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# Mixing Dynamics of Heart Rate Variability

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## ABSTRACT

The theoretical Erlang distribution of the $k$ –fold Poincaré return time of a mixing dynamical system is a very good fit of the experimental RR histograms of normal subjects. From this perspective, a heartbeat is emitted when the state of the attractor has returned $k$ consecutive times to some finite region of the phase space of an abstract dynamical system that generates the RR sequence. The higher frequency, $k$ times that of normal heartbeats, is hypothesized to be related to the synchronization of the array of pacemaker cells in the SA node. For arrhythmia patients, the RR histogram deviates from the Erlang distribution, significantly to the point that it is bimodal. In this case, the distribution can be fitted with the weighted average of an Erlang and another distribution, revealing that the heart in arrhythmia cases operates near the boundary between a mixing attractor and a more complicated one.

## INTRODUCTION

In this chapter, we develop a statistical dynamical systems theory approach to heart dynamics. While there are many variables that can be associated with the cardiovascular system, here we only retain the RR sequence. Recall that the RR interval is the amount of time between consecutive heartbeats (R waves). In a sense, we propose corroborative evidence of a hypothesis emitted in [1] where it is argued that the RR interval is a Poincaré return time.

In heart physiology, the sinus node (also called sinoatrial (SA) node) is known as the dominant cardiac pacemaker, which is under the influence of the vagal nerve. The SA node cells have the capability of self-excitation and they behave like a large population of electrically coupled oscillators (pacemakers) with differing intrinsic frequencies [2], [3]. Hence, no single cell in the SA node serves as pacemaker, and by Michaels et al. hypothesis [2], the pacing rate is not that of the intrinsically fastest pacemaker, but it may actually be generated from a “democratic consensus” dynamical process of contribution of all cells to establish the rhythm. The SA node depolarization events are transmitted to both the antrioventricular (AV) node and the Purkinje fibers. The new impulse from the SA node discharges both the AV node and Purkinje fibers before their own threshold for self-excitation can occur in either of these [4]. Thus, the SA node actually controls the heartbeats and it is virtually always the pacemaker of the normal heart.

More specifically, this chapter develops a new heart dynamics paradigm based on two hypotheses that are consistent the clinically observed fact that the RR interval is Erlang distributed for control subjects. A tentative explanation of this phenomenon has already been put forward for atrial fibrillation (AFib) patients [5]. The hypothesis was that the AV node would transform the exponentially-distributed arrivals from the many ectopic sources on the atria to an Erlang-distributed process. However, our data support Erlang distribution on *normal* subjects! The discrepancy can be explained on the basis that [5] failed to take into consideration the effect of digitalis, on which the patients had been put. Our paradigm, on the other hand, is rooted in recent results [9] of ergodic theory, saying that the *k*-fold Poincaré return time of a mixing dynamical system is Erlang distributed. The return time rate, *k* times faster than heart rate, is conjectured to be resulting from the synchronization of the pacemaker cells in the SA node. Under some cardiac risk conditions, the distribution becomes bimodal, which can be dynamically explained within the ergodic theory paradigm that the heart dynamical system operates near the boundary between two attractors: a "universal" mixing attractor and another one that seems to depend on the specific cardiac risks [1]. Our corroborating studies have revealed a correlation between departure from Erlang fit and abnormal heart condition.

