Review

Fractals and power law in pulmonary medicine. Implications for the clinician

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SUMMARY. Physiological data often display fluctuations, which have been traditionally considered as noise. However, as Goldberger has emphasized, biological systems are deterministic systems with noise. This noise reflects inherent dynamics and is responsible for the adaptation of the organism to its surroundings. Various techniques derived from statistical physics have already been applied to biological signals, especially in the field of cardiovascular medicine, unravelling potential pathogenetic mechanisms of disease and leading to the construction of more accurate prediction models. Recently, considerable effort has been devoted by several research groups to the assessment of the inherent variability and complexity of the respiratory system, concerning both structure and function. A few clinical studies, mainly involving patients with asthma and chronic obstructive pulmonary disease (COPD), have demonstrated that identification of loss of complexity of respiratory signals can be of significant value in both diagnosis of disease and monitoring of therapy. This review presents results from these studies and describes the basic methods for the assessment of dynamics that govern respiratory physiology in health and disease. ***Pneumon 2010, 23(3):250-259.***

'We the living exist in a complex regimen in the phase transition between order and chaos. We are there because that is the only place we can be both ordered but adaptable, stable but able to evolve…I believe we are on the threshold of a new theory of disease based on the consequences of living in a phase transition'.

Peter Macklem 2006

INTRODUCTION

Physiological data measured at the bedside often display fluctuations at scales spanning several orders of magnitude. These fluctuations are extremely inhomogeneous and appear irregular and complex, whereas in the medical literature, they are often regarded as noise and are therefore neglected. They may, however, carry information, for example, about the underlying structure or function of the heart and lungs. Examples include fluctuations in heart rate, respiratory rate, lung volume and blood flow.[1]

The central task of statistical physics is to study macroscopic phenomena that result from continuous microscopic interactions among many different components. Specific physiological systems, such as the cardiovascular and respiratory systems, are good candidates for such an approach, since they include multiple components and are affected by varying neuro-autonomic inputs, continuously over time. Fractal analysis constitutes a subset of such complex methods.

FRACTALS AND POWER LAW: BASIC CONCEPTS

Fluctuations of a variable can be characterized by its probability density distribution. A way of estimating its characteristics is the construction of a histogram after normalization, so that the area under it will be equal to one. Often, this distribution N(x) of a variable x follows the so called power law form: $N(x) = x^{-d}$ meaning that the relative frequency of a value x is proportional to x raised to the power of –d. If we plot the logarithms of this relationship we have a linear equation: $\log(N) = -d*\log(x)$, whereas d is the negative slope of a straight line fit to N.[2] This slope is frequently called β slope or exponent.

Power law distribution behaves differently from Gaussian distributions. Its tails are very long (long-tail distribution), representing the relative frequency of occurrence of large events. This means that the probability of large or rare events is much higher than in a Gaussian distribution. Power laws describe dynamics that have a similar pattern of change at different scales and they are called 'scale invariant'. Conversely, Gaussian distributions are characterized by typical values, such as those corresponding to their peaks.[3] The power law describes a time series with many small variations and fewer and fewer large ones, while the pattern of variation is statistically similar regardless of its size. Magnification or shrinkage of the scale of the signal reveals the same relationship, a property that has been called 'self-similarity' and is a fundamental characteristic of fractals.[2,4]

Fractals are self similar objects because small parts of the structure at increasing magnification appear similar to the entire object. Akin to a coastline, fractals represent structures that have no fixed length, since they increase with increased magnification of measurement. This is why all fractals have noninteger dimensions, the so called fractal dimensions (FDs).[2,5]

The concept of fractals can be applied not only to structures that lack a characteristic length scale, but also to signals that lack a characteristic time scale. In this case, the relationship between the statistical properties of the fluctuations of the signal and the time window of observation follows the power law. The meaning of such behaviour is that future values in a time series are dependent on the past, displaying correlations over time, while the system that produces the signal exhibits a kind of memory.[2-6]

