A Markovian formalization of heart rate dynamics evinces a quantum-like hypothesis

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Abstract. Most investigations into heart rate dynamics have emphasized continuous functions, whereas the heart beat itself is a discrete event. We present experimental evidence that by considering this quality, the dynamics may be appreciated as a result of singular dynamics arising out of non-Lipschitz formalisms. Markov process analysis demonstrates that heart beats may then be considered in terms of quantum-like constraints.

1 Introduction

Some considerable discussion has revolved around the correct characterization of heart beat intervals. Although power spectral analysis has identified several peaks relating to autonomic control (Kitney and Rompelman 1987), it has also been noted that some variability modulation may be related to mechanical modulations of intrathoracic pressure changes of breathing (Zbilut et al. 1988). There remains much confusion regarding the very low frequency ranges (Sapoznikov et al. 1994). Certainly some of the difficulty is due to the various methods employed for sampling intervals, as well as the methods of calculating the spectrum; however, it has also been pointed out that some of the modulations may act nonlinearly, and are also influenced by such factors as tidal volume. To avoid these contentious aspects, some investigators have used methods from nonlinear dynamics to support the idea that the heart beat intervals are governed by deterministic chaos, although this has also been disputed.

Recently it has been proposed that given the need for some determinism, while maintaining the flexibility of beat-to-beat control, the dynamics can best be modeled by nondeterministic equations of motion (Zbilut et al. 1994). Such a model is in a sense piece-wise deterministic, but not dependent upon initial conditions. Randomness in such dynamics is generated by the dynamics themselves, and not from some error functional. Furthermore, complex nonlinear interactions can be obtained at the singular points. Between singular points, the dynamics are then constrained in a deterministic way. The advantage of this paradigm is that the organism is allowed to adjust the dynamics according to environmental influences at the singular points. Preliminary evidence suggests that in the case of an isolated, perfused rat heart, the heart beat does follow a predicted random walk. The present study seeks to extend this paradigm by a Markovian formalization of the non-Lipschitz dynamics, and suggests reformulation of ideas originally suggested by Gerstein and Mandelbrot (1964).

2 Theory

During the last several decades, biologists have expressed increasing interest in methods of signal processing such as the fast Fourier and other transforms for the elucidation of hidden periodicities of biological variables. Certainly, many useful and important observations regarding the time-varying properties of such variables have been demonstrated. Amidst this activity, however, there has been a growing realization that the algorithms themselves have numerous drawbacks, including questions of noise level and stationarity, which prohibit their uncritical application (Grassberger et al. 1991; Eckmann and Ruelle 1992). Even if these drawbacks were resolved, a more fundamental problem lies in their application: by definition, chaotic systems are fully determined by initial conditions, and they are unpredictable only because of our lack of precision. Certainly, one of the main features of living organisms is that they are adaptive throughout a range of time scales. To suggest that biological dynamics

are fully characterized by attractors, strange or otherwise, would limit this adaptability (Haken 1991; Zbilut 1991; Ruelle 1994; Webber and Zbilut 1994; Zbilut et al. 1994). Nowhere is this fact more evident than in the workings of the brain: this once static organ has now become appreciated as a fully dynamic, plastic, and adaptive entity, with billions of interconnected cells responding to thousands of chemical and electrical forces, and 'noise'. By suggesting that it is in any way classically chaotic, would force its activity into some narrow predetermined way, incapable of responding to new environmental conditions.

It may be argued that these objections can be countered by the existence of 'control parameters,' which can retune the system. As yet, however, there has been no demonstration of how such an *adaptive* control apparatus is realized in a biological entity.[1] Furthermore, given the tremendous amounts of noise in biological systems, and the extreme sensitivity to initial conditions of chaotic systems, the energy expended to run adaptive controllers would be considerable. Certainly the stability of such systems would come into question, since often infinitesimal differences in control parameters can result in enormously different effects. Consider, for example, the implications for the conduction system of the heart, which must work relatively flawlessly for decades.

