; Hoekstra *et al.*, 1997; Zhang *et al.*, 1999]. However, no conclusive evidence has been provided. In this paper we infer the existence of a period doubling bifurcation route to chaos prior to the onset of ventricular tachyarrhythmia in humans through the analysis of nonlinear models of clinical ECG data. Whereas alternans is an easily observable and measurable phenomenon (Fig. 3) we apply nonlinear modeling techniques to search for more subtle features, not visually apparent in the original data. A period doubling bifurcation is *not* apparent from a cursory examination of the data in Fig. 1. We deduce the existence of such a bifurcation in a model of this data.

To search for time dependent nonlinear dynamic structure we employ powerful nonlinear radial basis modeling techniques described in [Judd & Mees, 1995] and generalized in [Small & Judd, 1998]. These modeling methods have the necessary nonlinearity to accurately describe cardiac dynamics (unlike linear or polynomial models) and are amenable to analysis with the techniques of nonlinear dynamical systems theory (unlike neural networks or local linear methods). Furthermore, these models are generic and the modeling algorithm is (in general) assumption free. By employing an information theoretic model selection criteria this algorithm chooses the simplest model that is consistent with the observed dynamics. To accurately model bifurcation in cardiac dynamics these existing methods must be modified. By embedding time as a state variable [Small *et al.*, 2001] we observe a period doubling bifurcation and chaotic dynamics during sinus rhythm and ventricular tachycardia (VT) immediately preceding VF. However, we find that successive runs of the modeling algorithm do not produce quantitatively identical results. Therefore, we explicitly calculate an index which we use as a surrogate for the true

(hidden) bifurcation parameter and embed this as a state variable. This technique produces characteristic and reproducible results. We observe a transition from pseudo-periodic chaos (sinus rhythm prior to VT and VF) to a stable limit cycle (during VT) and to (distinct) pseudo-periodic chaos (VF).

By pseudo-periodic chaos we mean the commonly observed type of chaos in systems such as the Rössler equations. A periodic orbit becomes bi-periodic and cascades through successive period doubling bifurcations; in the Poincaré section; to chaos. In the chaotic regime the system exhibits chaotic, approximately cyclic behavior. The modeling described in this paper characterizes the transition from the physiological states of sinus rhythm to VT and VF as a period doubling bifurcation.

We must emphasize that applying this modeling algorithm to experimental time series data cannot *prove* the existence of a bifurcation to chaos in the dynamical system underlying the observed data. However, this information theoretic modeling algorithm estimates the simplest dynamical system (model) that is consistent with the observed time series. We may then apply computational dynamical systems theory to estimate the bifurcation behavior of that model. From this we are able to show that this observed behavior is both consistent with the time series and also the simplest consistent behavior; from the class of models employed.

1.1. *Data*

We examine four recordings of spontaneous initiation and evolution of VF in human subjects. Such time series data are limited and difficult to obtain. Using a new data collection facility [Small *et al.*, 2000a] we have been able to record time series showing spontaneous evolution from sinus rhythm to VF, and subsequent treatment. In two of these recordings VF is preceded by VT. One of the other two recordings shows a direct transition from sinus rhythm to VF. The fourth recording shows bradycardic (slow rhythm) behavior prior to onset of VF. For each of these four recordings we selected an approximately 90 second (45000 data point) sub-sequence covering the transition from sinus rhythm, through any intermediate rhythms to VF. We down-sampled the time series by taking a four point moving average and sampling every fourth point, yielding 90 second episodes of approximately 11250 data points. Down sampling was done

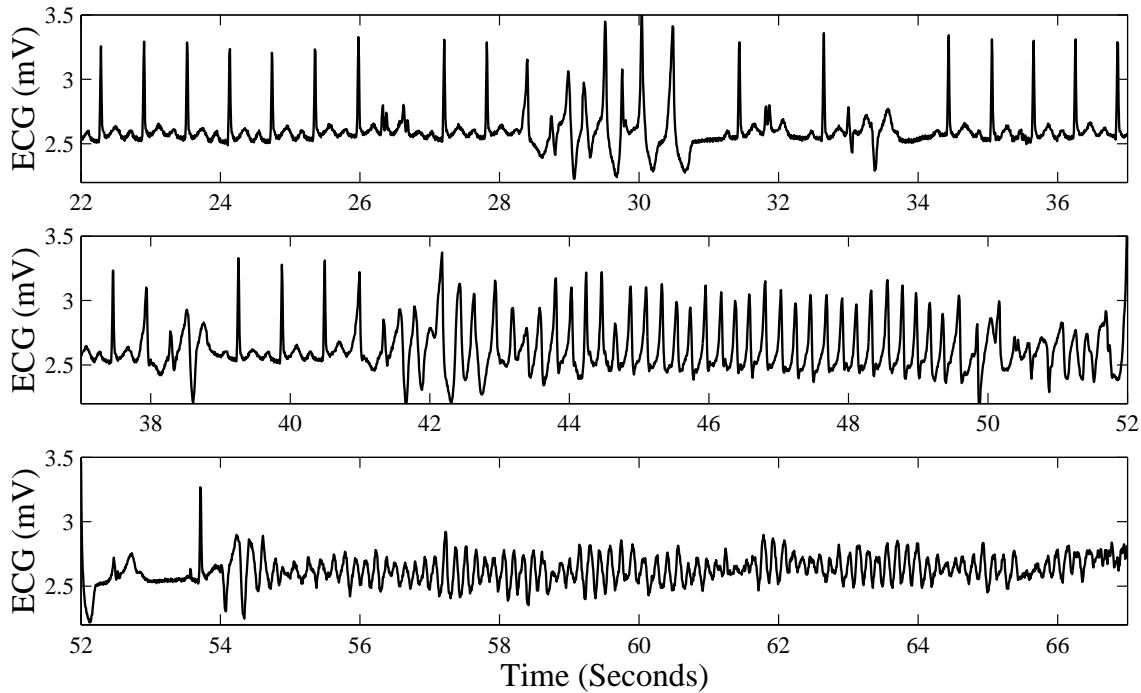


Fig. 1. **Spontaneous evolution of VF in a human.** The data shown here has been down-sampled to 125 Hz. On each plot the horizontal axis is time in seconds and the vertical axis is surface (ECG) electrical potential in milli-volts (mV). The top plot shows a short section of sinus rhythm, including ectopic beats. The second plot shows initiation and evolution of VT and the third shows VF. These plots are contiguous and the horizontal axes are equal. The entire data set is shown in Fig. 4(a).