In order to evaluate the power law of a signal it is necessary to compute the so called power spectrum. For this reason, a fast Fourier transformation (FFT) is applied to the signal in order to decompose it into different frequency components that are included within the time series. Every time series can be considered as a sum of sinusoid oscillations with different frequencies. The FFT transforms a signal to a sum of cosine and sine oscillations whose amplitudes determine their contribution to the whole signal. This frequency domain analysis displays the contribution of each sine wave as a function of its frequency, while its square is the power of that frequency in the whole spectrum of the signal. The total power of spectral analysis (the area under the curve of the power spectrum) is equal to the variability within the signal.[4] Increased variability/complexity is a hallmark of health, whereas many large clinical studies in cardiovascular medicine have shown that loss of variability is associated with sudden cardiac death, post-myocardial infarction (MI) heart failure and ventricular fibrillation.[7]

In the case of power law calculation, the plot of the log-log representation of the power spectrum (log power versus log frequency) gives rise to a straight line with a slope of approximately -1. As the frequency increases the size of variation drops by the same factor (scale invariance).

The values of the β slope/exponent can reflect the inherent dynamics of a system. Values near 1 are supposed to reflect fractal-like behaviour, whereas values lower than 0.5 represent a system without any correlations, lack of memory and finally chaotic-like and unpredictable evolution in time (white noise). Conversely, values of β slope higher than 1 or even near 1.5 characterize strong correlations within the signal and a highly predictable and almost periodic evolution in time (brown noise).[4,5] Ary Goldberger has studied cardiovascular dynamics in health and disease and found that both unpredictable (random-walk) and periodic behaviours represent loss of physiological function and correlate with lack of fractal properties of heart rate signals in patients with cardiovascular disease.[8] Similar findings have been demonstrated in critically ill patients with severe sepsis and septic shock (Figures 1-3).[4]

FRACTALS AND POWER LAW IN PULMONARY PHYSIOLOGY

Many organs in different biological systems have a fractal structure. Fractal branching reduces the distances over which materials are transported, providing rapid and efficient delivery of nutrients.[9] The lung offers many examples of self-similarity properties. Weibel and Gomez first measured the morphology of human airways and found an exponential relationship between the diameter

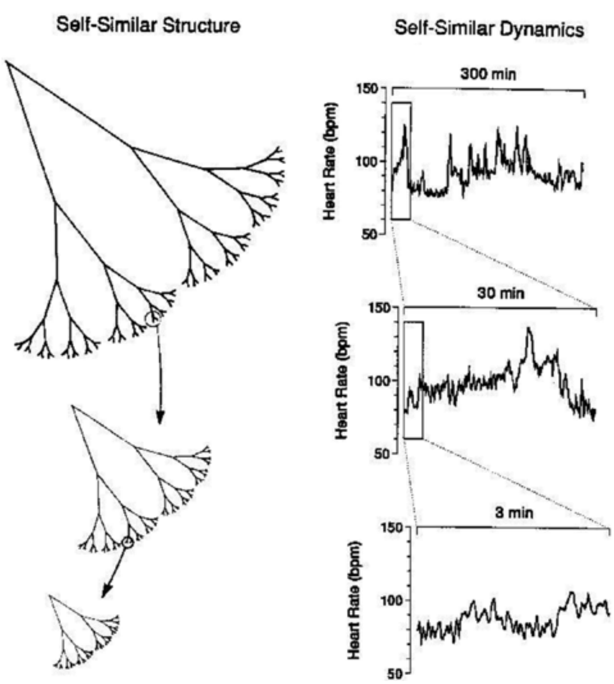


FIGURE 1. Left: the schematic of a tree-like fractal has self-similar branchings such that the small scale (magnified) structure resembles the large scale form. Right: a fractal process such as heart or respiratory rate regulation generates fluctuations on different time scales (temporal "magnifications") that are statistically self-similar. [Adapted from Goldberger AL. Non-linear dynamics for clinicians: chaos theory, fractals, and complexity at the bedside. Lancet 1996; 347:1312-1314, free downloaded from the website physionet (www.physionet.org)].