At this juncture, one is reminded of the statement by Einstein: 'So far as the laws of mathematics refer to reality, they are not certain. And so far as they are certain, they do not refer to reality' (Einstein 1983). Indeed, one of the main problems of chaos theory with respect to biological systems is its lack of ability to explain the singular points of physiological processes where repetitive, stereotypical (orbital) behavior is encountered. Certainly, the qualitative features of the firing can be well modeled, but the pauses between events cannot. Even the use of stochastic differential equations encounters considerable difficulty, especially when their time dependence is considered. This is not even to consider the separate issue of noise characterization: do biological organisms harbor different kinds of noise generators? All these points suggest that nonlinear chaotic dynamics fail to describe many biological systems in one of their most important points, namely adaptability.

In response, we would suggest that a main difficulty is not the nonlinear dynamics *per se*, but in one of the time-honored conditions for differential equations. Specifically, we point out that uniqueness criteria are required for the solution of differential equations (Coddington and Levinson 1955; Arnold 1989). In fact there is no absolute need to require such conditions. Certainly, uniqueness makes matters convenient from
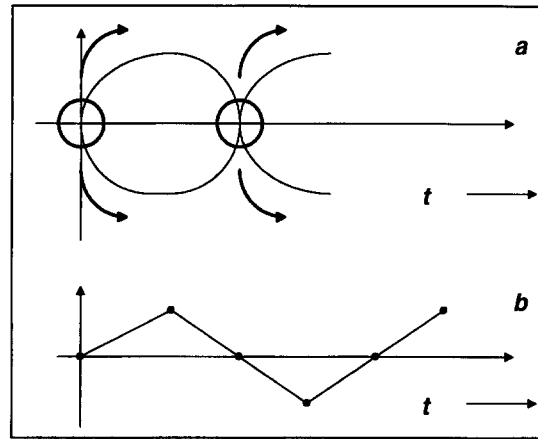

Fig. 1. Random walk in time (b) generated by non-Lipschitz singularities with equiprobable trajectories (a)

a mathematical standpoint, but it might be counterproductive to biology.[2]

One way to demonstrate uniqueness is to require Lipschitz conditions (boundedness of derivatives). If this requirement is relaxed, the dynamics become not only more 'adaptable,' but also more tractable with respect to noise without specifically requiring random terms. Consider, for example, a simple equation without uniqueness.[3] For the equation (Fig. 1)

$$\dot{x} = x^{1/3}\cos\omega t \qquad (1)$$

at the singular solution, $x \equiv 0$ (which is unstable, for instance, at $t = 0$), a small noise drives the motion to the regular solutions, $\pm (2/3\omega \sin t)^{3/2}$, with equal probabilities. Then the function $\dot{y} = x$ describes a random walk in one dimension. Although the present example demonstrates a random walk, it has been shown that any probability distribution can exist (Zak 1993). It is important to emphasize, however, the fundamental difference between the probabilistic properties of these non-Lipschitz dynamics and those of traditional stochastic or differential equations: the randomness of stochastic differential

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[1] The focus here is on the fact that traditionally, feedback mechanisms have been employed to help explain normal physiological control. It has even been pointed out, however, that many of the so-called negative feedback systems do not exist when subjected to experimental verification (Somjen 1992)

[2] We note here the subject of phase resetting experiments, and ostensibly discontinuous dynamics, which have produced a long tradition of important research (Winfree 1990). In the present case we are not specifically dealing with such external perturbations; nonetheless, we do see a possible role insofar as a persistent problem with phase resetting is the fact that the dynamics consistently must deal with theoretically infinite time limits. Additionally, non-Lipschitz dynamics can allow for greater flexibility and a richer dynamics than deterministic limit cycles through the exploitation of stochastic attractors. Finally, the energy for the motion in non-Lipschitz dynamics comes from an instability, whereas the perturbations in phase resetting experiments are considerably larger external perturbations (see, e.g., Zak 1994, p. 1151, eq. 170)

[3] Existence and uniqueness theorems are mathematical formalisms, and do not necessarily follow from physical reality. The term 'determinism,' and its mathematical and physical representations, came after Newton, and often revolved around philosophical or theological concepts. We further emphasize that other physiological phenomena may indeed be best modeled by deterministic chaos. For some perspectives on the evolution of the understanding of determinism see, e.g., Cohen (1971), Earman (1986), Lenzen (1954) and Yates (1993)

equations is caused by random initial conditions, random force or random coefficients; in chaotic equations small (but finite) random changes of initial conditions are amplified by a mechanism of instability. But in both cases the differential operator itself remains deterministic. In contradistinction to that, in nondeterministic dynamics, randomness results from the violation of the uniqueness of the solution at equilibrium points, and therefore, *the differential operator itself generates random solutions* (Zak 1993). Furthermore, the singular point can be part of a larger chain of oscillators which become self-organizing. Interestingly enough, when such dynamics are analyzed numerically for Lyapunov exponents, positive values are obtained, which is not surprising since the solutions are characterized by an infinite divergence (Zak 1994). Real-world examples of such dynamics include whip cracking (Zak 1970), seismic waves (Zak 1983), ball motion (Stelzel et al. 1988), and double pendulums (Hübler 1992).

