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Nonlinear Cardiac Dynamics

Charles L. Webber, Jr.

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1. Introduction

1.1. The pulse as window into the heart

The beating heart has attracted attention since antiquity and probably before recorded history [1]. Some cultures have centered the human soul within the heart because of its vivacious and incessant actions. Careful reading of the Hebraic Psalms, for example, attributes thinking, feeling and soulish behaviors to this remarkable organ. Consider King David's anguish: "I am benumbed and badly crushed; / I groan because of the agitation of my heart. / Lord, all my desire is before You;/ And my sighing is not hidden from You. / My heart throbs, my strength fails me; / And the light of my eyes, even that has gone from me" [2]. Since time immemorial the cardiac pulse has been viewed as a window into the heart [1].

To the modern observer, the vigorous motions of the heart are a strong reminder that living physiological systems are dynamical in nature. Over the last century the dynamics of the heart have been refined and redefined by analogy to naturally rhythmical systems of nature extending to mathematical modeling and simulations. Indeed, the whole concept of homeostasis, a foundational so-called law of physiology, is even under revision. If homeostasis implies that a system is static with no motion, maybe the prime exemplar of homeostasis is the cadaver state! Possibly a simplistic but meaningful redefinition of physiology is "If it wiggles, it's physiology; if it stops wiggling it's anatomy" [3]. In this sense and beyond homeostasis, homeodynamics is being promoted as a better descriptor of living systems [4]. In terms of the heart, there are a variety of pressures fluctuations and heart rates that are permitted and even necessitated by the extant dynamical state (sleeping, sitting, running, etc.).

2. The sinusoidal cardiac pulse

The ubiquitous sine wave holds a unique position in the history of linear motions from sea-wave patterns to planetary revolutions around the solar mass. As shown in Figure 1, the sine wave may be considered a good first approximation to the waxing and waning of

ventricular and aortic pressure traces, both of which are attributed to alternations between ventricular muscle contractions (active phase) and relaxations (quiescent phase). The heart beats through the lifespan of the individual, but this does not infer that the heart gets no rest. It is good to remember that the "wake/sleep" cycle of this automatic organ is measured in terms of milliseconds, not hours or days. Rest in this context means that the myocardium is electrically silent, but the heart still continues to consume energy throughout both systolic and diastolic phases.

On closer inspection, however, the mechanical motions of the heart are highly complex and ventricular pressure waves and arterial pressure pulses are not well-fit by the simple sine wave. A single sine wave has a characteristic amplitude and period that repeats forever (infinite series), and knowing the details of one wave allows one to accurately extrapolate into the future with mathematical confidence. But the heart is not like this. Each beat and each period of the heart is different, unique to the moment and suited for the current environmental challenge. Besides this, the heart is a noisy system (noisy dynamic) simply because it resides within a noisy world. There is dynamical noise arising from within the organ itself, the heart is jostled by breathing and stepping motions, neuronal reflexes are constantly modulating cardiac function, and external noise from the environment shape and
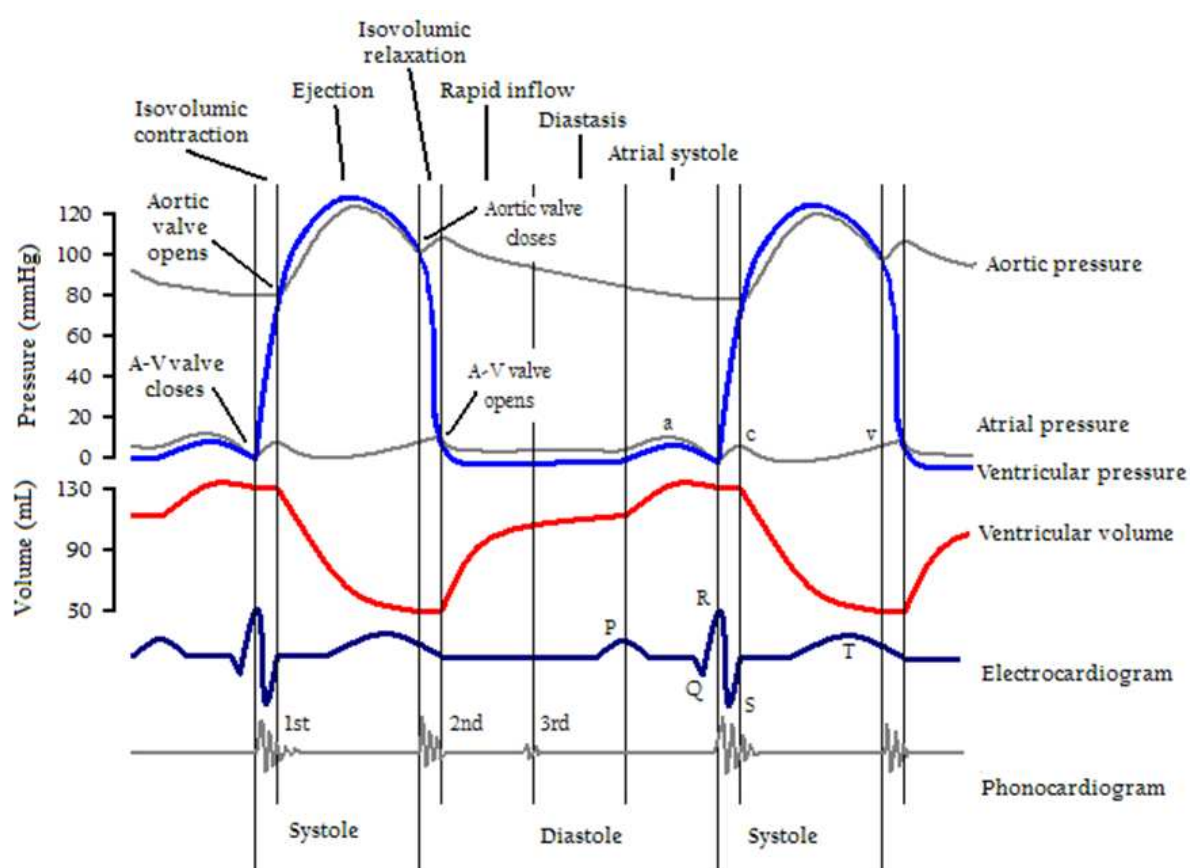