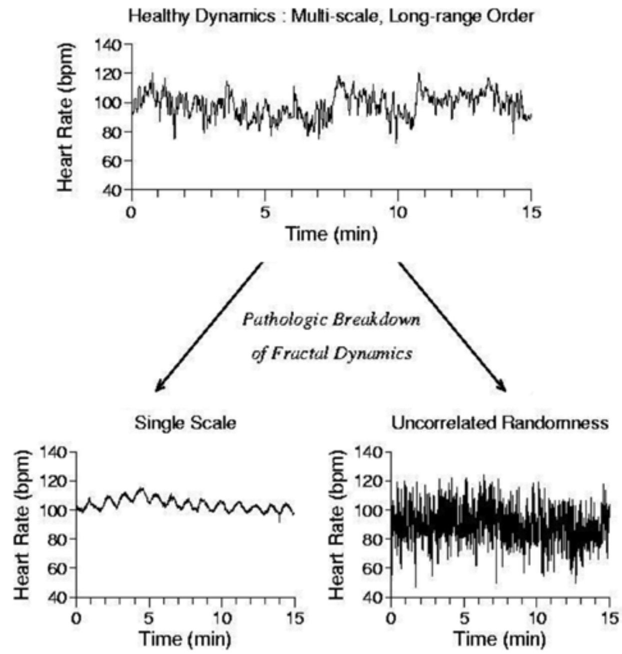
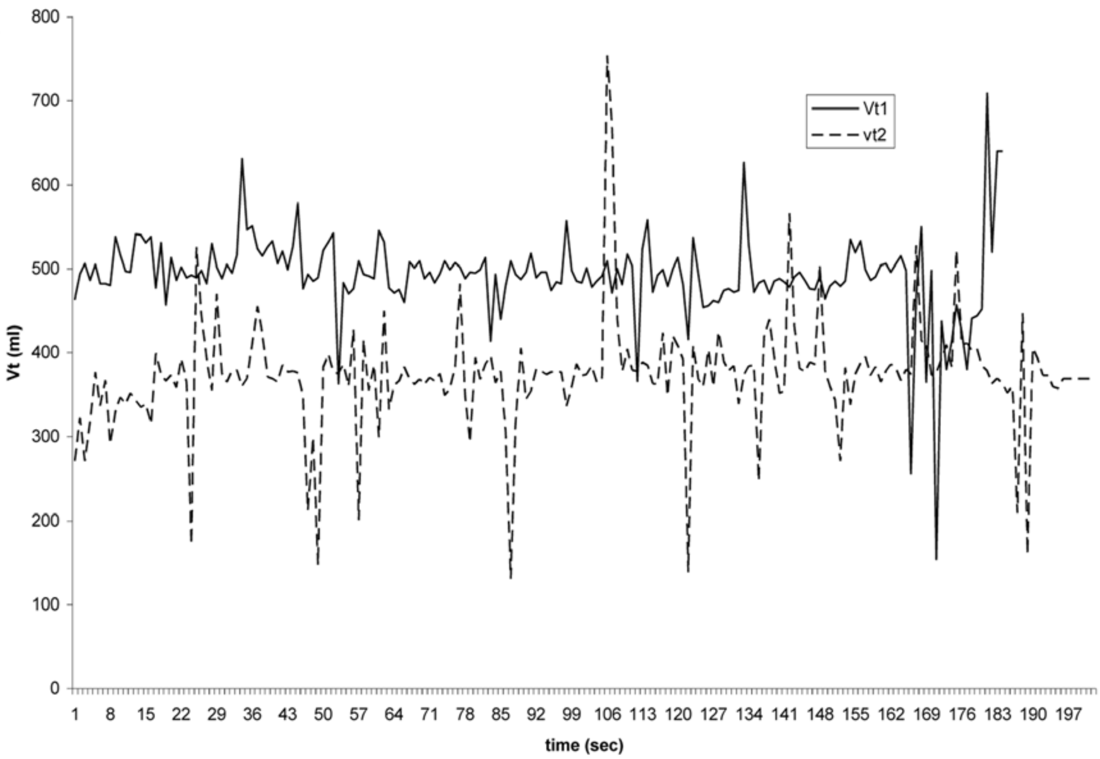