3 Methods

Plausibility of such dynamics in biological preparations is difficult due to the large amounts of noise which are amplified and filtered along with the signals of interest (e.g., in electrocardiography). The trajectories arrive at singular points in finite time, and as a result, the second derivative diverges (Zbilut et al. 1994). This divergence, which is a delta function in simulated data, appears as a smooth function because of signal conditioning; however, indirect evidence might be obtained by studying the probabilistic structure of such signals. Under the assumption that heart beats are punctuated by singular points, governed by nondeterministic equations, we sought to determine whether Markov analysis would provide new information regarding their characterizations.

3.1 Preparatory operative procedures

Animals [6-month-old ($n = 6$) and 24-month-old ($n = 18$) Fischer 344 rats from Charles River Breeding Laboratories (Calco, Como)] were anesthetized (Nembutal Na, 30 mg/kg intraperitoneally) and settled on a small surgery table. Two 1-cm-long skin incisions were made over the anterior and posterior ends of the sternum and two ring electrodes were soldered to 20-cm-long insulated wires (outer diameter 1 mm), which were then tied to subcutaneous tissue by means of a silk suture. A third incision was performed over the skull and the free tips of the wires were passed subcutaneously to the skull, cut to suitable lengths, and soldered with two male contact pins. Pins were fixed to the skull by dental cement, and the incisions closed with sutures. The animals were housed in individual cages, and after 2 days the rats had fully recovered from the operation.

3.2 Electrocardiographic recording

Starting from day 2, the rats were connected to the electrocardiograph (Hewlett Packard model 1188D) by means of two wires about 60 cm in length, and soldered to female pins. This habituation period lasted a week; thereafter the electrocardiogram (ECG) was recorded for 10 min after about 30 min of animal stabilization. ECG recording and analysis were performed by a computer (Hewlett Packard, Vectra 386/16N) using an analog-digital interface (TL-1 DMA Interface, Axon Instruments). R-R intervals were timed using pClamp software (Axon Instruments).

4 Analysis

The analysis presented is relative to the baseline ECG recordings of two young rats (GIO4 and GIO6), and is consistent with the results from the other animals. The original series was embedded 15 times, and the resulting multivariate matrix was analyzed by a principal components analysis (PCA) on the relative correlation matrix. This procedure is very effective for singling out the main order parameter organizing the temporal variability of the numerical series (Ghil and Vautard 1991; Vautard et al. 1992). The choice of analyzing the first component instead of the original series derived from the need to deal with a clearer signal with respect to the original series, and to maintain the high-dimensional information linked to the embedding.

The baseline tracings highlighted a very strong 'leading' first principal component explaining from 60% to 95% of total variance, the only exception being a rat with a high number of spontaneous arrhythmias, in which 37% of the variance was explained by the first principal component (PRIN1). The distribution of variance explained by different components for a typical tracing is given in Table 1.[4]

The two recordings were both characterized by an extremely high value of variability explained by the first component (85%). The goal of the present analysis was to characterize the dynamics along the first component (PRIN1) in terms of a Markovian process in order to demonstrate the possibility of a probabilistic characterization of the dynamics. By the Markov formalism (Feller 1968) the dynamical system is described via its transition matrix (TM), representing the conditional probabilities of going from a certain state i at time t to another state j (which could even be identical to i) at time $t + 1$. A prerequisite for the application of this analysis is the possibility of describing the dynamics by means of discrete states as well as of subdividing time into discrete steps. While the second feature is inherent in the discrete character of the

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[4] We have also performed similar preliminary analysis on isolated perfused rat hearts, as well as on humans. The isolated perfused rat heart has a first component explaining approximately 50% of the variance, and follows a constrained random walk. In this we point out that deep Nembutal anesthesia probably affects local cellular mechanisms, and thus confounds simplistic statements regarding autonomic control. Seventeen healthy human volunteers (ages 25–52 years) as well as 7 cardiomyopathic and 2 heart transplant individuals were also studied. They all had the same dynamical behavior for the non-oscillating component as described