## MIXING DYNAMICS IN THE HEART—A GENTLE INTRODUCTION

In order to define mixing heart dynamics, we proceed from much easier physics: Consider a cylinder-shaped glass, standing vertically (along the z-axis) and full of water. Assume we can number the molecules as $i = 1,2,...,N$ and assume that at every time *t* we can register both the positions $q_i(t) = (x_i(t), y_i(t), z_i(t))$, $i = 1,2,...,N$, and the velocities $v_i(t) = (\dot{x}_i(t), \dot{y}_i(t), \dot{z}_i(t))$, $i = 1,2,...,N$, of all molecules. In the preceding, $z_i(t)$ is the coordinate along the vertical axis of the *i*th molecule, while $(x_i(t), y_i(t))$ are its coordinates in some horizontal plane. A "dot" notation denotes the rate of change (time-derivative.) We define the state of the ith molecule as $\omega_i(t) = (q_i(t), v_i(t))$ and define the *state* of the overall system (all molecules together with their interactions) as $\omega(t) = (\omega_1(t), \omega_2(t),..., \omega_N(t))$. The positions are constrained to lie in the cylinder; the velocities could in theory be as fast as possible along any direction, except that on the boundary they should be tangent to the walls of the glass. The set of all possible positions and velocities is denoted by $\Omega$, the so-called *phase space* or *sample space* of the system.

If the water is still, $\omega(t)$ would be constant, except for some microscopic thermal agitation. Here, however, on top of this we will consider larger scale motion created, for example, by agitating the liquid with a spoon. In general, we need a rule that allows us to predict the state of the system at any time in the future, knowing its previous state. Under the spoon agitation motion, the equations of the overall system could be $\omega(t + \Delta t) = T(\omega(t))$, where $\Delta t$ is the sampling period and $T(\cdot)$, the time-shifted operator, is a nonlinear function . Another model, over a very short amount of time, takes the form $\frac{d\omega(t)}{dt} = f(\omega(t))$, where $f(\cdot)$ is in general a complicated nonlinear function. Regardless of discrete or continuous evolution, such a micro-canonical model can hardly be constructed in such a manner as to accurately anticipate the motion, *but its usefulness comes if it successfully reproduces some large-scale measurable quantities*, like the water temperature. Via the Boltzmann constant $k$, the water temperature is defined as the average kinetic energy of the molecules, where the average could be understood either as the time-average $\lim_{T\to\infty} \frac{1}{T} \frac{2}{3k} \frac{m\|v(t)\|^2}{2}$ or the ensemble average $\int_\Omega \frac{2}{3k} \frac{m\|v\|^2}{2} \mu(d\omega)$. In the preceding, $\mu(d\omega)$ is the probability of finding the state in a small "box" around $\omega \in \Omega$. (Precisely, $\mu(\cdot)$ is the ergodic measure defined to be invariant along the motion.) It is very much in this spirit that we will conjecture existence of a micro-canonical model of the heart that reproduces some specific features associated with the ECG measurements, more specifically the histogram of the RR interval. Naturally, this dynamical model of the heart is not about water molecules, but about the hydrodynamics of the blood, the ion channels, the conductivity between the SA and AV nodes, etc.

Under mild conditions, a motion that has an ergodic measure has Poincaré return, that is, if we isolate a subset $A$ of the water glass, any molecule initially in the subset will eventually return, and it will return infinitely often, in the subset $A$. The time it takes to return, the so-called *Poincaré return time*, is of paramount importance in dynamical system theory. If indeed it can be measured, it indicates some qualitative properties of the dynamics, no matter how complicated it is, no matter our degree of confidence in the model.

The equality between the time and the ensemble averages mentioned in the simple case of the kinetic energy of water molecules is a fact of *ergodic theory*. The motion of water molecules (to take a simple case) is said to be *ergodic* if it has no invariant sets. An invariant subset $A$ is such that, if initially the state is in $A$, it remains in $A$ during the rest of the motion. For example, if the water is stirred in such a way that every molecule rotates around the axis of symmetry of the cylinder, the movement is certainly not ergodic (and should there be some drops of ink in the glass, the ink and the water will not “mix.”)