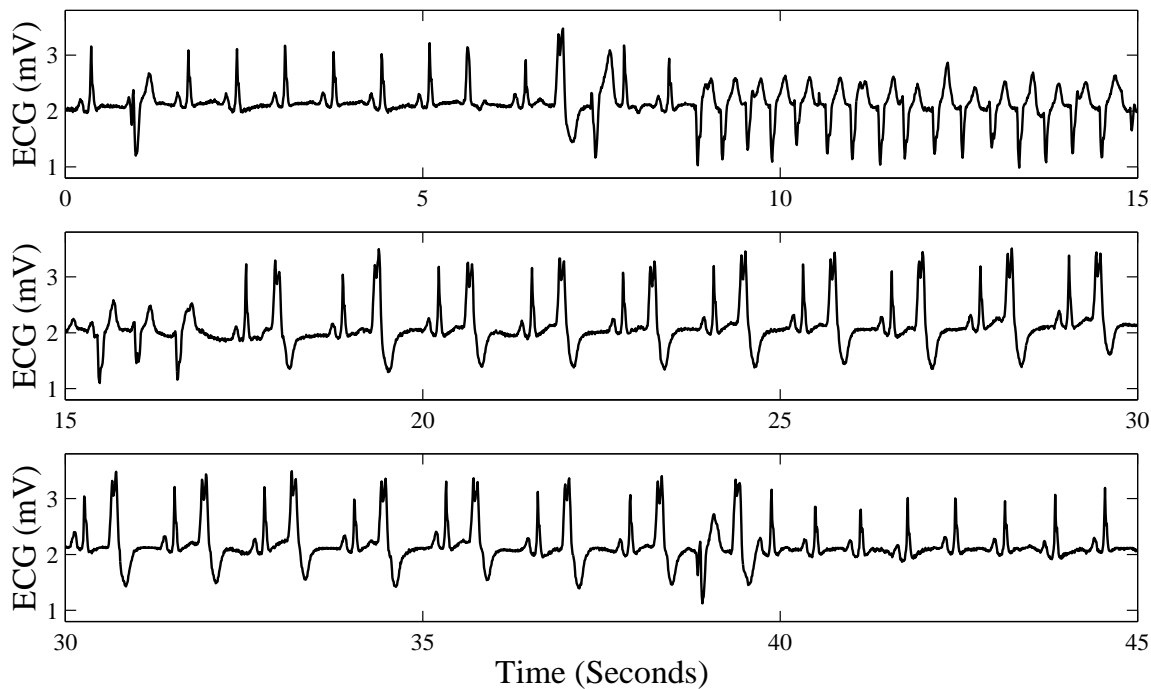


Fig. 2. **Spontaneous evolution of VT and bigeminy in a human.** The data shown here has been down-sampled to 125 Hz. On each plot the horizontal axis is time in seconds and the vertical axis is surface (ECG) electrical potential in milli-volts (mV). The top plot shows a short section of sinus rhythm and spontaneous evolution of VT. The second plot shows self-termination of VT, following this regular QRS complexes (normal heart beats) and ectopic (abnormal) beats alternate. In the third panel sinus rhythm is restored. These plots are contiguous and the horizontal axes are equal.