Table 1. Percentage of explained R-R variability (adult rat in basal conditions)

PRIN1	85.3	PRIN5	1.1
PRIN2	2.1	PRIN6	0.7
PRIN3	2.0	PRIN7	0.6
PRIN4	1.3		

The major part of variability is explained by PRIN1. The minor components are sin/cosin associated pairs with an approximately equal variability. PRIN1 does not oscillate in the studied range

Table 2. GIO4: cluster profile

	Raw frequency	Observed probability	Mean	SD
A	467	0.2351	0.11	0.21
B	469	0.2361	0.80	0.20
C	494	0.2487	− 0.65	0.19
D	205	0.1032	− 1.42	0.24
E	262	0.1319	1.44	0.14
F	89	0.0448	− 2.19	0.18

Proportion of variability explained by the clustering = 0.96

Table 3. GIO6: cluster profile

	Raw frequency	Observed probability	Mean	SD
A	195	0.0982	1.05	0.13
B	46	0.0232	− 3.06	0.18
C	562	0.2830	− 0.18	0.28
D	84	0.0423	− 2.51	0.24
E	177	0.0891	− 1.51	0.32
F	922	0.4642	0.56	0.18

Proportion of variability explained by the clustering = 0.95

R-R time series, the validity of the first prerequisite was checked by the high percentage of explained variability of a cluster analysis of the studied time series.

The cluster analysis technique (Everitt 1980) used was the k-means algorithm: the methodology aims to construct classes (clusters) that are as compact as possible (minimum intra-cluster variability), while at the same time maintaining the clusters themselves as separate as possible (maximum inter-cluster variability). The k-means algorithm is a non-hierarchical technique. Unlike the situation with hierarchical methods, the number k of classes into which the data set is divided are decided in advance. In order to decide the partition endowed with the maximum explanatory power with respect to the investigated data set, use is made of the proportion of explained variability (R-square) relative to the different choices of number of classes. The explained variability of the particular partition is calculated as the ratio between the variance relative to the data set in which the actual values of each different unit are expressed in terms of the correspondent cluster mean values and the total variance of the original data set. By increasing the number of classes, the explained variance is increased. This procedure is terminated when a plateau of explained variance is reached.

Clustering techniques are well suited to the need for objectively organizing time series data (Shaw and King et al. 1992). In fact, the clusters, in the case of a trajectory, simply indicate particular areas of the state space: this partition of the state space is not arbitrary and corresponds to the criteria of structural optimality described above (maximal internal compactness, maximal separation between classes). Such an analysis of a numerical time series results in the related discrete-states dynamics in which each original value of the time series is replaced by the name of the correspondent cluster which can be considered a discrete state of the dynamics. The percentage of explained variance allows for the estimation of the proportion of original information retained after this transformation.

The filtered series (PRIN1) was submitted to this cluster analysis, and resulted in tracings with a very clear-cut structure, composed of six clusters explaining almost all the variability. The clusters can be made to correspond to discrete states of the dynamics (Tables 2, 3). The general mean of the time series is 0.0 with a standard deviation of 1. As expected, the structure is of normal type with the most frequent classes positioned near the general mean. The time series represented

by the subsequent states (clusters) was then analyzed in terms of transition probabilities (Markov chains). The rows (i) of the TM represent the conditional probability of going from state i to state j (column) in a single step. The matrices correspond to a phase space diagram having as rows the X_t values and as columns the X_{t+1} values, while the TM_{ij} elements correspond to the observed conditional probabilities $P(j|i)$ at subsequent time steps.

The TM formalism is very straightforward, because it permits an immediate look at the fundamental characteristics of the studied dynamics: if the previous history of the studied phenomenon has no effect on the actual behavior, then the columns of the TM correspond to the general probability of the correspondent state, and the rows of the TM simply reproduce the probability distribution over the states. This kind of behavior is termed a random walk. Conversely, if there is a marked departure from this purely random behavior, it can be speculated that there exists some form of control (Delcour 1993). The TMs for the two rats GIO4 and GIO6 are reported in Tables 4 and 5.