Unfortunately, ergodicity is inadequate to answer such questions as to whether the motion is chaotic. (It is tempting to define Heart Rate Variability as chaos in the RR sequence; however, this concept is flawed.) There is no universal definition of chaos, but here we shall follow the formal mathematical way and equate chaos to *mixing*. To define mixing intuitively, put a few drops of ink in the glass and stir it. If the stirring is complicated enough with both vertical and horizontal components, the ink and the water will mix and the water will have homogeneous color. To somewhat formalize the concept, in physics, a dynamical system is said to be *mixing* if subsets $A, B$ (ink, water, resp.) of the phase space of the system become strongly intertwined as time goes on. Another canonical example is the Cuba libre: suppose that a glass initially contains 20% rum and 80% cola in separate regions, formalized as subsets $A$ and $B$, resp. After properly stirring the glass, any region of the glass will contain approximately 20% rum. Furthermore, the stirred mixture is in a certain sense inseparable: no matter where one looks, or how small the region one looks at, one will find 80% cola and 20% rum. The formal definition of mixing is in the Appendix.

It appears a daunting task to determine whether such a motion mathematically specified as $\omega(t+\Delta t)=T(\omega(t))$ is mixing, let alone to come up with the time shift operator $T(\cdot)$ from first principles. However, the key point is that the return time, assuming it can be measured in some way, allows us to determine whether or not a system is mixing. The mixing criterion is whether or not the return time $\tau$, viewed as a random variable that can be sampled, follows the Erlang distribution $f(\tau;k,\lambda)=\frac{\lambda^k \tau^{k-1} e^{-\lambda k}}{(k-1)!}$ for some integer $k$ and some real $\lambda > 0$. The paradigm proposed in this paper is to treat the R-wave as a Poincaré return, so that the RR interval becomes the Poincaré return time. Hypothesis testing on the Erlang distribution of the histogram of the return time either confirms or denies the hypothesis. Our key observation is that, on databases of subjects without or with arrhythmia, the mixing hypotheses passes or is rejected, respectively.

# METHODS

## Patient Recruitment

The electrocardiogram (ECG) data were taken from patients in the cardiac intensive care unit (CCU) of either the Johns Hopkins Hospital or the Good Samaritan Hospital in Baltimore for standard care. They were recruited and their cases were studied according to a protocol approved by the Institutional Review Boards (IRB's) of the respective institutions. Patients who experienced an event of sustained (N30 seconds) monomorphic ventricular tachycardia (MVT), polymorphic ventricular tachycardia (PVT), or ventricular fibrillation (VF) were considered. Patients with a minimum of 12 hours of ECG data before the event constituted the study group. In addition, patients who did not experience any arrhythmic events while in CCU were considered as control group. Patients who belong to the following categories were excluded from study:

- Patients who had bundle-branch block, atrial fibrillation, or the data of whom had excessive background noise
- Patients with more than one major event in 12 hours of recording

This is to avoid difficulty and ambiguity in data analysis.

## Data Collection

Electrocardiographic tracings were downloaded from the specialized intensive care unit MARS telemetry system (GE Medical Systems, Milwaukee, WI), which is capable of retaining up to 28 hours of multi-lead ECG tracings, filtered between 0.3 and 50 Hz and sampled at 120 Hz, and transferred to a computer for analysis. Each tracing was considered by event type—MVT, PVT, VF, or control—as determined by an experienced observer. Determination of heart rate and number of PVC's was done automatically, using the ECG lead with best signal-to-noise ratio for each patient. All variables were evaluated by 1-hour epochs for the 12-hour period before the event and in 5-minute epochs for the 1-hour period immediately preceding the event.

Automated analysis was reviewed by investigators for correctness and integrity, for example, removal of noisy segments in the raw ECG signals. Specific information such as administration of β-blockers or other antiarrhythmic drugs or other related conditions during the data recording were obtained by chart review [6].

## Normal Data

This database includes 18 long-term ECG recordings of subjects referred to the Arrhythmia Laboratory at Boston's Beth Israel Hospital (now the Beth Israel Deaconess Medical Center). Subjects included in this database were found to have had no significant arrhythmias; they include 5 men, aged 26 to 45, and 13 women, aged 20 to 50 [7].