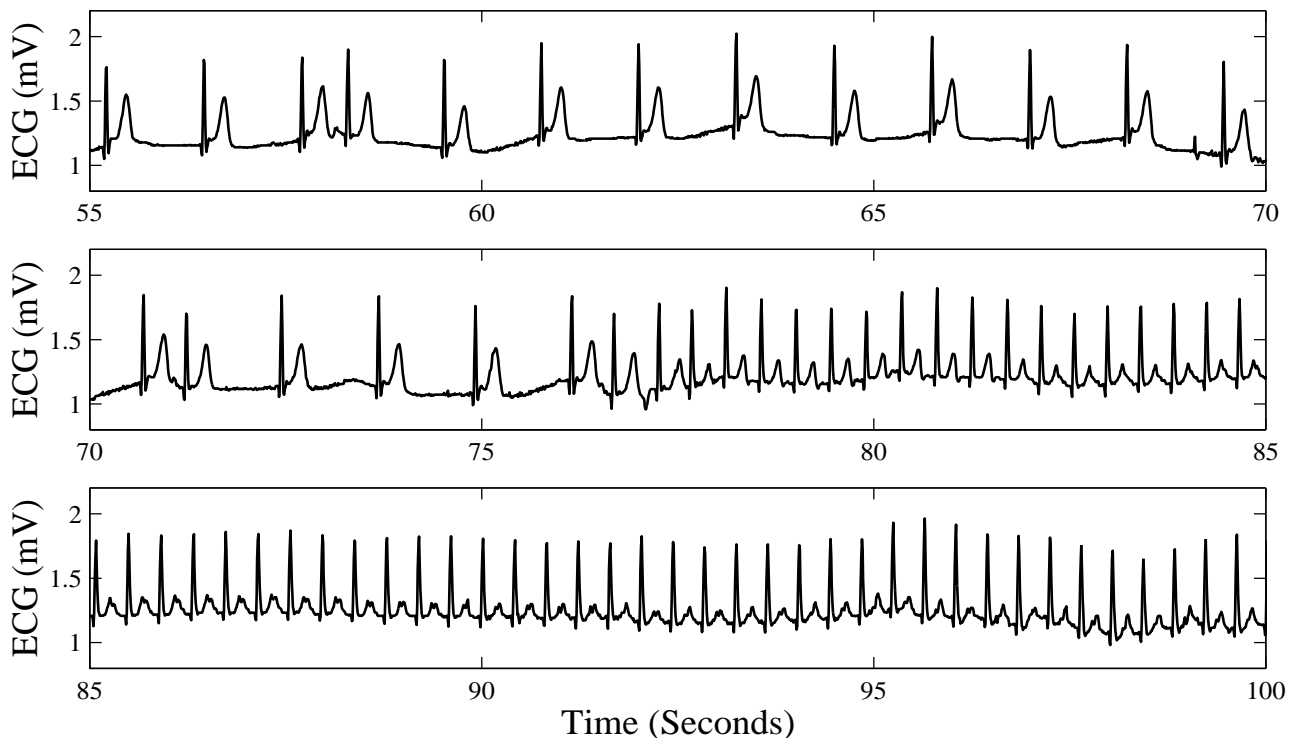


Fig. 3. **Period doubling in human ECG.** The data shown here has been down-sampled to 125 Hz. On each plot the horizontal axis is time in seconds and the vertical axis is surface (ECG) electrical potential in milli-volts (mV). This data shows a spontaneous period doubling in the respiratory rate of a human subject (at around 76 seconds). Prior to this several ectopic (premature) beats are observed (for example, at 57 and 71 seconds). These plots are contiguous and the horizontal axes are equal.

to reduce the computational load to a manageable level. By taking a four point moving average before down sampling we reduced the amount of temporal information in the time series but increased the spatial resolution. After down sampling, the first 11000 data points were used to construct a cylindrical basis model.

Figure 1 shows one of the recordings used in this study. For comparison we have also applied this analysis to recordings of other spontaneous evolving physiological rhythms. Figure 2 shows a recording of bigeminy (a phenomenon where normal and abnormal beats alternate) and Fig. 3 shows spontaneous alternans.

1.2. Overview

We apply nonlinear cylindrical basis modeling techniques to these data in two slightly different incarnations. In Sec. 2 we describe the nonlinear cylindrical basis modeling methodology we employ. Section 3 describes the application of this method

with no further assumptions about the underlying bifurcation. In Sec. 4 we assume that visually apparent structure in the time series is indicative of the underlying bifurcation and estimate a scalar time dependent parameter as a first approximation to the bifurcation parameter.

2. Cylindrical Basis Models and Minimum Description Length

Cylindrical basis models are a generalization of the well known radial basis models [Powell, 1992]. Let $\{y_t\}_{t=1}^N$ be a scalar time series on N observations. For an embedding window d_w , a cylindrical basis models is a function $F : \mathbf{R}^{d_w} \mapsto \mathbf{R}$ such that

$$F(z_t) = a_0 + \sum_{i=1}^k a_i y_{t-\ell_i} + \sum_{j=1}^m \lambda_j \phi \left(\frac{\|P_j(z_t - c_j)\|}{r_j} \right), \quad (1)$$

where $z_t = (y_{t-1}, y_{t-2}, \dots, y_{t-d_w}) \in \mathbf{R}^{d_w}$, $a_i, \lambda_j \in \mathbf{R}$ are the *weights*, $c_j \in \mathbf{R}^{d_w}$ are the *centers*, and $r_j \in \mathbf{R}^+$ are the *radii*. The lags ℓ_i satisfy $0 < \ell_i < \ell_{i+1} \leq d_w$ and the functions $P_j(\cdot)$ are orthogonal projections from \mathbf{R}^{d_w} to some subset of the coordinate axis. The functions ϕ are typically some class of C^2 functions satisfying $\int_0^\infty \phi(x) dx < \infty$. For the computations in this paper we use a combination of Gaussian basis functions and Morlet wavelets.

The essential difference between cylindrical basis models and standard radial basis models is the inclusion of the projection functions $P_j(\cdot)$. These functions allow for the projection onto different, significant, subspaces of \mathbf{R}^{d_w} in different parts of phase space. This is both useful and intuitive since the complexity of most nonlinear dynamical systems varies with location in phase space. For example, the Lorenz attractor is basically two dimensional on the “wings”, but the central separatrix contains a three-dimensional structure [Judd & Mees, 1998].

The function F is used to approximate the evolution operator of a dynamical system by

$$F(z_t) = F(y_{t-1}, y_{t-2}, \dots, y_{t-d_w}) = y_t. \quad (2)$$

With the *model size* (k, m) fixed, our modeling algorithm selects $a_i, \ell_i, \lambda_j, c_j, r_j$ and $P_j(\cdot)$ such that the model prediction error

$$\text{Error} = \sum e_t^2 = \sum_{t=d_w+1}^N (F(z_t) - y_t)^2, \quad (3)$$

is minimized. The optimal model size is then selected by finding the values of k and m such that the model *description length* is minimized. The description length of a model is roughly the amount of compression of the original data that is achieved by describing the model and model prediction errors, over specifying the original data values [Judd & Mees, 1995; Small & Judd, 1998; Small *et al.*, 2001]. The idea of minimum description length was originally described in [Rissanen, 1989].

For a given model (1) with error specified by (3) the description length is approximately

$$\frac{N - d_w}{2} \left(1 + \ln \frac{2\pi e^T e}{N - d_w} \right) + \left(\frac{1}{2} + \ln \gamma \right) (k + m) - \sum_{j=1}^{k+m} \ln \delta_j \quad (4)$$

where γ is the constant number of (binary) orders of magnitude required to cover the range of the data

and δ_j are the precision with which one must specify each of the $(k + m)$ model parameters (the a_i and λ_j terms in (1)). The δ_j terms are computed as the solution of $(Q\delta)_j = 1/\delta_j$ where Q is the second derivative of (1) with respect to the model parameters A_i and λ_j .