It is important to note that the matrix is completely different from a matrix governing a 'no-memory' process with independent states in which the conditional probabilities are simply the raw probabilities of the corresponding states. Here the control (autonomic system?) acts to constrain the system in the last visited state, whatever the general probability of the state itself. This feature is evident from the very high values (near to unity) of the main diagonal of the TM, even for states with a very low general probability such as cluster F for GIO4 and cluster B for GIO6. The observed distribution is different from a random-walk ($P < 0.00001$, chi-square statistic).

Another important point is that the transitions between different states can take place only between adjacent

Table 4. GIO4: transition matrix between clusters (states)

	A	B	C	D	E	F
A	0.9486	0.0278	0.02355	0	0	0
B	0.0298	0.9488	0	0	0.02132	0
C	0.0202	0	0.9656	0.01417	0	0
D	0	0	0.02927	0.95129	0	0.0146
E	0	0.4198	0	0	0.95801	0
F	0	0	0	0.0337	0	0.966

Table 5. GIO6: transition matrix between clusters (states)

	A	B	C	D	E	F
A	0.9538	0	0	0	0	0.071
B	0	0.9565	0	0.043	0	0
C	0	0	0.9555	0	0.0089	0.034
D	0	0.024	0	0.964	0.012	0
E	0	0	0.028	0.0056	0.9661	0
F	0.0152	0	0.0217	0	0	0.963

Table 6. GIO4: distance matrix between clusters (states)

	A	B	C	D	E	F
A	0.0	0.69	0.76	1.54	1.33	2.29
B		0.0	1.448	2.22	0.64	2.98
C			0.0	0.78	2.08	1.54
D				0.0	2.86	0.76
E					0.0	3.62
F						0.0

Table 7. GIO6: distance matrix between clusters (states)

	A	B	C	D	E	F
A	0.0	4.11	1.23	3.56	2.56	0.49
B		0.0	2.88	0.55	1.55	3.62
C			0.0	2.33	1.69	0.735
D				0.0	1.01	3.066
E					0.0	2.07
F						0.0

Table 8. Normal: cluster profile

	Raw frequency	Normalized frequency	Mean	SD
A	34	0.0171	− 2.52	0.24
B	183	0.0921	1.69	0.30
C	811	0.4083	− 0.39	0.32
D	10	0.0050	2.85	0.31
E	282	0.1420	− 1.49	0.32
F	666	0.3353	0.62	0.32

Proportion of variability explained by the clustering = 0.90

Table 9. Normal: transition matrix between clusters (states)

	A	B	C	D	E	F
A	0.029	0.088	0.4705	0	0.20	0.20
B	0.016	0.093	0.4208	0.005	0.131	0.33
C	0.020	0.090	0.3925	0.005	0.154	0.339
D	0	0.200	0.400	0.100	0	0.30
E	0.020	0.063	0.411	0.0035	0.135	0.365
F	0.012	0.104	0.420	0.0045	0.132	0.326

Table 10. Normal: distance matrix between clusters (states)

	A	B	C	D	E	F
A	0.0	4.21	2.13	5.38	1.03	3.14
B		0.0	2.08	1.17	3.18	1.07
C			0.0	3.25	1.10	1.01
D				0.0	4.35	2.34
E					0.0	2.11
F						0.0

Table 11. Anesthesia: cluster profile

	Raw frequency	Normalized frequency	Mean	SD
A	1154	0.655	159	0
B	299	0.172	156	0
C	283	0.163	162	0

Proportion of variability explained = 1.00

states. This last feature can be appreciated by the inspection of the distance matrices between the states (on the basis of their mean value reported in Tables 2 and 3) (Tables 6, 7). Obviously the impossibility of a transition between non-adjacent states has to be intended in probabilistic terms, in the sense that the series of 1986 points are not sufficient to exclude rare transitions.

If these results are compared with the dynamics corresponding (Tables 8–10) to a normal distribution (random walk) with a mean of 0 and standard deviation of 1, the differences are evident. In the case of a normal distribution (no phasic information, no memory, no active control), the columns of the TM correspond (stochastically) to the general probabilities of the corresponding states, giving rise to a very different picture with respect to the TMs relative to the physiological series. The transition between states, in the case of the random walk, is ruled only by the relative probabilities with no adjacency constraints.