# RESULTS: ERLANG FIT VERSUS BIMODAL DISTRIBUTION

Histogram results showing Erlang distribution of 24-hour RR intervals are shown in Figure 1 and Figure 2. For the results depicted in Figure 1 for normal subjects, the RR-interval histograms have good fit to an Erlang distribution. However, for the patients, the distribution of RR intervals deviates significantly from its best Erlang fit, as shown in Figure 2. Even worse, bimodal and multimodal distributions are observed for patients.

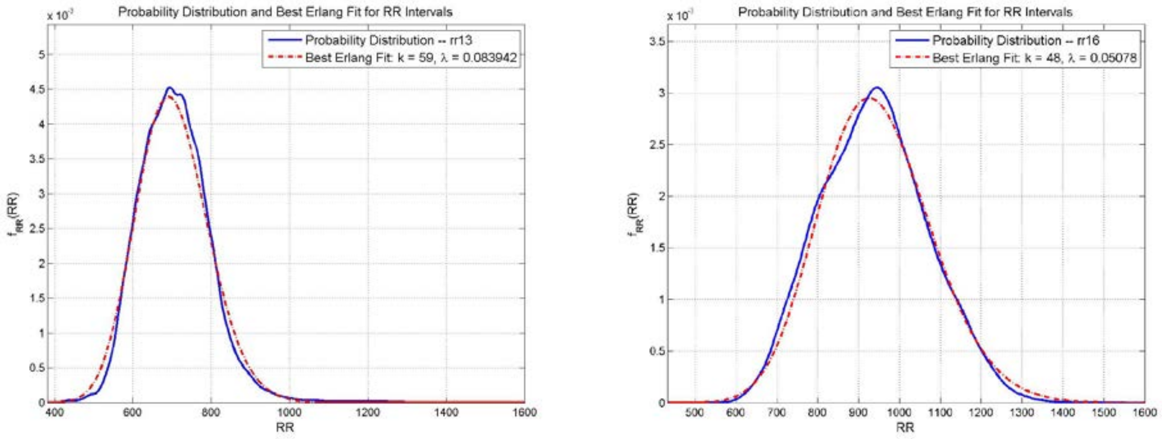

**Figure 1 Probability distribution and best Erlang fit for normal subjects; solid line: Probability distribution of RR intervals following Kernel density estimate; dot-dash lines: Best Erlang distribution fit.**

The statistical analysis of goodness of Erlang distribution fitting through the box plot analysis of Error Sum of Squares (SSE) is shown in Figure 3. Normal subjects’ box plot is significantly shorter than patients and suggests that, overall, normal subjects have better Erlang fit. Patients’ box plot is also much higher than normal subjects, suggesting a significant difference between the two groups in favor of better Erlang fit for normal subjects. More outliers are present among the patient group.

As shown in Figure 4, the left head of the bimodal (multimodal) distribution has a good fit to an Erlang distribution; however, in general the right tail of the bimodal distribution does not appear to admit an easy fit to any of the classical distributions. Haydn and Vaienti [9] developed theoretical “toy examples” amazingly consistent with this experimentally observed phenomenon.