FIGURE 2. Fractal complexity of physiological signals (i.e., heart or respiratory rate) can be lost during aging and disease. The pattern of change can be either a totally periodic process (left down panel) or a random process (right down panel: chaos-like). [Adapted from Goldberger AL. Non-linear dynamics for clinicians: chaos theory, fractals, and complexity at the bedside. Lancet 1996; 347: 1312-1314, free downloaded from the website physionet (www.physionet.org)].

and the generation number of the conducting airways.[10] Mandelbrot, who first introduced the term fractals, discovered a unifying scaling pattern of the branching in the lung. A higher fractal dimension corresponds to a more complex branching, whereas a lower fractal reflects a more homogeneous structure.[11] Moreover, regional pulmonary blood flow has been shown by Glenny to exhibit spatial and temporal fractal patterns.[12] The structure of the alveolar surface has also been found to be well described by power laws, reflecting scale invariance.[13] The probability distribution of airway opening during inspiration also behaves according to the power law.[14]

Another property of fractals and power laws in pulmonary physiology is error tolerance during development. In simulations of airway morphogenesis during lung development, West compared a power law branching rule with an exponential decaying one and found that in the first case, the system was less susceptible to errors introduced into the branching process.[15] These properties suggest that living systems are capable of operating

A



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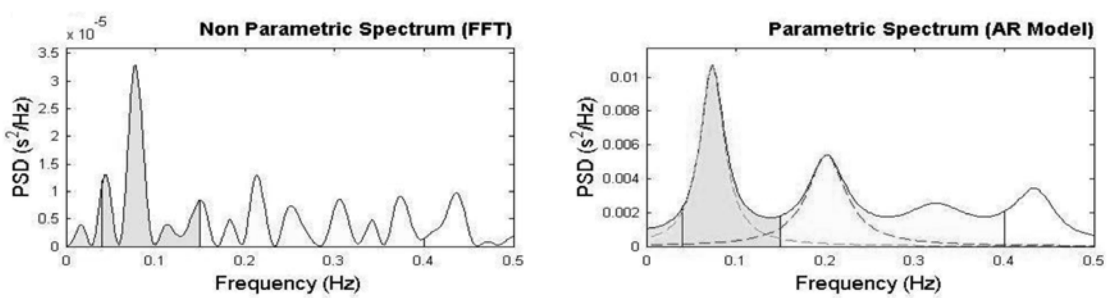

Frequency Band	Peak (Hz)	Power (ms^2)	Power (%)	Power (n.u.)
VLF	0.0391	0	5.2	
LF	0.0781	1	45.7	48.2
HF	0.2129	1	49.2	51.8
LF/HF			0.929	

Frequency Band	Peak (Hz)	Power (ms^2)	Power (%)	Power (n.u.)
VLF	0.0000	0	0.0	
LF	0.0723	521	57.0	24.3
HF	0.2012	394	43.0	18.4
LF/HF			1.323	

FIGURE 3. 3A: Recordings from a patient in the clinic - distribution of tidal volume before (Vt1) and during the performance of a spontaneous breathing trial (Vt2), exhibiting inherent variability. 3B: The FFT of the first signal of 3A (The software (Kubios HRV) displays the different frequency components (LF: low frequency, HF: high frequency and VLF: very low frequency) of the signal.

similarly at different scales, meaning that when environmental conditions change they can adapt more easily to their surroundings.

Aging has been proved by Lipsitz and Goldbereger to be significantly associated with loss of complexity of physiological signals, leading to decreased ability to adapt to different physiological insults. Using different algorithms for estimating fractal properties and power law behaviour, these authors found that the β slope of different signals in elderly was either reduced (decreased to lower than 1) or augmented (increased to higher than 1) compared to younger adults, indicating chaotic or periodic behaviour, respectively.[8] Peng and co-workers showed that aging was associated with a breakdown of fractal dynamics of respiratory signals via a decrease in the β slope towards 0.5 (randomness).[16] Concerning the early stages of development in humans, one study found that ultrasonographic (US) patterns for assessment lung maturity showed fractal properties with a power law behaviour. In addition, the β slope increased with gestational age from 28 to 38 weeks.[17] Szeto and co-workers, calculated β slopes of different respiratory signals in the human foetus and showed its movement from randomness towards fractal behaviour with increasing gestational age.[18] In conclusion, it appears that there is great variability in complexity according to age in early life, after which complexity decreases with aging.