Figure 1. The famous Wiggers diagram displaying the time variations in cardiac electrical and mechanical functions as recorded by a polygraph. Note that the shape of the ventricular and aortic pressure traces can, on first pass, be mimicked by a simple sine wave. (from Wikepedia: http://en.wikipedia.org/wiki/Wiggers_diagram)

mold the activity of the heart. Thus, not only is the heart dynamic in nature, it is also very flexible, perfectly suited to the world in which we live.

3. Electrical underpinnings of the cardiac pulse

Cardiac dynamics go way beyond mechanical pressure generation (which can be sensed by arterial vessel palpitation), but also depends upon electrical activities inherent within the myocardium (which are insensible, save by electronic amplification and display). The heart remains mechanically silent until it is electrically activated. But activation depends upon electro-mechanical coupling which is calcium dependent in cardiac myocytes. The physiological principle (cause → effect) as shown in Figure 2 is this: electrical activity (phase 0) → calcium induced calcium release (CICR of phase 2) → mechanical contraction of atrial and ventricular muscle cells [5]. In one study, the median left ventricular electromechanical delay (EMD) of 103 control subjects was 17 ms, with calcium release preceding mechanical force generation [6]. The summation of electrical depolarizations of ventricular action potentials (phase 0 in Fig. 2) are registered as the QRS waves in the ECG (electrocardiogram in Fig 1). Likewise, the summation of electrical repolarizations of ventricular action (Phase 3 in Fig. 2) are registered as T waves in the ECG (electrocardiogram in Fig 1). Note that because of the long phase 2 plateau of the ventricular action potential, there is an isopotential phase between the Q and T waves, the QT interval.
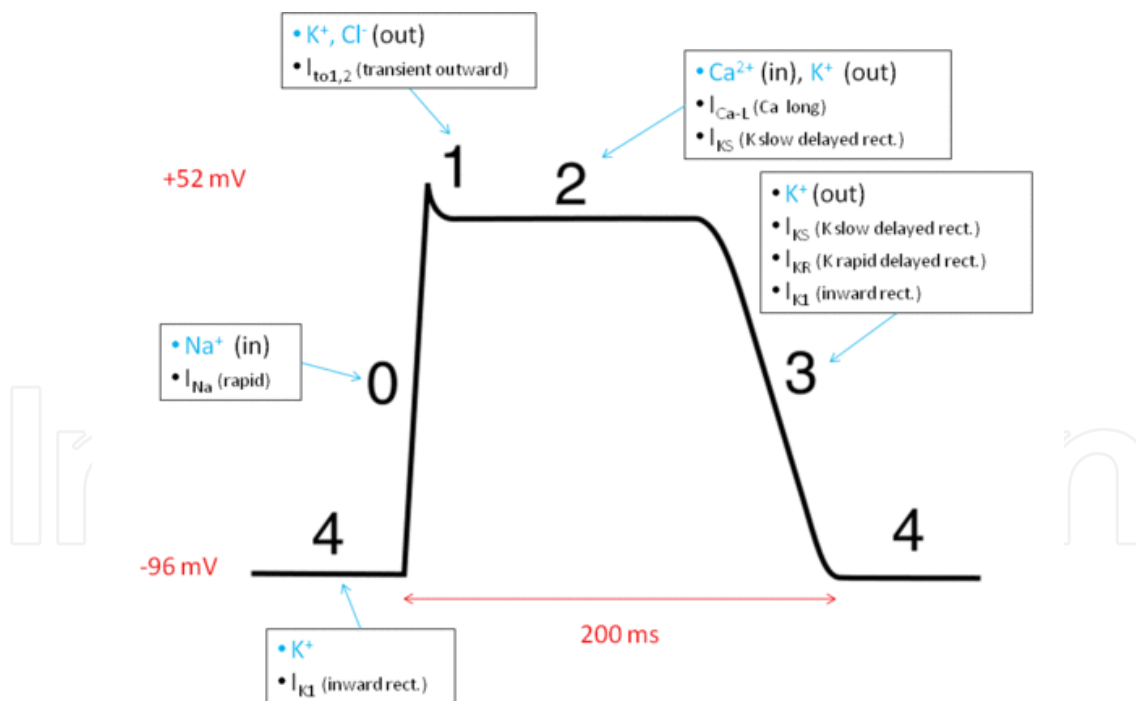