To decide whether the particular character of the observed physiological time series was due to the autonomic control or was a basic characteristic of cardiac rhythm independent of the control, we applied the same analysis to the R-R tracing of an anesthetized rat. If the hypothesis of identifying the controller with the autonomic system is true, random-walk dynamics should be obtained in the case of anesthetized rats.

The cluster analysis applied on the R-R of the anesthetized rat gave rise to an exact distribution into three classes explaining all the variance of the data set (Table 11). The units in this case are the length, in milliseconds, of the R-R intervals. Clusters B and C are at the same distance (3.00) from the main cluster (A) at the opposite sides of the distribution (distance between B and C = 6.00). The TM relative to this situation is reported in Table 12 and, as expected, is a random walk. From the analysis emerges a picture of autonomic control as constraining the probabilistic fluctuations of the R-R

Table 12. Anesthesia: transition matrix

	A	B	C
A	0.647	0.220	0.132
B	0.649	0.084	0.267
C	0.749	0.071	0.180

Table 13. Small-scale dynamics (inside cluster C of GIO6): cluster profile

	Raw frequency	Normalized frequency	Mean	SD
A	210	0.373	0.091	0.055
B	120	0.213	− 0.483	0.082
C	52	0.092	0.725	0.065
D	180	0.320	− 0.128	0.082

General mean and (SD) = 0.18 (0.28)
Proportion of variability explained = 0.94

Table 14. Transition matrix

	A	B	C	D
A	0.89	0.0	0.0	0.11
B	0.0	0.87	0.06	0.07
C	0.0	0.15	0.85	0.0
D	0.11	0.05	0.0	0.84

intervals around the last achieved state (a quantum-like scenario). The control does not try to level the system to the most probable (ground) state; rather, it only constrains the size of oscillations. When the system (probabilistically) escapes the constraint of one state, it is adjusted to the new state reached. When the autonomic control is off (anesthesia) the R-R dynamics can be represented by a simple random walk between states. At this point, the clinical and physiological implications could be very important: the philosophy of trying to constraint the system to only one ground state could be misleading and the implications of the multiplicity of 'quasi-stable' states have to be taken into account.

A particularly important question because of its relation to the potential multiplicity of time scales relevant for the autonomic control is the behavior inside a single cluster of the time series. With respect to this point, when submitted to a Markov analysis, the dynamics inside a particular cluster (cluster C of GIO6), the observed behavior is completely superimposable on the large-scale dynamics. Cluster C was studied as the larger time series: the first step was to perform a cluster analysis on the data set represented by the points pertaining to cluster C (Table 13), then the units of C of the GIO6 dynamics were eliminated at the boundaries with other clusters in order to deal only with true 'inside C' dynamics. On this restricted basis (537 points out of 562), the TM was extracted (Table 14). In this case too, the control tries to maintain the system on the last visited state and the jumps are observable only between adjacent states. The analysis inside cluster F of GIO6 gives the same results.

The obvious implication is the one frequently mentioned in the literature, namely scale-invariance (fractal).

5 Discussion

Although a majority of the literature regarding heart rate variability has centered around modulating frequencies, relatively little research has dealt with the intrinsic beating mechanisms devoid of external influences. Recently, Wilders (1993) has extended this research and has concluded that individual and cell clusters beat stochastically (Wilders and Jongsma 1993). This has not fully resolved the question of coupling to the atrium, but the present research suggests that a random walk paradigm may be appropriate. This model is consistent with non-deterministic dynamics and, moreover, allows for a convenient resolution of the need to be adaptable on a beat-to-beat basis. Continuous, deterministic models fail adequately to account for this need. Specifically, it is noted that inspection of ECGs reveals pauses of varying length which account for beat-to-beat variability; these are not explained by continuous models which include modulations. Although power spectra have been traditionally employed to demonstrate modulating frequencies, it must be remembered that clear, sharp spectral peaks are rare, and represent time averages. Indeed, time-frequency spectra clearly reveal this fact.

Nondeterministic dynamics may be a preliminary solution to this difficulty. This framework can deal with the singular, discrete event dynamics as well as the physiological requirements of adaptability to environmental influences. Additionally, the Markov analysis of these dynamics provides more detail to the apparent fractal (scale invariant) structure, and also underscores the importance of noise in biological systems (Wiesenfeld and Moss 1995). Changes in the 'states' of the dynamics may provide the basis of a quantum-like formalism for the analysis of pathological circumstances.

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