FRACTAL PROPERTIES OF THE LUNG IN DISEASE: DATA FROM CLINICAL AND EXPERIMENTAL STUDIES

Alterations to fractal properties are related to different types of pathology and could have clinical implications for diagnosis and treatment. Physiological time series of such characteristics as heart and respiratory signals show similar alterations in their power law behaviour in different disease states. Mackey and Glass have introduced the term 'dynamic diseases' to describe states with loss of fractal properties of organs and power law dynamics of these signals.[19] For example, loss of heart rate variability (HRV), that is the variability of the R-R in the electro-cardiogram, has been found in patients with heart failure,[20] atrial fibrillation,[21] septic shock and multiple organ dysfunction syndrome (MODS).[22] In respiratory disorders, a classical example is the highly periodic variation in respiratory frequency, seen in Cheyne-Stokes respiration. Penzel has observed loss of fractal properties of heart rate signals during episodes of obstructive sleep apnoea.[23]

Macklem was the first to raise the question of whether airway function can be studied using tools from chaos theory and the paradigm of complex systems.[24] Que and co-workers studied the distribution of forced oscillatory resistance in patients with asthma and demonstrated that lung function exhibits loss of fractal properties during severe asthma.[25] Frey and colleagues applied fractal methods to twice-daily measurements of peak expiratory flow (PEF) in patients with asthmatic and showed a reduced β slope which become more regular with standard long-acting β2-agonist treatment and more random with short-acting β2-agonist treatment. They were able to demonstrate that the higher the β exponent when a patient was not on treatment, the larger the improvement of the condition on administration of long-acting β2-agonist therapy.[26]

Suki and co-workers studied the dynamics of airway opening and crackles, using a simple mathematic model of the periphery of airway tree.[27] Forgacs was the first to propose that crackles are associated with sudden opening of closed airways.[28] Suki found that the time series of crackles emitted during airway opening follows a power law distribution. Additionally, as the crackles propagate up the respiratory tree, the sound amplitude is attenuated at successive bifurcations, while its distribution follows the power law. The same phenomenon has been found for the time intervals of the 'jumps' by which airway resistance decreases upon lung inflation by a constant flow. In a study of Boser and colleagues, the fractal dimension of airways was computed using autopsy material from three groups: fatal asthma, non-fatal asthma and non asthma control subjects. The authors were able to show that the average FD of both the fatal (1.72) and non-fatal asthma groups (1.76) were significantly lower than that of the non asthma control group (1.83, $p<0.05$), while the lower fractal dimension correlated with decreased overall structural complexity and the pathological severity of disease.[29]

Venegas and colleagues, using positron emission tomography (PET) imaging and computer modeling, showed that in cases of bronchoconstriction and when smooth muscle activation reaches a critical level, localized clusters of poorly ventilated lung regions can develop abruptly in discrete steps.[30] These steps are called *avalanches* and can lead to new stable conditions. Because of the fractal structure of the airways, small initial heterogeneities that are always present, particularly in the diseased lung, can be amplified, leading to sudden patches of poorly ventilated lung regions. Another implication is that since the airways are organized into a fractal network embedded in the elastic parenchyma, the constriction of one airway can propagate and cause an avalanche-like constriction in large parts of the lung. The same holds true for the opposite process, where opening of airways during inhalation takes place in discrete steps.[31,32]

Suki has also demonstrated that airway opening upon inflation occurs in avalanches with power law distribution of both the size and time intervals between them.[27] The significance of these findings is that the probability of a large avalanche occurring is much higher than it would be if the distribution were Gaussian or exponential, so both the magnitude and timing of pressure excursions applied to the airways (i.e., using mechanical ventilation) may be critical in triggering the avalanche process of alveolar recruitment.[2,32]