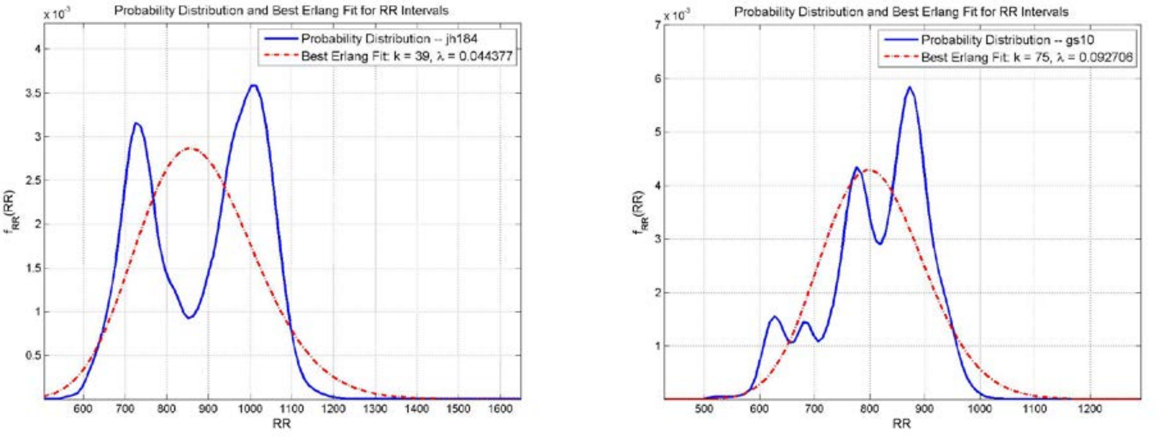

**Figure 2 Probability distribution and best Erlang fit for patients; solid line: Probability distribution of RR intervals; dot-dash lines: Best Erlang distribution fit.**