Figure 2. The five phases of the ventricular muscle action potential. (from Wikepedia: http://en.wikipedia.org/wiki/Cardiac_action_potential)

What all this means is that there are different levels or different dimensions of cardiac rhythmicity. One could study cardiac mechanics and blood pressures, one could examine electrocardiological signals of the whole organ or isolated cardiac myocytes, or one might

delve into the dynamics of calcium fluxes within single heart cells. Dynamical details abound for the clever investigator to mine, interpret and hopefully apply to cardiac patients with abnormal dynamics for a myriad of different, sometimes subtle, reasons. But before one can discuss abnormalities in cardiac functioning, normal rhythms, beatings and cyclings of the heart must first be comprehended as best as possible. What is normal in this respect must cover a wide territory or legal (healthy) dynamical possibilities (homeodynamics). Because so many demands are placed on the heart, the normal heart must be flexible enough to survive environmental challenges and heavy workloads. It is.

4. The rate of the heart

Starting off most simply, cardiac dynamics can be captured in the variable heart rate. As an aside, some reports in the literature erroneously label as adjustable fixed parameters those observables which are in reality fluctuating physiological variables [7]. Heart rate can be detected manually by palpitation of the radial systolic pulse or automatically measured from an intravascular catheter (beats per minute). Heart rate of a different flavor can be recorded from surface electrocardiograms or cardiac muscle electrograms (electrical pulses per minute). These two heart rates are similar but not identical. Notably, in some diseased hearts it is possible for the developed ventricular pressure to be so weak that cardiac ejections occur only on every other contraction cycle. In this case the radial pulse rate would be half that of the ECG rate. Since artificial pacemakers take their cues not from hemodynamic feedbacks, but from non-physiological indicators, their clinical effectiveness can be compromised in certain situations.

However measured, the fundamental problem with heart rate is that it represents an average over several beats in which case beat-to-beat periods (instantaneous rates) are not identical. Here the variability of the dynamic can be captured in the standard deviation. Still, this is not a fool-proof definition of variability since these deviations from the mean may not be normally distributed (non-Gaussian). To the extent that these physiology-math mismatches are real, attempting to capture natural variability in terms of homestatic and Gaussian statistics is a huge error both conceptually and practically [8]. Means and standard deviations are linear descriptors fully appropriate for linear systems. But what if, in fact, cardiac dynamics are actually non-linear? The truth is that it is now widely recognized that the functions and fluctuations of the heart are highly nonlinear [9]. Might it be concluded that as the sine wave is to the arterial pressure pulse, so are the mean and standard deviation to cardiac dynamics?

As second point to grasp is that taking the mean filters out and minimizes (morphs, contorts or even destroys) dynamical details. Worse yet, taking means create fictive realities that do not exist in nature. For example, it is well known that the heart accelerates as one starts exercising. And even when the heart rate levels off at some plateau correlated to the work load of the exercise regime, it is proper to stay the system is in some kind of "steady-state?" What does steady-state really mean anyway? Again, in the spirit of homeodynamics [4], maybe such states are better comprehended as quasi-steady states or simply dynamic states

within a corralled boarder consistent with the status of the individual. And over time, the dynamic state can move in time and space either by following deterministic rules within a narrow regime or by allowing for some stochastic expansion of the perimeter border in which multiple motions are permitted and encouraged.

5. The cardiac period

If the cardiomyocyte is the functional unit of the myocardium, the cardiac period is the fundamental time signature of the heart cycle. This cardiac period can be measured in different ways and yielding different values, yet time intervals are superior to rates since no ratios are encountered. The absolute interval (neither relative nor ratio) could span the time from one systolic beat to another between aortic pressure pulses, or it could be the time lapse from one R wave to the next in the ECG (see Fig. 1). RR intervals must be understood as discrete events weather or not they form random point processes or are connected entities with deterministic structures. Quantitative analyses can distinguish the two possibilities, but the discrete RR interval remains the fundamental marker of cardiac timings.

The second marker of cardiac timing represents the smooth flow of events occurring between beats. In this case (see Fig. 1) the variable could be the continuous ventricular or aortic pressure trace, the simple ECG presented as a time series, or even a cardiac electrogram measured with electrodes embedded in the heart. In either case, mechanical or electrical, the variable of interest is a single continuous function, one that is not discretized into intervals (e.g. analogous to a sine wave). Many models of cardiac function, mechanical or electrical, can take the form of continuous differential equations that are parameterized to captures the contours of the wave being mimicked. High digitization rates are, of course, required to faithfully capture accurate waveforms.