3. Assumption Free Modeling

The model described by Eqs. (1) and (2) is time independent. The process we are modeling exhibits time dependent features and these equations are unlikely to provide an adequate model. One possible solution is to model each of the parameters $a_i, \ell_i, \lambda_j, c_j, r_j$ and $P_j(\cdot)$ as a function of time. However, this approach is somewhat impractical. A more feasible approach is to extend the embedding

$$z_t = (y_{t-1}, y_{t-2}, \dots, y_{t-d_w}) \quad (5)$$

to

$$\hat{z}_t = (y_{t-1}, y_{t-2}, \dots, y_{t-d_w}, \xi(t)) \quad (6)$$

so that time t is explicitly included as a dependent variable of $F(\hat{z}_t)$ [Small *et al.*, 2001]. The affine transformation ξ is included so that the time index “stretches” the attractor. If ξ is too large, then the embedded points \hat{z}_t will be too sparse in phase space, if ξ is too small then there will effectively be insufficient separation. For this data we have found that it is sufficient to choose ξ so that the maximum and minimum values of $\xi(t)$ are the same as the maximum and minimum of y_t . In general, a more robust choice may be to define ξ in terms of the standard deviation of y_t .

The modeling algorithm we apply in this paper must minimize a nonlinear function (description length) of several variables ($a_i, \ell_i, \lambda_j, c_j, r_j$ and $P_j(\cdot)$). To solve this problem completely is beyond our limited computational resources. For this reason the algorithm we have implemented involves a stochastic search for a local minimum of description length. For many data sets this is sufficient to obtain reproducible and consistent results [Judd & Mees, 1998, 1996; Judd & Small, 2000; Small *et al.*, 1999a; Small *et al.*, 1999b]. We have tested this modeling algorithm with four systems with known bifurcation structure and obtained good agreement between actual and predicted results [Small *et al.*, 2001]. This modeling methodology is able

to accurately uncover bifurcation structure from time series simulations of (i) the Rössler equations, (ii) FitzHugh–Nagumo type simulations of ventricular arrhythmia, and (iii) nonstationary noise processes as well as from (iv) experimental data of infant respiration [Small *et al.*, 2001]. The computational simulations examined in [Small *et al.*, 2001] have well known and easily verifiable dynamics, this provides a test of the accuracy of this approach. We were able to correctly extract a nonstationary trend from an i.i.d. noise simulation [Small *et al.*, 2001] with a slight nonstationarity. When applied to a noisy simulation of the Rössler system undergoing a period doubling bifurcation the modeling algorithm was able to correctly identify the qualitative features of the bifurcation from the noisy data (5000 observations) [Small *et al.*, 2001].

The model we utilize here is an ordinary iterative map with a tunable parameter. This bifurcation parameter has been allowed to vary in the construction of the model. By keeping this parameter fixed and observing the iterated behavior of the model we have an estimate of the asymptotic dynamics of the system for that (fixed) value of the bifurcation parameter. For each such trajectory we estimate the (asymptotic) peak and trough values observed. For a periodic orbit these will be fixed; for period 2 dynamics there will be two distinct amplitudes; and for chaos the sequence of amplitudes will be irregular. It is these estimates of the asymptotic amplitudes that are plotted in Figs. 4 and 6 as a function of the bifurcation parameter. Representative trajectories for various values of the bifurcation parameter are depicted in Fig. 5. For example,