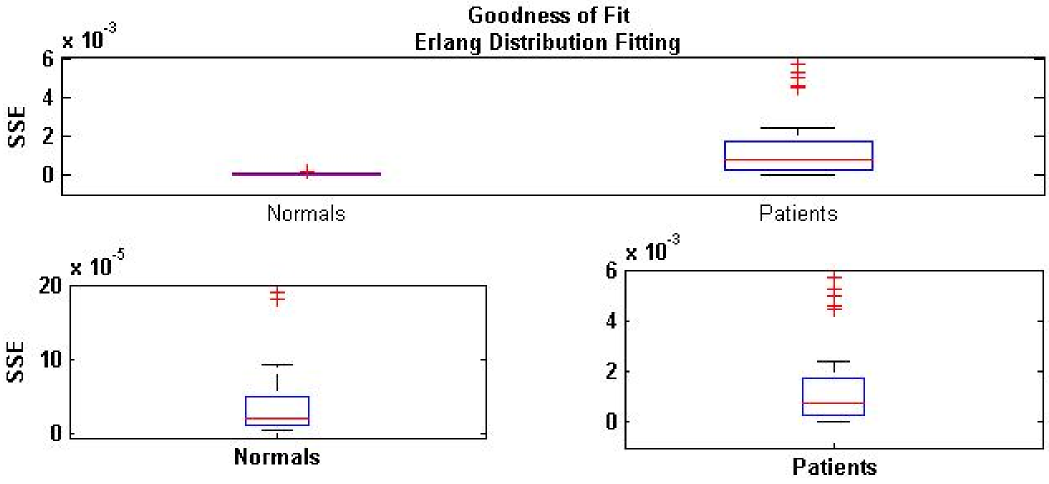

**Figure 3 Statistical analysis of Erlang distribution fitting to normal subjects and patients.**

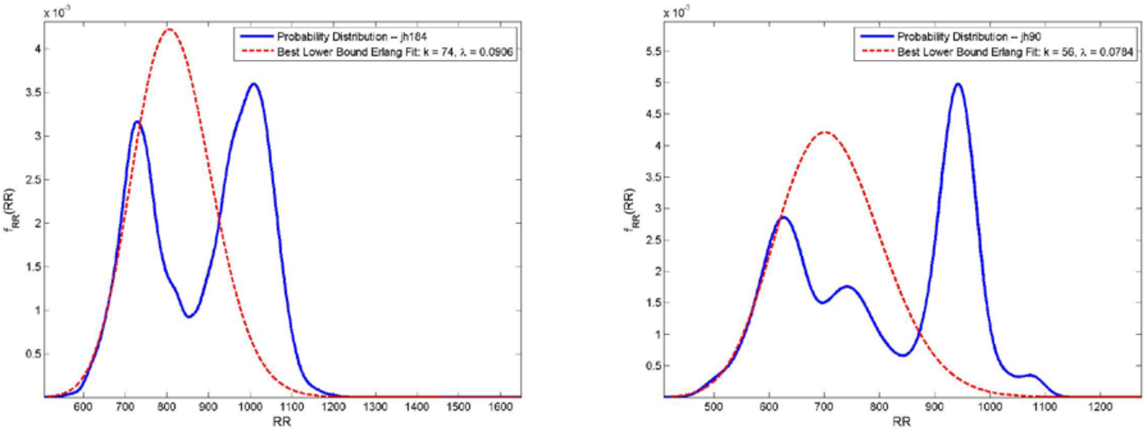

**Figure 4. Left Erlang fit to the experimental probability distribution of RR interval.**

# DISCUSSION

Analysis of the experimental data reveals that the RR interval for normal subjects has Erlang distribution. The RR sequence is weakly correlated, in full agreement with the theory developed by Haydn [9]. We reconcile the latter clinical observation with the Haydn and Vaienti mathematical result by hypothesizing that the RR interval contains $k > 1$ return times:

*Hypothesis (normal subjects):* The theoretically exponential distribution of the Poincaré return time is not a fit of the experimental RR histograms. However, the Erlang distribution of the $k$-fold return time is a *very good* fit of the experimental RR histograms. Thus it appears that a heart beat is emitted after $k$ returns of the state $\omega$ of the abstract underlying dynamical system to some subset $A \subset \Omega$. The explanation for the latter can be found along the recently developed paradigm that the SA node consists of an array of self-exciting cells, *of slightly different intrinsic frequencies*, $f_1, f_2, \ldots$ Through the network interactions among the various cells, their firings become synchronized. The nonlinear synchronization process generates integer multiples of $f_1 + f_2 + \cdots$, which account for the $k$-fold faster frequency.

Next to the control subjects, the RR-histograms of the patients do not have a good Erlang fit. However, they still manifest a structural feature, still revealing *something* about the dynamics:

*Hypothesis (arrhythmia subjects):* As shown in Figure 4, even though the RR-histogram is binomial and hence fails to be Erlang, it nevertheless has a good Erlang fit on the left head. This gives the hint that part of the dynamics might still be mixing, but not the overall dynamics. This experimental feature is consistent with the *"Nonergodic Coupled Dynamics and Bimodal Return Time Distribution"* developed in the Appendix. Namely, the state space can be decomposed in two regions, $\Omega_1$ and $\Omega_2$, with mixing holding in the first region and failing for another (integrable) dynamics in the second region. The return time is relative to a subset $A$ sitting across the two regions. The problem is that the theoretical distribution of the return time in $A$ is relative to a great many initial conditions $\omega(0) \in A$ spreading across the boundary between the two regions. However, in the experimental setup, the average is relative to the time, so that we need some process to allow the system to jump from one invariant region to another. This process is probably the effect of the vagal nerve. The left-sided Erlang fit would reveal an invariant mixing set, hence generating Heart Rate Variability (HRV), while the right tail fitting distribution reveals an integrable dynamics, generating less Heart Rate Variability, hence a pathology.

## CONCLUSION

An Erlang distributed RR interval corroborates normal heart dynamics and can be explained under the hypothesis that the RR interval contains $k$ Poincaré returns of a mixing dynamics. Bimodal (multimodal) distribution on the other hand is indicative of abnormality and the dynamical interpretation is that the heart operates near the boundary between a "good" (mixing) and a "bad" (non mixing) attractor.

## APPENDIX: MIXING DYNAMICS—MATHEMATICAL RIGOR

### Dynamical Systems

The theory of dynamical systems is a major mathematical discipline closely intertwined with all main areas of mathematics. It has greatly stimulated research in many sciences and has given rise to the vast new area of endeavor, varyingly called *applied dynamics, nonlinear science,* or *chaos theory*.