Sequences of discrete cardiac intervals and continuous heart variables can be studied in the time domain (functions of time) as displayed on polygraph recordings. However, another perspective on discrete and continuous events is to transpose the signals into the frequency domain. For example, if one computed the frequency spectra of the ECG, the resultant spectrum would consist of the power of the signal at different frequency bands (not shown). One of the most useful techniques, however, has been computing the frequency spectra of sequenced cardiac periods using the Fast Fourier transform [10]. Three typical peaks emerge from such an approach as shown in Figure 3. High frequency oscillations (HFO. 0.15-0.40 Hz) are typically attributed to ventilation effects on the cardiac cycle due to the waxing (inspiration) and waning (expiration) of vagal efferent inputs to the sinoatrial node. This is known as the classic respiratory sinus arrhythmia (SA) [12]. The HFO peak (hatched area) near 0.3 Hz represents a breathing frequency of 18 breaths per minute. Low frequency oscillations (LFO, 0.04-0.15 Hz) are associated with sympathetic activity with some parasympathetic contamination as it were. Nevertheless, the LFO/HFO ratio is commonly computed as a measure of autonomic imbalance with high ratios favoring sympathetic tone and low ratios favoring parasympathetic tone. Lastly, the origination of very low frequency oscillations (VLFO, 0.01-0.04 Hz) is very controversial but may be related to heart period

changes driven by the very slow oscillation in the renin-angiotensin-aldosterone system or thermoregulation [13]. One major clinical investigation has produced standards of RR spectral measurements, physiological interpretation, and clinical utilization [14].
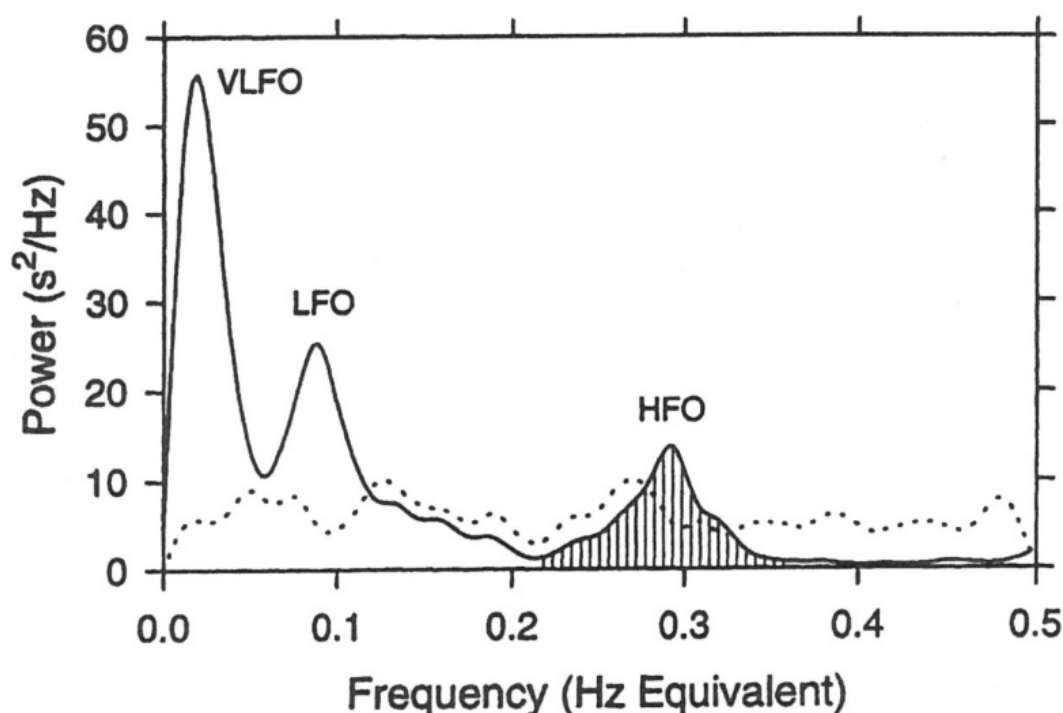

Figure 3. Power spectrum of human PP intervals before (solid line) and after random shuffling (dotted line) of intervals. Reproduced from reference [11] with permission.

The spectral analysis of RR intervals is commonly known as heart rate variability (HRV). The name is kind of a misnomer, because the spectral analyses are performed on heart periods not heart rates (a ratio). Nevertheless, all such computations are classified as linear and one dimensional. That is, the Fourier spectrum consists of the linear sums of sine and cosine waves which reconstruct the time domain signals (even square waves can be approximated with an infinite number of summations of wide ranging frequencies). With the growing appreciation that physiological signals are, among other things, highly nonlinear, another popular methodology has come to the forefront, approximate entropy (ApEn) [15]. This technique uses RR intervals as the input and treats then as chains of information. Low values of ApEn indicate that the cardiac signals have a deterministic structuring, whereas high ApEn values signal that the signals are more random or stochastic. There are technical problems associate with ApEn measures of complexity [3], but the utility of the approach cannot be denied.