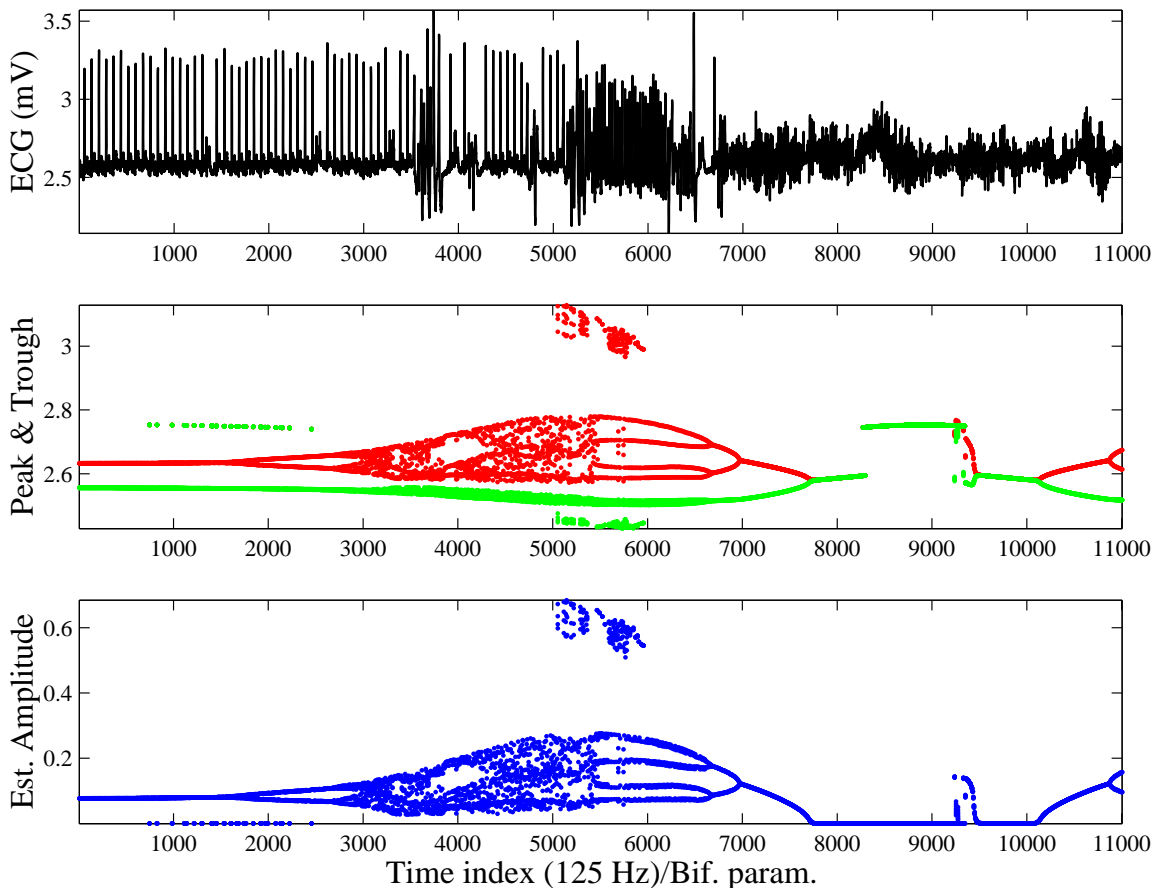


Fig. 4. **Period doubling chaos prior to onset of VF.** The top panel shows the original time series. The second panel shows the estimated asymptotic peak (red) and trough (green) values for fixed values of the bifurcation parameter. The bottom plot shows the estimated asymptotic amplitudes (blue). The horizontal axis is time series datum number, the model bifurcation parameter is an affine transformation of this. Sinus rhythm is characterized as a periodic orbit, prior to initiation of VT this periodic orbit undergoes a period doubling bifurcation and becomes chaotic. At onset of VT the chaotic behavior bifurcates to pseudo-periodic chaos and period 8 dynamics. At the transition to VF this behavior changes to a stable limit cycle and eventually a stable focus.

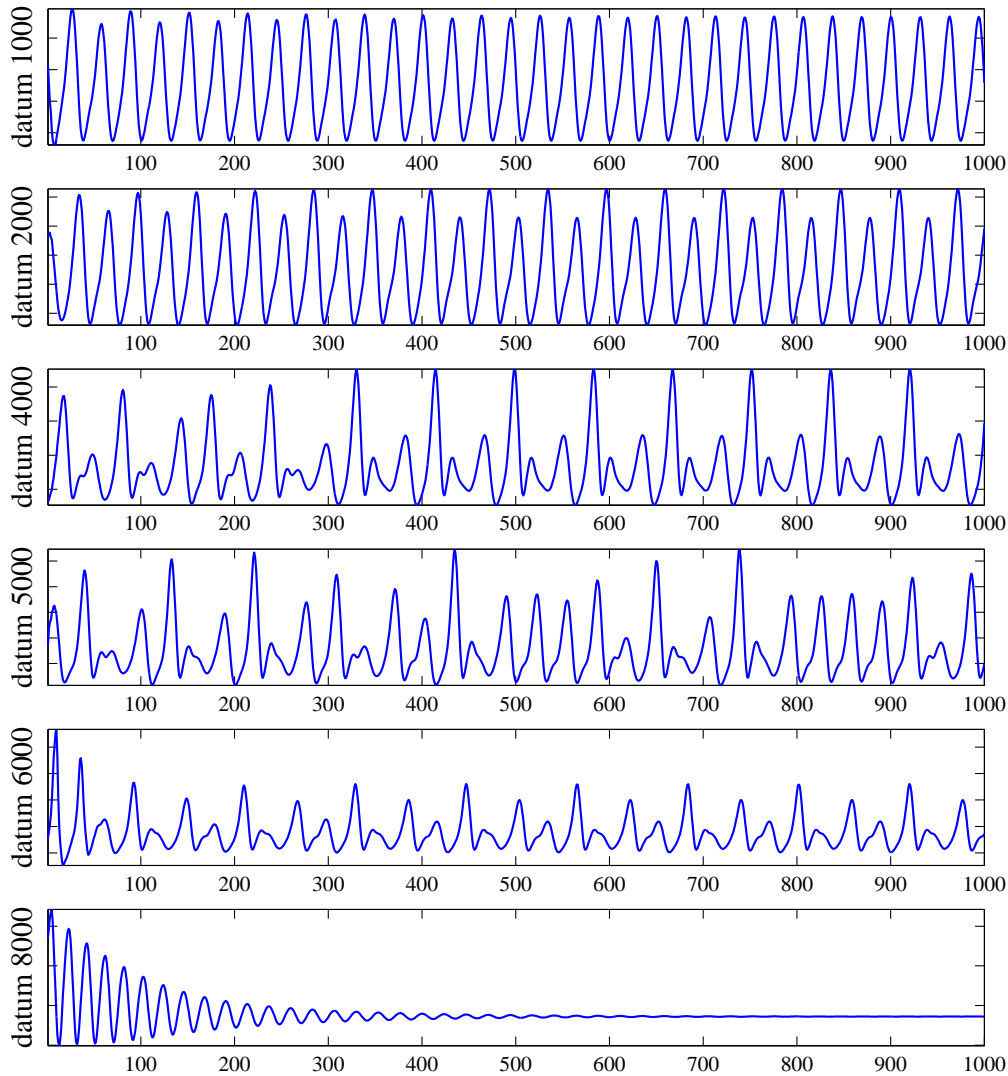


Fig. 5. **Trajectories estimates from a model.** For fixed values of the bifurcation parameter, the system is run for 1000 iterations. The dynamic behavior for various values of the bifurcation parameter are shown (from top): periodic, period 2, period 3, chaos, period 4 and a fixed point. The chosen fixed values of bifurcation parameter correspond to datum 1000, 2000, 4000, 5000, 6000 and 8000 of Fig. 4 (respectively). Trajectories such as these are used to estimate the amplitudes shown in Figs. 4 and 6. Note that while these trajectories do not capture the exact quantitative features of the system (for example, the periodic behavior observed at datum 1000 is unlike sinus rhythm ECG) these features are quantitatively appropriate.

from the representative trajectories shown in Fig. 5 we would deduce (from top to bottom): a periodic orbit with only one observable amplitude, period 2, period 3, chaos, period 4, and a fixed point (zero amplitude).

In Figs. 4 and 6 we provide an estimate, derived from a single application of our modeling scheme to the data set of Fig. 1. This estimate is representative of our other results. The dynamics presented in this figure contain all the various complex behaviors observed in separate runs of the modeling

routine. Some iterations of the modeling routine did not produce the complete period doubling bifurcation illustrated here. However, they all exhibited a complex bifurcation from pseudo-periodic regime (corresponding to sinus rhythm) to chaos (VT) and a stable periodic orbit or focus (VF). Models from each of the four recordings of onset of VF are qualitatively similar.