A dynamical system generally includes the following ingredients:

- A phase space or sample space $\Omega$, which contains all possible states of the system;
- A time $t$, which could be continuous ($t \in [0,\infty)$) or discrete ($t = 0, T, 2T, 3T, \ldots$);
- A time-evolution law.

More precisely, an abstract dynamical system in the sense of Kolmogorov is a quadruple $(\Omega, \Sigma, \mu, T)$, where $\Sigma$ is a $\sigma$-algebra of subsets of $\Omega$, $\mu$ is an invariant measure, and $T$ is the time shift operator or "flow" [8]. A subset $A \in \Sigma$ can be thought of as an event; $\mu(A)$ is the probability of that event; the $\sigma$-algebra property means that events can be combined with logical “and,” “or,” and negation operations. The probability law $\mu(\cdot)$ is defined from the dynamics in the sense that it does not change along the motion, that is, $\mu(A) = \mu(T^{-1}A)$, where $T^{-1}A$ is the set of past events that lead to the current event $A$.

## Mixing Inferred from Return Time Statistics

**Definition *(Ergodicity and mixing):*** A Kolomogorov dynamical system is said to be *ergodic* if there does not exists a $\mu$ partitioning $\Omega = \Omega_1 \cup \Omega_2$ into invariant sets $\Omega_i : i = 1,2$. A subset $\Omega_i$ is *invariant* if $\Omega_i = T^{-1}\Omega_i$.

A central aspect of ergodic theory is the behavior of a dynamical system when it is allowed to run for a long period of time. By the ergodic theorem, under certain conditions, the time-average of a function along the trajectories exists almost everywhere and is related to its ensemble-average.

Mixing is a stronger notion than ergodicity. Roughly speaking, this means that, after a long time, every set $A \in \Sigma$ will spread evenly over the entire space (its contribution in every set B will be nearly proportional to the size of B ) such that the phase space of the system becomes strongly intertwined. Every mixing system is ergodic, but the inverse is not always true [8]. The concept of mixing is not yet adequate to make it a property that can be checked from measurements done on the system. To give it such a property, the mixing has to be fast enough.

**Definition *(ϕ-mixing):*** A measure-preserving transformation $T$ is said to be $\varphi$*-mixing* if there exits a sequence $\phi(\ell) : \ell = 1,2,\ldots$ of positive numbers satisfying $\sum_{\ell=1}^{\infty} \phi^{1/2}(\ell) < \infty$ and such that $\left|\mu\left(A \cap T^{-\ell-n}B\right) - \mu(A)\mu(B)\right| \le \phi(\ell)\mu(A)\mu(B)$, where $A$ and $B$ are any measurable sets (that is, sets in $\Sigma$) and $\mu$ is the invariant measure.

*Poincaré recurrences:* The Poincaré recurrence theorem states that a system having a finite amount of energy and confined to a finite spatial volume will, after a sufficiently long time, return to an arbitrarily small neighborhood of its initial state. The Poincaré recurrence time is the amount of time elapsed until the return (see Figure 5).

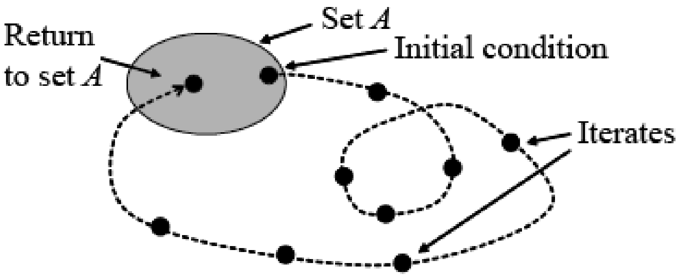

Figure 5 Poincaré recurrence time.