In conclusion, these studies in asthma show that when the airways are likely to approach their critical closing threshold pressure, a small stimulus can provoke a catastrophic cascade of airway closure and this is reason why there is such poor correlation between the trigger and the outcome in patients with asthmatics. Moreover, the history of symptom fluctuations appears to be related to the structural changes of the airway tree (power law distribution of airway diameter).[32]

Airway recruitment may affect alveolar recruitment. Sujeer and co-workers found in mathematical models that the recruited volumes upon inflation with constant flow are distributed according to a power law with a β slope equal to 2.[33] Based on these findings it can be supposed that since alveolar recruitment is influenced by airway structure, then the pressure-volume curve may carry information about the airway tree.[2] Whether such models have any value in acute lung injury (ALI) is unclear. In this syndrome, it has been found that the opening pressure distribution does not always appear to have a Gaussian distribution, something that is assumed to be the case in the avalanche model.[34] Further studies are needed to investigate the pattern of recruitment in ALI, particularly in the case of the effect of gravity on ventilation-perfusion mismatch at the alveolar level.[35]

The application of fractal analysis has also shed light on the morphology of the lung in cases of emphysema. Computed tomography (CT) is a sensitive method for assessing lung structure in different forms of pathology. In general, low attenuation area (LAA) clusters are depicted in pixels with density of less than 950 Hounsfield units. These areas incorporate mostly air and are assigned a value of 1, whereas pixels with a density of higher than 950 include tissue with a value 0. Summing the number of pixels in a cluster gives the cluster size. In that way, a binary map of the lung can be constructed and a few studies have shown that in normal conditions, this map is highly heterogeneous.[2] Mishima and colleagues found that the probability distribution of LAA clusters follows a power law for both normal subjects and patients with chronic obstructive pulmonary disease (COPD). However, patients exhibited significantly smaller β slopes or exponents, which did not correlate with pulmonary function tests except for the diffusion capacity of the lung. The authors suggested that the neighbouring smaller LAA clusters tend to coalesce and form larger clusters as the weak elastic fibres separating them break under tension.[36] This process does not change the % LAA, but it decreases the number of small clusters in favour of larger ones, which result in a reduction of the β slope. Another assumption derived from this study is that the likelihood of finding large LAA clusters is much higher in COPD patients than in normal control subjects.[32]

Another possible application of fractals in pulmonary medicine includes the mechanical ventilation of critically ill patients. In an oleic acid injury animal model, Mutch and colleagues introduced fluctuations according to an algorithm, to mechanical ventilation (biological variable tidal volume and respiratory frequency proportional to pre-defined minute ventilation values). Compared with conventional ventilation (with similar minute ventilation), this approach increased respiratory arrhythmia and oxygenation and decreased dead space.[37] According to Suki, when fluctuations in the form of symmetrically distributed random noise are added to peak airway pressures (noisy ventilation), the mean does not change, but isolated values can be augmented, leading to significant alveolar recruitment.[2,38] In a mathematical model, the authors found that the recruited lung can be 200% larger in the case of biological variable ventilation than during conventional ventilation. Moreover, the standard deviation (SD) of the noise can be manipulated in order to achieve better oxygenation (system's output), a phenomenon called 'stochastic resonance', which has already been confirmed in animal models of ALI.[38]

CONCLUSIONS AND FUTURE SUGGESTIONS

According to Macklem, there is a continuum of thermodynamic systems that do not follow the 2nd thermodynamic axiom (increase in entropy), since they exchange energy with their environment (open systems): from near to equilibrium, such as crystals to far from equilibrium systems, such as the weather. 'The amount of energy dissipated determines where the system is situated along the continuum. Between the crystals and weather a sudden phase transition occurs over a small range of energy consumption. It is only there where life can flourish'.[39] From the above statement it is concluded that both a decrease in energy consumption, i.e., during myocardial ischaemia, or an increase, may contribute to a shift away from stable state. It has been shown by Que that during asthma, the local increase in metabolic rate is associated with increased variability of respiratory impedance to flow.[25] Que has proposed the term 'homeokinesis' instead of homeostasis, as a basic property of living systems that 'describes the ability of an organism to utilize external energy sources to maintain a highly organized internal environment fluctuating within acceptable limits in a far from equilibrium state'.[25]