6. The cardiac period in recurrence space

Physiological systems, including the cardiovascular system, are not only nonlinear, but they can be nonstationary, high-dimensional, and noisy. Such "miss-behaved" dynamics are characteristic of real-world systems. To tame the signals rendering them suitable for

classical analyses often requires filtering, smoothing, clipping of outliers, detrending, interval replacements, etcetera, all of which contort the original signals. For this reason the first introduction of recurrence plots in the physics literature [16] became highly attractive to physiologists [17, 18]. Recurrence plot can be generated from any time-varying (or space-varying) signals consisting of either discrete intervals or continuous flows. The attraction of recurrence plots is that they are distribution-free, model-free, and have utility in dissecting out meaningful information from signals living on a dynamical transient and buffeted by noise. Higher dimensions are captured in surrogate variables by employing the principles of the embedding theorem of Takens [19]. What this means is that the windowed signal is divided up into short vectors of length EMBED and compared with each other exhaustively. If two vectors "match" by falling beneath a threshold radius value, then the leading points of the paired vectors are said to be recurrent. To render the data visible, a point is placed at the intersection of each and every vector i and vector j (e.g. for i = 1 to 500 and j = 1 to 500) falling within the allowed radius.


```
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    first=1
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     mean=0.836
  randseq=no
     norm=Euclid
    delay=1
    embed=5
  rescale=maxdist
 meandist=27.760
  maxdist=100.000
   radius=10
 colorbnd=1
     line=2
   matrix=500*500
  #recurs=5709
   #lines=1353
   %recur=4.576%
  %determ=82.098%
     dmax=17
  entropy=2.393
    trend=-1.860
 %laminar=52.251%
     vmax=9
 traptime=2.375
```
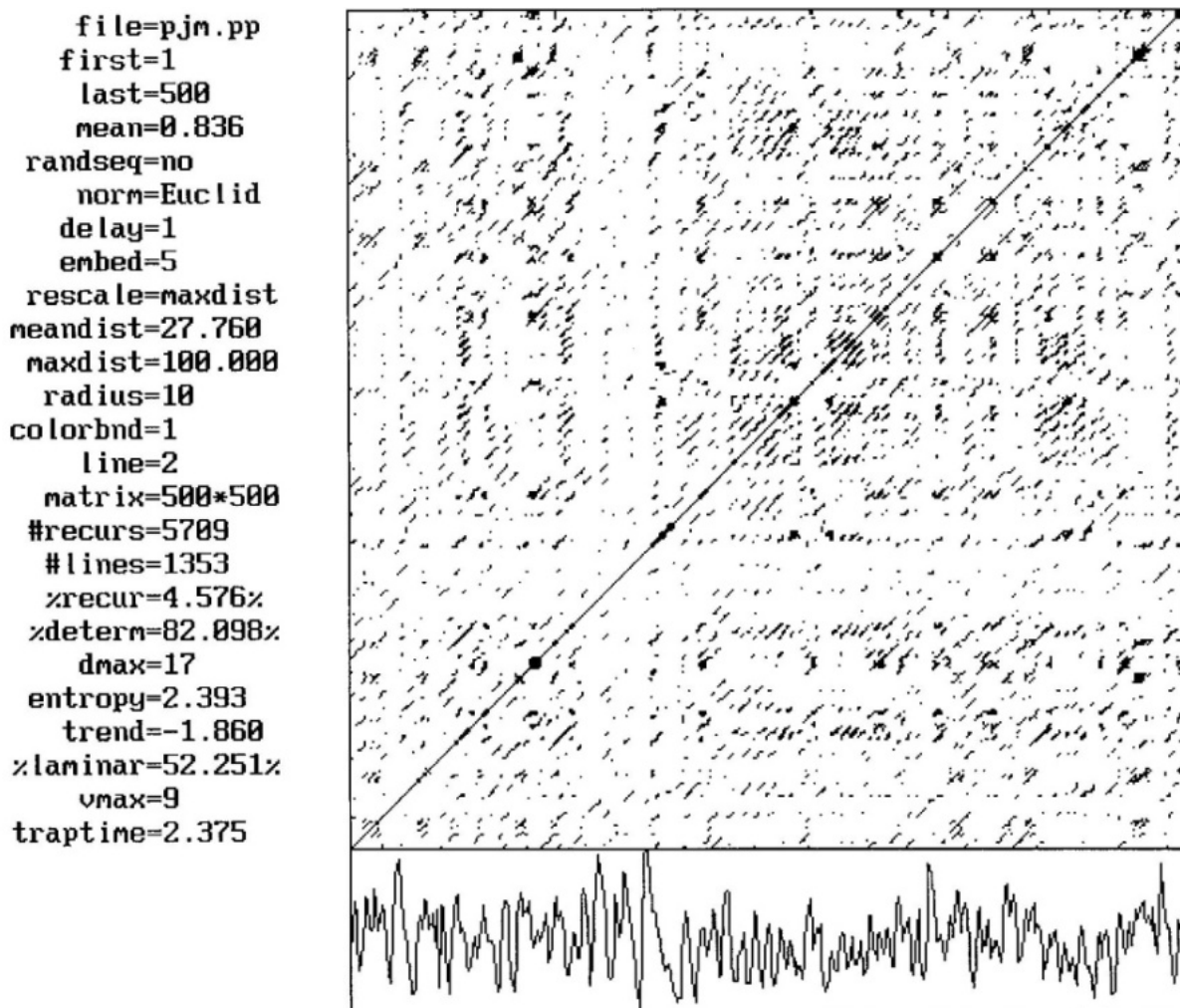
Figure 4. PP time series (bottom) and RR recurrence plot (top) along with recurrence parameters and quantifications (left). The plot is symmetrical on either side of the line-of-identity. The PP time series has 500 points displayed (417.9s) with HRV fluctuations centered on mean of 71.8 beats per min.