**Theorem *(Poincaré Recurrence Theorem):*** For any $A \in \Sigma$, the set of those points $\omega \in A$ such that $T^n \omega \notin A$ for all $n > 0$ has measure zero. That is, almost every point $\omega$ of $A$ returns to $A$. In fact, almost every point returns infinitely often; i.e. $\mu(\{\omega \in \Omega : \exists N : T^n(\omega) \notin A, \forall n > N\}) = 0$.

*Return times statistics:* The statistics of return times (also known as Poincaré recurrences) has been extensively studied over the last few years [9], [12]-[16], mainly to characterize the ergodic and statistical properties of dynamical systems. It has been proved that the asymptotic distribution of Poincaré recurrences is exponential for a wide class of mixing systems, even if they are not uniformly hyperbolic [14].

We briefly recall some of the basic definitions about the statistics of return times from [14]. For a given measurable subset $A \in \Sigma$ and a point $\omega \in A$, the *first return time* of $\omega$ into $A$ is defined as

$$\tau_A(\omega) = \min(\{n = 1, 2, \ldots : T^n(\omega) \in A\} \cup \{+\infty\})$$

and the *mean return time* is given by $\langle \tau_A \rangle = \int_A \tau_A(\omega) d\mu_A$, where $\mu_A$ denotes the conditional measure with respect to $A$, that is, $\mu_A(B) = \mu(A \cap B) / \mu(A)$ for any measurable set $B \in \Sigma$. For ergodic dynamics, Kac's theorem [14] says that the expectation of the return time to $A$ starting from $A$, is just $(\mu(A))^{-1}$. The statistics of the first return times then is defined as $F_A(t) = \mu_A(\{\omega \in A : \tau_A(\omega) / \langle \tau_A \rangle > t\})$. The limit statistics $F(t) = \lim_{\mu(A) \downarrow 0} F_A(t)$ exists when the set $A \in \Sigma$ shrinks around a point $\omega \in \Omega$. For a wide class of mixing systems (see [15], [16], [9]), it has been proved that the limit spectrum decays exponentially, that is, $F(t) = e^{-t}$, if $A$ is taken either as a ball or as a cylinder shrinking around $\mu$-almost every point.

## Return Time

Given a subset $S \in \Sigma$, the successive return times of the state ω in S are denoted as *τ k* . By a recently developed theoretical paradigm, the distribution of *τ k* reveals the dynamical properties of a system. The main point of this chapter is that the return time *τ* is related to the RR interval, so that the distribution of the latter would reveal heart dynamics.

## Erlang distribution

N. Haydn and S. Vaienti have proved that, for a large class of mixing dynamical systems, the return event is a Poisson process [9]; hence the return times are independent and exponentially distributed. Recall that the Erlang distribution is a continuous distribution, parameterized by the shape *k*, which is an integer, and the rate λ, which is a real. The Erlang distribution is the distribution of the sum of *k* independent, exponentially distributed random variables. It is used to predict waiting times in queuing systems, etc. where a Poisson process is in operation. The probability density function of the Erlang distributed random variable $\tau$ is $f(\tau; k, \lambda) = \frac{\lambda^k \tau^{k-1} e^{-\lambda k}}{(k-1)!}$ for $\tau > 0$.

## Nonergodic Coupled Dynamics and Bimodal Return Time Distribution

If the system is not ergodic with a partitioning $\Omega = \Omega_1 \cup \Omega_2$ ( $\mu$ mod 0 ) and $\mu(\Omega_1 \cap \Omega_2) = 0$ into invariant sets, and for a subset $A$ across the boundary, $\mu(A \cap \Omega_1) > 0$, $\mu(A \cap \Omega_2) > 0$, a general result [9] states that the distribution of $\tau_k$ is some weighted average of the distribution of $\tau_k$ in $\Omega_1$ and the distribution of $\tau_k$ in $\Omega_2$.

Thus if $\Omega_1$ is mixing with a faster return time than $\Omega_2$, it can be expected that the left "head" of the weighted distribution would be exponential for the first return time and Erlang for the $k$-fold return time.

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