The study of physiological signals of patients, such as heart and respiratory rate can easily lead to the identification of 'hidden' information concerning inherent dynamics and overall variability within time series. Recognition that physiological time series contain hidden information related to the extraordinary complexity that characterizes physiological systems defies the traditional mechanistic approaches based on conventional biostatistical methodologies, and has fueled growing interest in applying techniques from statistical physics to the study of living organisms. Through these techniques various different 'physio-markers' can be estimated that fulfill the requirements of contemporary medicine for better and more accurate early warning signs, since they are based on high-frequency measurements (sampling rate at least 250 Hz). These efforts have already boosted research on heart rate and blood pressure dynamics through standardization of signal processing techniques, frequency and duration of measurements and signal quality assessment, and has stimulated the development of more accurate diagnostic and prognostic indices in cardiovascular disease. A number of international databases of heart rate signals have been developed with free access by various investigators, such as the Web Site Physionet (www.physionet.org).[40]

We believe that such efforts must also be undertaken by pulmonary physicians and those who treat patients with severe respiratory diseases, such as Intensive Care specialists. In conclusion, we suggest that implementation of fractal analysis in respiratory physiology will result in better understanding of the different dynamic changes that occur during various pathological states, while its impact upon the prediction of severe complications will add value to these methods. Clinicians must start to understand the basic principles of complex systems theory and support an interdisciplinary approach for understanding pulmonary diseases, in order to be in a position to treat their patients more effectively.

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APPENDIX

Although there are different methods for the assessment of fractal properties of a signal, Glenny has proposed the use of a method that is called relative dispersion analysis (RD), which needs much less computational load. Using this algorithm it is very easy to perform calculations of fractal properties of different respiratory signals, in an EXCEL file. The following paradigm is modified from reference 7. The first file includes the distribution of the random values of the tidal volume in the second column, the average of every 2 values in the third, the average of every 2 values of the third column in the fourth, every 2 of the forth column in the fifth and every 2 of the fifth in the sixth column, respectively. In the second file calculation has been made of the mean, the standard deviation (SD), the RD% (= 100*SD/mean), its natural logarithm (ln), and the scale of time interval (τ) that describes how many times averaging is performed, and its natural logarithm ln(τ), for every column of the first file. If the ln (RD %) is plotted against the ln(τ), this gives diagram 1, while the application of a least square linear fit of data gives an equation that calculates the slope of the line. In

File 1

t	v(t)					t	v(t)					
1	10.31					26	35.78	27.57				
2	19.03	14.67				27	35.77					
3	34.70					28	64.38	50.08	38.82			
4	19.26	26.98	20.83			29	10.04					
5	65.42					30	19.10	14.57				
6	34.79	50.11				31	18.82					
7	19.07					32	35.52	27.17	20.87	29.85	46.62	32.73
8	35.34	27.21	38.66	29.74		33	35.36					
9	34.82					34	19.28	27.32				
10	18.80	26.81				35	19.00					
11	18.69					36	10.06	14.53	20.93			
12	10.28	14.49	20.65			37	35.78					
13	19.03					38	18.94	27.36				
14	10.12	14.58				39	66.09					
15	5.58					40	34.90	50.5	38.93	29.93		
16	10.05	7.83	11.2	15.92	22.83	41	64.76					
17	35.52					42	34.91	49.84				
18	19.28	27.4				43	35.16					
19	35.88					44	18.89	27.03	38.43			
20	64.40	50.14	38.77			45	64.39					
21	66.83					46	35.09	49.74				
22	35.66	51.22				47	66.18					
23	121.34					48	121.58	93.88	71.81	55.12	42.52	
24	64.34	92.84	72.03	55.4		49	122.48					
25	19.35					50	229.45	175.97				

File 2

mean	41.592	41.5936	35.99417	35.99333	37.32333
SD	39.01875	35.70512	19.43409	15.86818	12.7179
RD%	93.77	85.83	53.98	44.06	34.05
lnRD(%)	4.540845	4.452369	3.988614	3.785552	3.52783
τ	1	2	4	8	16
ln(τ)	0	0.69	1.39	2.08	2.77

this case, the slope is -0.271. The fractal dimension (FD) of the signal can be calculated as: slope = 1-FD or FD = 1- (-0.271) = 1.271. When FD values range between 1 and 1.5, the studied process is considered to have fractal-like properties. The FD and the β slope are related between each other with the equation: β = 3-2*FD.