We compared this technique and the bifurcation behavior estimated from models with traditional frequency domain methods applied directly

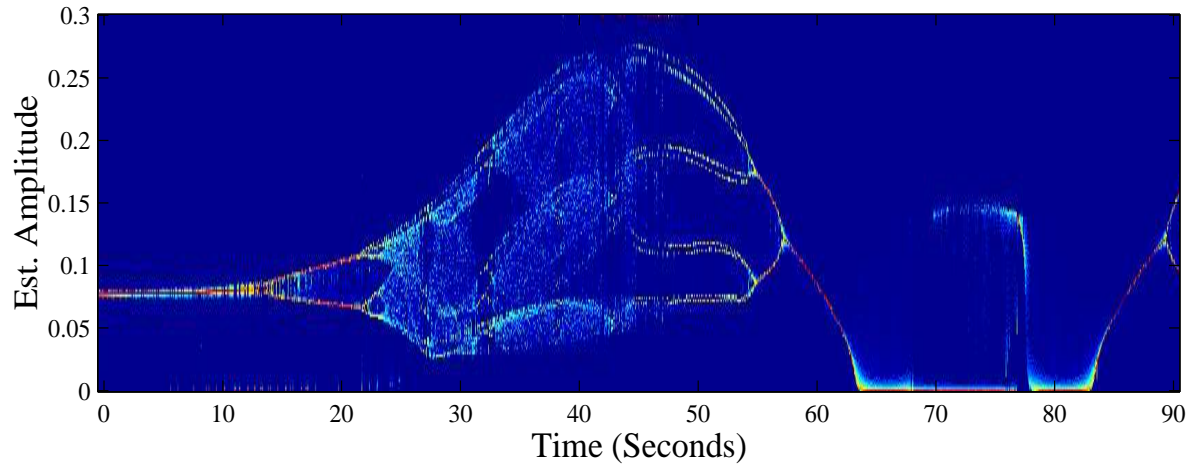


Fig. 6. **Period doubling chaos prior to onset of VF.** The calculation of Fig. 4 is shown here as a probability density plot. The figure depicts the estimated distribution of asymptotic oscillation amplitudes as a function of time (in seconds). High likelihood is depicted in bright red and low likelihood in dark blue.

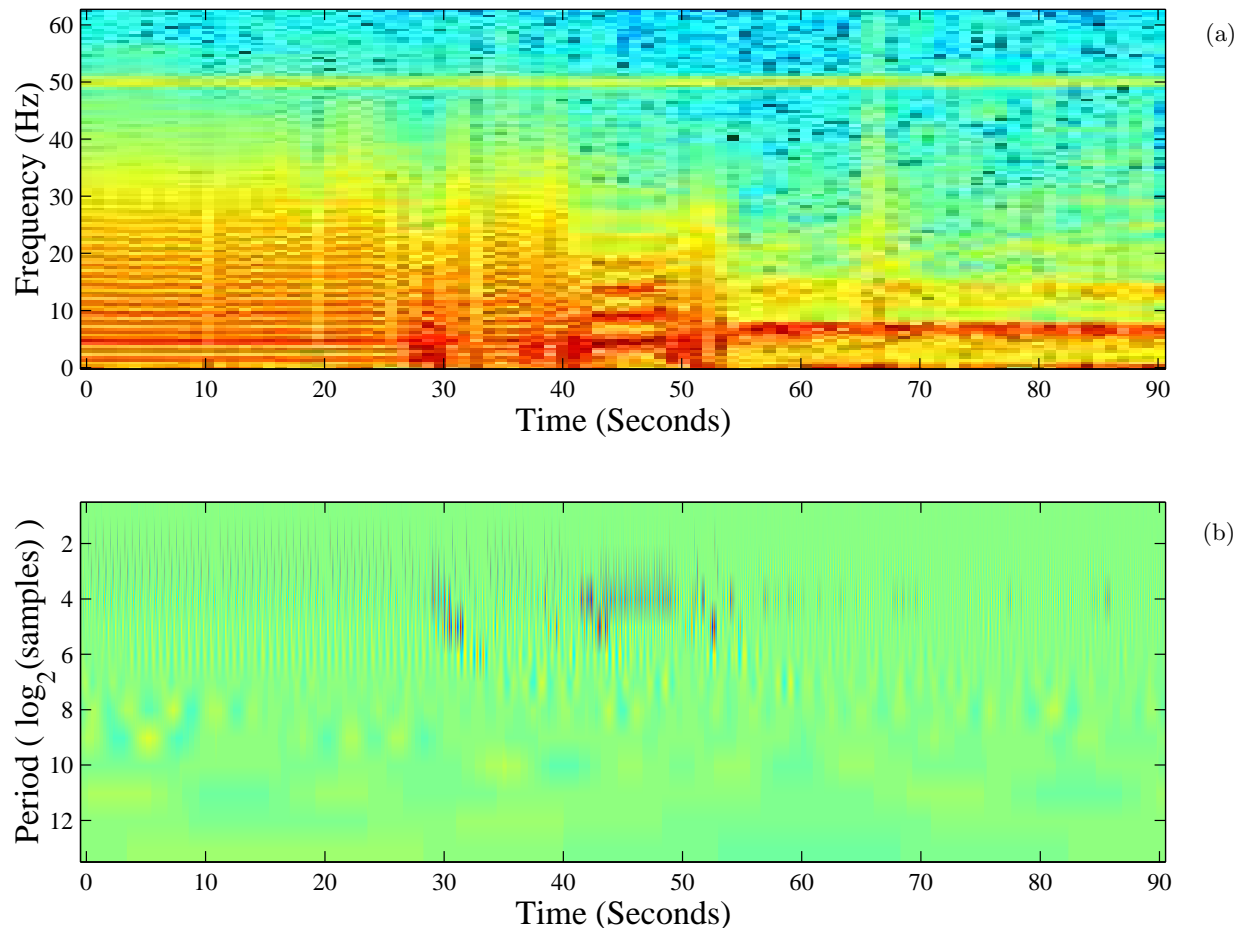


Fig. 7. **Period doubling chaos prior to onset of VF.** (a) Fourier spectrogram (256 FFT with an overlap of 128 points) and (b) wavelet analysis of the data used in Figs. 4 and 6. In contrast to the analysis in Figs. 4 and 6 these calculations provide little additional information compared to the original time series. Most of the change in frequency content that is observable from these plots is also observable directly from the original time series. High density is shown in red and low density in blue.