The recurrence plot of a 500 sequential PP intervals from a disease-free human is shown in Figure 4. In this case the embedding dimension was set to 5 such that all possible vectors of 5 points were compared with each other. The plot presents with lacelike delicacy revealing hidden patterns that are not seen in the one-dimensional time series beneath the plot. For quantitation, however, eight recurrence variables are extracted from the plot (%recur, %determ, dmax, entropy, trend, %laminar, vmax, traptime). Each variable has a critical, non-biased definition [20, 21] which report eight unique perspectives on the data derived from the time series. In the example shown, the density of points in the plot (%recur) is 4.576% and the probability of diagonal lines in the plot (%determ) is 82.098%. However, after randomly shuffling the PP intervals into a "nonsense" sequence (destroying the dynamical structure), %recur fell to 0.162% and %determ fell to 46.535% (not shown). These shuffling changes indicate that the original time series had deterministic structures attributed to physiological laws of the heart.

Proper implementation and interpretation of recurrence strategies requires careful selection of recurrence parameters for which a tutorial primer has been written [22] and freeware developed [23]. Recurrence windows can also move through very long time series, converting the eight unique recurrence variables into separate time series for further analysis. Little to no changes in these variables after random shuffling indicates rule-free signals. But such pure stochasticities are very rare in the world of structured physiological systems.

7. Partitioning the cardiac period as a terminal dynamic

Most modern quantifications of the cardiac dynamics, either linear or nonlinear, revert back to the fundamental RR or PP interval. Electrically speaking, during this time period two specific and alternating dynamics are occurring, electrical depolarization/repolarization during the beat and electrical isopotential between beats. Clean separation of these two phases can be realized by simply dividing the PP interval into two parts: the PT interval (the dynamic trajectory) and the TP interval (the stochastic pause) as shown in Figure 5A. Most interesting is Figure 5B in which the PP interval, the PT interval and the PT interval are all plotted as functions of time (or cardiac cycle number). The PP interval shows the typical respiratory sinus arrhythmia as expected. However, most of the variability is carried by the TP intervals when the heart is at isopotential rest, not the PT intervals when the heart is self-excited, actively contracting, and repolarizing. This arrangement forms what is called a terminal dynamic [24].

What is a terminal dynamic? Simply stated, a terminal dynamic is a dynamic the reaches its terminus [25]. It comes to its end and simply stops. The incoming plane (active) is not asymptotic to the runway, but it actually lands and comes to a standstill at the gate (resting). The ant that runs (active) makes intermittent pauses along its path (resting). In the same way the heart follows an almost stereotypic trajectory while being electrically depolarized and repolarized (active) before it come to its rest during the inter-beat isopotential of the ECG (resting). The key here is that while the dynamic is "living" on the transient trajectory,

it is robust against noise. On the other hand, once the dynamic has ended and the dynamic is paused, it is at this point (technically, its singularity) when it becomes most vulnerable to external noise. This is why cardiac pacemakers can only pace the myocardium (e.g. select the next active trajectory) between beats during quiescent phases of the electrical cycle. The complex interplay of ion channel activation and inactivation during the active phase generates a refractory period for external stimuli.
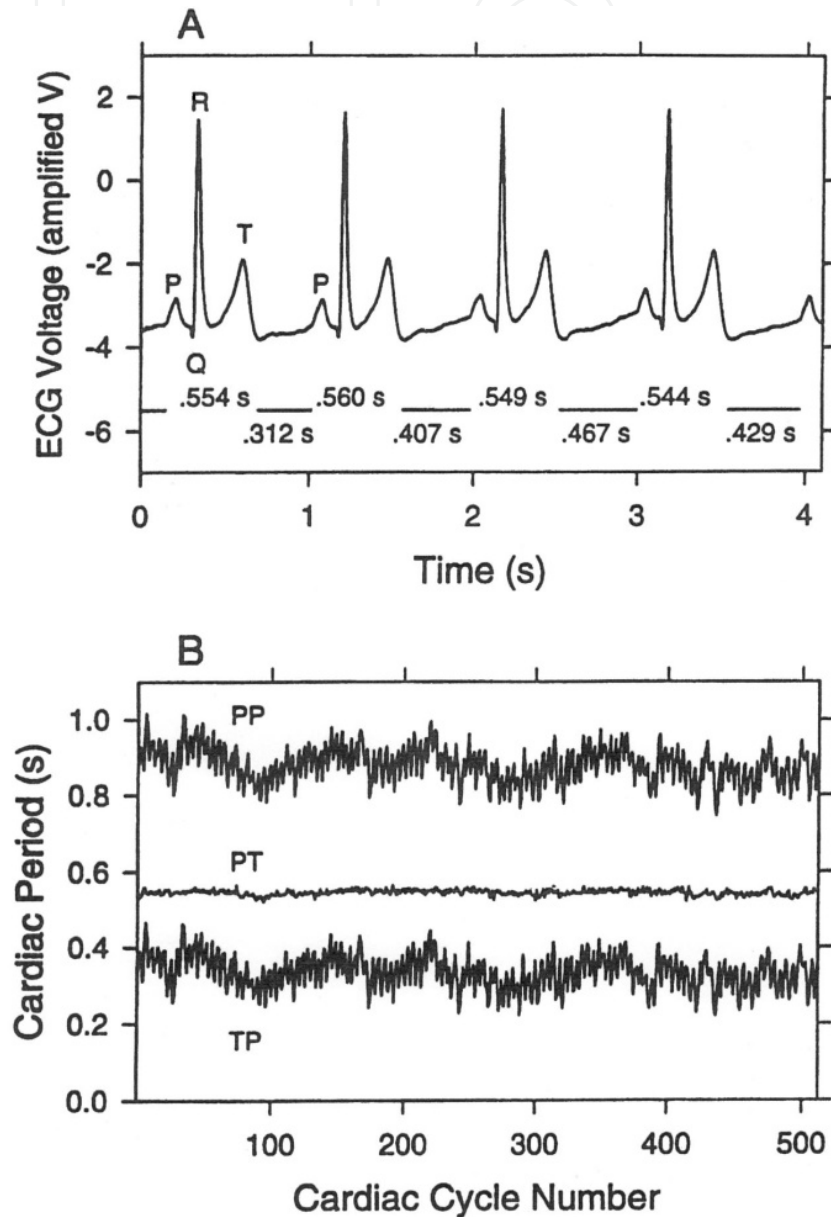