In diagram 2, the 'noise' that exists in the signal of tidal volume can be seen, which displays increased fluctuations over time.

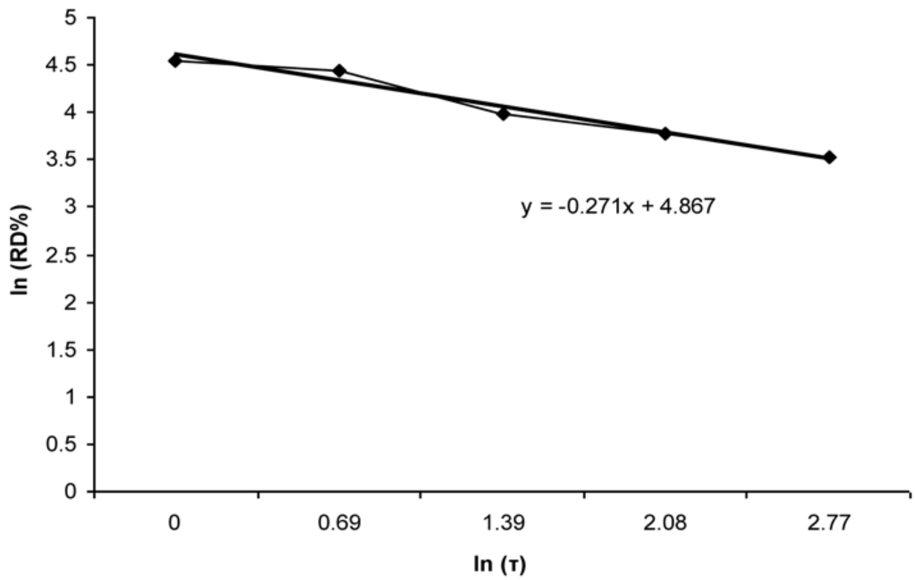

Diagram 1.

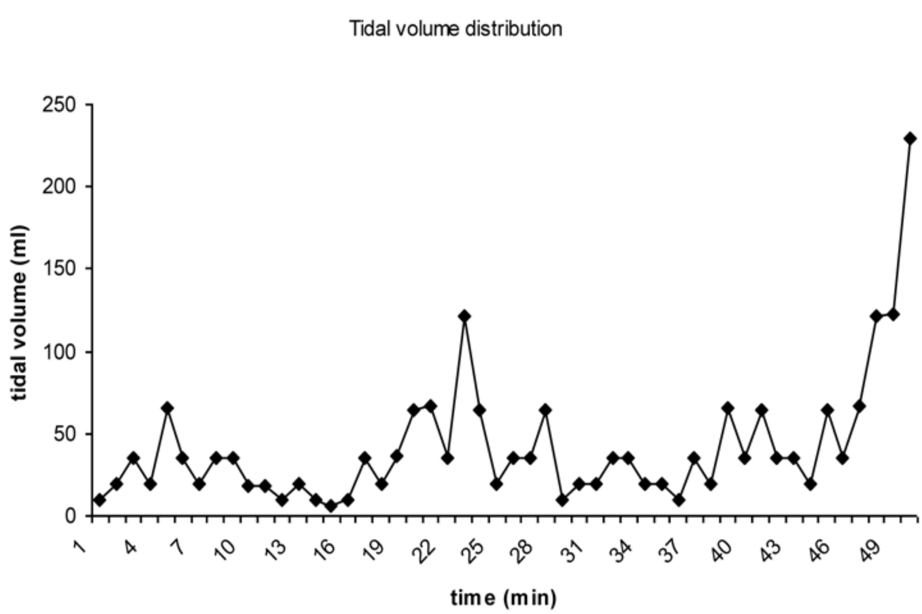

Diagram 2.