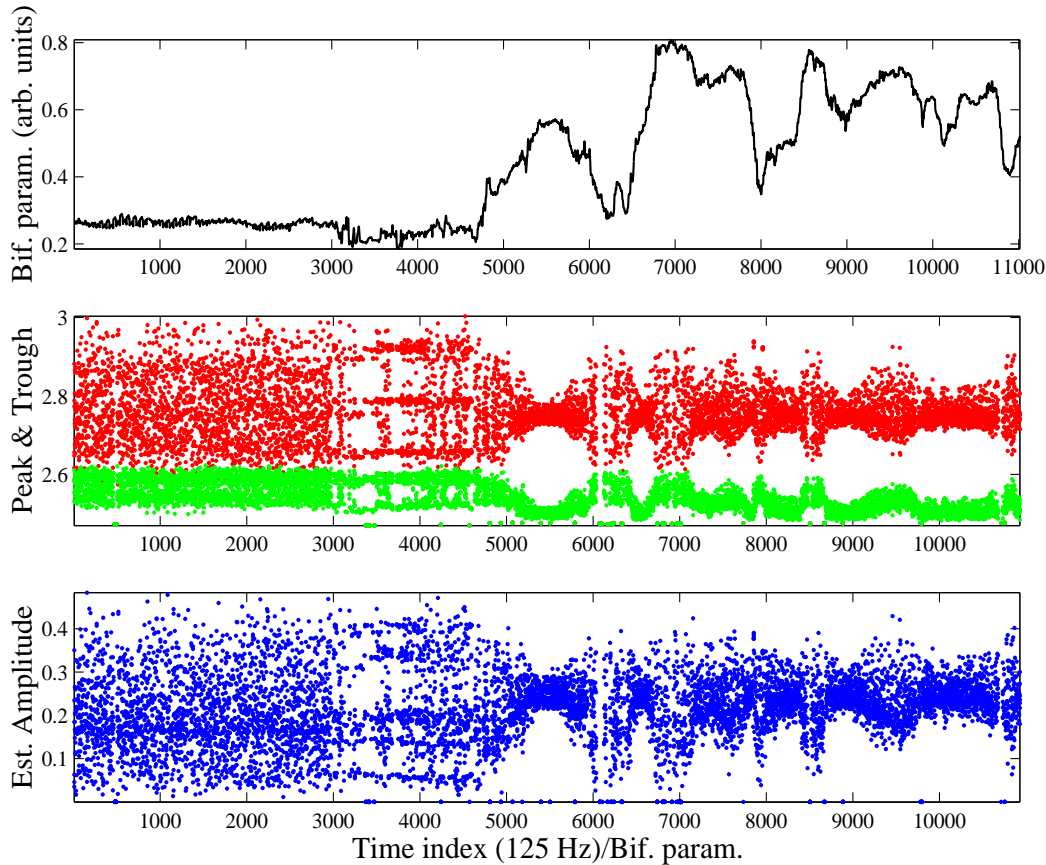


Fig. 8. **Bifurcation diagram estimated with surrogate bifurcation parameter.** The top plot shows values used for the bifurcation parameter as a function of the time index (sampled at 125 Hz) for the same data set as Fig. 1. The second plot shows the asymptotic peak (red) and trough (green) values as a function of the time index and the third plot shows the estimated amplitude behavior (blue). The complex period doubling bifurcation evident in Fig. 4(b) is absent, but a clear transition from large scale Rössler type chaos (for sinus rhythm preceding VF) through period 6 behavior (VT) to another pseudo-periodic chaotic regime (VF), is apparent.

to the data. Figure 6 is an estimate of the probability distribution of the amplitude of system orbits for various values of the bifurcation parameter (time index). The data is the same as the lower panel of Fig. 4, expressed as a probability distribution. For comparison we computed a windowed spectrogram and wavelet transform from the original data (Fig. 7). While the coarse time dependent features are evident in these plots, we find very little information not evident in the original time series. The asymptotic time behavior displayed in Fig. 6 is achieved by extrapolating the model dynamics for a model fitted to the data.

Qualitative features of period doubling and onset of chaos are present in each of the models despite this complex structure not being obvious in the original time series. The modeling algorithm is fitting subtle features of the asymptotic dynamics that

may not be observed directly during the comparatively rapid change in the system dynamics prior to (and during) onset of ventricular arrhythmia.

Although essential features are consistent between most models, this variation between models is somewhat unsatisfactory. The problem is that in addition to estimating unknown dynamics we are relying on the modeling algorithm to estimate an unknown bifurcation parameter at each point in time. To overcome this problem we estimated the bifurcation parameter *a priori* and built a model based on this bifurcation parameter.

4. *A priori* Bifurcation Parameter Estimation

Generically, the time series recordings of evolution of VF exhibit two or three of four distinct dynamical

regimes: sinus rhythm, VT, bradycardia and VF. A bifurcation parameter must reflect this. For the data presented in this paper, we found that the proportion of the power spectral content between 4 and 8 Hz performed well. Alternative indices including entropy, complexity and point-wise correlation dimension were also considered. However, we found that spectral power content provided the best separation between different physiological rhythms. In our experience spectral power content also performed best for real time identification of arrhythmia [Small *et al.*, 2000a]. Spectral power captures many of the essential features of the time series (Fig. 7). However, this spectral variation alone is insufficient to deduce the period doubling bifurcation and onset of chaos observed in models of this data. Figure 8 shows estimates of this quantity for the same time series as in Fig. 4.