Figure 5. (A) Partitioning of PP intervals into PT and TP intervals for 512 beats. (B) HRV in PP intervals is carried almost exclusively in the TP intervals, not the PT intervals. Reproduced from reference [11] with permission.

How can a terminal dynamic be modeled? Well, instead of devising some fancy differential equation depicting beat after ECG beat, a better approach would be to write a single equation for the active phase of the heart which starts and comes to its end [26]. Then a

pause or varying duration can be interposed before initiating the next beat. To impart more reality to the picture, the trajectory selection could come randomly, say, from a dozen slightly different differential equations (imparting a realistic wobbling in the active trajectory path). Likewise, the pause period could be randomly selected from a collection of actual cardiac isopotential times.

Thus the cardiac dynamic recorded in the ECG is really an alternation between a deterministic trajectory (which can be modeled by a differential equation) and a stochastic pause (which can only be randomly sampled from a collection of measure real-time pauses). This pause is termed the cardiac singularity, from which one of many trajectories can be selected for the next beat. The dynamic is also called a terminal dynamic, because the active heart actually stops (rests) at a terminus each and every beat. When one thinks about it, this type of modeling constitutes a piecewise deterministic system. The trajectory is the deterministic piece and the pause is the stochastic piece. Thus during the PP interval the heart alternates between determinism (PT interval) and stochasticity (TP interval).

8. Atrial fibrillation

One of the most common arrhythmias in human medicine is atrial fibrillation due to ectopic foci with possible spiral wave reentries [27]. Modeling of these three-dimensional patterns is very difficult, and control of atrial fibrillation is not fool-proof [28]. The thesis of a recent report is that atrial fibrillation may arise from unstable cardiac singularities [21]. As hinted at in the previous section, a singularity can be understood as the disruption or termination of an otherwise continuous event. For example, a sine wave has two singularities, one at its peak and another at its nadir. Under the influence of gravity, a ball tossed up into the air reaches its first unstable singularity at its peak. Then falling back to earth (the trajectory) again, the ball experiences a few bouncing cycles (unstable singularity-trajectory alternations) before finally coming to rest on the ground (stable singularity). Balancing a pencil on it stub end is easy (stable singularity), but balancing the same pencil on its point is very difficult (unstable singularity).

Beyond sine waves, bouncing balls and balancing pencils, how can singularities be identified in the cardiac electrogram and what might they have to do with the detection of electrical patterns that may precipitate out as full atrial fibrillation? In the bottom panels of Figure 6, two atrial electrograms are shown as recorded from roving bipolar electrodes in human patients [21]. Each window consists of 2048 points spanning 2.10 seconds in time (digitization frequency 977 Hz). The first recording shows a spike pattern at 254 pulses per minute (4.2 Hz, Fig. 6A) and the second recording shows a spike pattern at 881 pulses per min (14.7 Hz, Fig. 6B). Although these rates are much too fast for each depolarization to be conducted through the atrioventricular node, the can still wreak havoc with arrhythmias in the main pumping chambers of the heart.

Recurrence plots of these two atrial signals clearly display singularities as square blocks stair-casing upward along the central diagonal line (line of identity, Fig. 6A and Fig. 6B). These singularities are coincident with the quasi-isopotentials periods in the electrograms. Off-central recurrences form rectangular boxes due to variability in isopotential durations among the windowed beats (analogous to the TP variability discussed above). Clearly, the faster the arrhythmia, the smaller the singularity that is inscribed. The postulate is that as atrial singularities become vanishingly small, then unrestrained atrial fibrillation is unleashed. Somewhere along the continuum to oblivion, the singularities become unstable, triggering fibrillation. The clinical application of this methodology may evolve such that mapped regions in the atria lacking singularities may be candidate sites for ablation in halting the dysrhythmia expressed within the larger tissue [29].
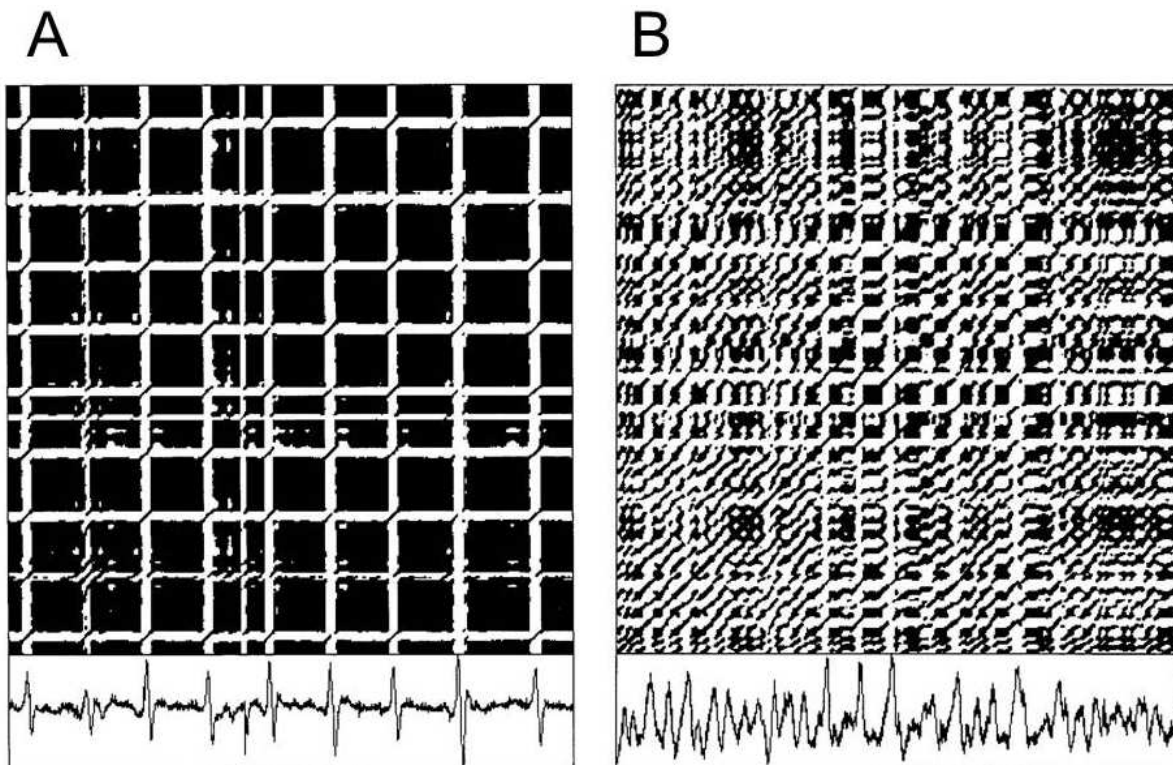

Figure 6. Singularities in atrial electrograms. (A) Fast atrial waves (4.2 Hz) with relatively long singularities. (B) Very fast atrial waves (14.7 Hz) with relatively short singularities. Recurrence parameters: delay = 1, embedding dimension = 15, norm = Euclidean, radius = 15% of maximum distance, line = 2. Data from reference [21].

9. Conclusions

The heart is a homeodynamic organ with automatic rhythms expressed in both mechanical electrical domains. Mechanical activities presume electrical underpinnings, but the reverse is not necessarily true except for possible stretch-activated electrical channels [30]. To get a window into cardiac dynamics, this chapter has majored on linear and nonlinear analyses that tease apart the cardiac cycle as defined as the R-R (or P-P) interval. For clinical medicine, the quest has been to define cardiovascular dynamics that may forecast unstable

patterns (arrhythmias) or fatal events (asystole). Can it be that dis-homeodynamics is a kind of dynamical disease [31]?

Numerous studies have examined heart rate variability (HRV) and concluded that high HRV is good (how high?) and low HRV is bad (how low?). There are methodological problems associated with the measurement of HRV restricted to linear the perspective (spectral analysis) and low-dimensionality perspective (approximate entropy). One thing is for sure – autonomic imbalance and heart rate variability are important risk factors for cardiovascular disease [32]. Importantly, the reciprocity or co-activation of the sympathetic and parasympathetic branches of the autonomic nervous system is decidedly non-linear [33] and non-Gaussian [34]. This being true, it becomes apparent and necessary to apply the proper nonlinear tools to assess the signals. One proven too is recurrence quantification analysis (RQA) which has a demonstrated utility in diagnosing nonstationary cardiac dynamics [35].

As can be seen, the normal cardiac dynamic (mechanical or electrical) has a wealth of descriptors. With these in hand, it becomes easier to detect and possibly predict heart dysfunction and failure. Returning to the concept of homeodynamics, as people age or become ill, the dynamic range of cardiac functionality becomes limited. The loss of complexity and high-dimensional dynamics become markers for dysrhythmias, fibrillations and possibly even death [36].

Although current implanted artificial pacemakers are limited in their computational capacity, advances in nonlinear dynamics are being investigated to augment signal filtering and facilitate event detection [37-38].

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