We estimated the power content between 4 and 8 Hz for a 2048 point sliding window (before down sampling the original recordings) and used this quantity as a surrogate for the true, unknown, bifurcation parameter. That is, the embedding (5) or (6) is replaced by

$$\tilde{z}_t = (y_{t-1}, y_{t-2}, \dots, y_{t-d_w}, \xi(p(y_t))) \quad (7)$$

where $p(y_t)$ is the above mentioned statistic, and $\xi(\cdot)$ is an affine scale transformation. The remainder of the modeling process is identical.

Figure 8 depicts a representative result of this calculation for the data illustrated in Fig. 4. Repeated runs of the modeling algorithm on the same data produced equivalent results. The results between data sets were similar. Whereas the calculation estimating both model and bifurcation parameter would typically yield smooth bifurcation from a periodic orbit, to chaos (sinus rhythm prior to VT and during VT) and back to a noisy periodic orbit (VF) this is not the case with an *a priori* estimate of the bifurcation parameter. For smooth and gradual change in the values of this bifurcation parameter the change in the underlying dynamics is similarly subtle. However, as this parameter is estimated directly from the time series the value often changes fairly rapidly (Fig. 8), and this in turn produces sudden changes in the underlying dynamics. Closer examination of small changes in the bifurcation parameter do show a period doubling bifurcation during the transition between sinus rhythm and tachycardia. The weakness of this approach is that we are constraining the time dependent dynamics

of the model to conform to our expectation of the system, i.e. $\xi(p(y_t))$.

5. Conclusion

In this paper we have described two alternative techniques to examine the changing dynamics in experimental time series. Although we consider only human ECG recordings the method itself is generic and equally applicable to any experimental time series. Estimating the model and bifurcation parameter simultaneously (Sec. 3) provides a method of examining the changing dynamics with no *a priori* information. For short, noisy, or experimental data this method has its limitations. Primarily, the computational burden to estimate the optimal model, model parameters, and bifurcation parameter from a single scalar time series is immense. This problem meant that it was difficult to get fully repeatable results (for a single time series). Rather than obtain *the* global minimum of (4) the modeling algorithm would halt at a locally optimal value.

To reduce the computational effort we provided an alternative approach — estimating the model bifurcation parameter *a priori* (Sec. 4). This approach meant that the models produced were more easily repeatable (for a single time series) and also consistent (between different time series). The main problem with this approach is finding a “reasonable” surrogate for the bifurcation parameter, and the restriction of the dynamics that this implies.

Estimating the bifurcation parameter and model simultaneously meant that the problem of reproducing the dynamics was reduced to finding the right nonlinear function from (an affine transformation of) the time index to the underlying bifurcation parameter. By assuming an appropriate value of bifurcation parameter first, the existence of an injective mapping from the surrogate bifurcation parameter $\xi(p(y_t))$ to the underlying bifurcation parameter is not guaranteed (i.e. $p(y_t)$ is not necessarily a 1-to-1 function of t). However, we hope that a “reasonable” choice of the surrogate parameter will provide a trivial transformation from $\xi(p(y_t))$ to the underlying bifurcation parameter.

When applied to recordings of initiation of VF these modeling techniques provide a description of the simplest dynamical system (within the model class) consistent with the observed data. Observations derived from these models are possible dynamical phenomena consistent with the data. This does

not imply that the data must have been produced by such phenomena, only that such phenomena are a simple and compact explanation for the observed data. Prior to onset of ventricular arrhythmia, sinus rhythm may behave as a noisy dynamical system exhibiting Rössler type chaos (i.e. chaotic pseudo-periodic orbits). We also find evidence that a period doubling bifurcation may precede imminent ventricular tachyarrhythmia. In the arrhythmic state this dynamical system behaves as either Rössler type chaos (Sec. 3) or a stable focus (Sec. 4). We believe that this possible contradiction is due to limitations of the modeling process. When modeling both dynamics and estimating bifurcation parameter (Sec. 3) the modeling algorithm is unable to extract sufficient information from the VF and VT states to model them as more than noisy periodic orbits. When the bifurcation parameter is assumed *a priori* (Sec. 4), and $p(y_t)$ is a nonmonotonic function of t (i.e. the value remains the same at different times, leading to a more densely populated phase space) arrhythmic (VT and VF) behavior can be better modeled as pseudo-periodic chaos (Rössler type chaos).

These results imply that both sinus rhythm and VF may be characterized as chaotic dynamical systems. However the underlying dynamics during sinus rhythm, VT and VF are all fundamentally different. This result is therefore consistent with earlier work estimating dynamical invariants from time series [Small *et al.*, 2000c; Small *et al.* 2000b; Ravelli & Antolini, 1992; Small *et al.*, 1999b; Yu *et al.*, 2000]. The similarity between this result and various observations of alternans is significant but not conclusive. We observe an increase in the *order* of periodic behavior in the amplitude of respiration whereas alternans typically manifests as a *doubling* in the underlying respiratory rate (and sometimes observed directly as two distinct amplitudes). We found no evidence for chaotic bifurcations in recordings of alternans or bigeminy.

We also found that prior to onset of tachyarrhythmia the pseudo-periodic chaos observed in models of these time series becomes strictly periodic and a period doubling bifurcation may be observed as a mechanism *consistent with* transition between these states. These results are preliminary, and certainly not clinically significant. A much larger sample needs to be considered before definitive statements may be made. Nevertheless, observation of period doubling bifurcations prior to onset of VF suggest that the human cardiac system

undergoes a fundamental change in its dynamical state prior to onset. Methods such as Lyapunov exponent and point-wise correlation dimension [Yu *et al.*, 2000] estimation may therefore be applied to predict imminent arrhythmia. However, such algorithms need to be substantially modified to be both sensitive and accurate for extremely short time series if they are to be applied as clinical indicators of imminent arrhythmia.

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