Chaos, Solitons and Fractals 95 (2017) 42–47

Contents lists available at ScienceDirect

Chaos, Solitons and Fractals

Nonlinear Science, and Nonequilibrium and Complex Phenomena

journal homepage: www.elsevier.com/locate/chaos

Review

A chaotic outlook on biological systems

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ARTICLE INFO

Article history:
Received 12 December 2015
Revised 16 April 2016
Accepted 14 December 2016

Keywords:
Chaos theory
Oscillation
Biological systems
Mitochondria
Evolution

ABSTRACT

Biological systems such as the cell are mostly analyzed by looking at the biophysical properties of their inner workers, such as proteins. However, some have suggested that biological systems have quantum properties in addition to their physical complexities. Thus, these systems can be measured by the displacement and geometry or the velocity of the acting agents inside them. In this paper I suggest that measurement of displacement or of biophysical properties does not suffice when calculating the dynamics of the system, and vice versa. Furthermore, I propose a theoretical background to approach and measure the dynamics of biological systems by using the chaos theory as means of calculation. This approach will be exemplified in evolution, development and cancer with a strong emphasis on endosymbiosis of the mitochondria and the cell in genetic aspects.

1. Introduction

The uniqueness of the eukaryotic cell has been widely discussed, especially in the context of its evolutionary processes. The eukaryotic cell has a cross-talk with the functional units within it. This cross-talk can tell a lot about the units and the cell's function. One of these cross-talks is the interaction between the nucleus and the mitochondria. Both of the units have DNA within them that differs in structure,[1] length,[2] inheritance and internal mechanisms and processes [1,2].

Despite these differences the nucleus and the mitochondria are interdependent. The mitochondria perform the Krebs cycle and oxidative phosphorylation to produce ATP that will serve as a fuel for the variety of functions of the cell. However, the mitochondrial DNA expresses only 13 key sub-units of the proteins participating in the oxidative phosphorylation. The remaining sub-units and the rest of the proteins acting in the mitochondria are encoded in the nucleus. Hence, the mitochondrial DNA and the genomic DNA developed a special co-evolution that might explain how the dynamical nature of the cell [1,2]. At the biochemical level metabolites are transported between the nucleus and the mitochondria, a process that is crucial for both their functioning. For example, in fat metabolism we can see a strong connection between degradation and synthesis of fatty acids with respect to the key players and metabolites [1,2].

One principal process in the cell that can shed some light on this co-evolution is transcription. In order to activate or repress this process, transcription factors (TFs) bind to RNA polymerase and to target sites on the DNA, to produce mRNA which is then translated into proteins. Thus, TFs have an essential part in regulating the expression of different pathways in the cell's depending on the cell external environment. TFs have a conserved, yet variable, structure depending on their function and adaptation to their environment [3–7]. Moreover, their concentration changes under different cell conditions and can affect the cell's phenotype (amongst other factors). For example, p53 at high and low concentrations can cause cancer. However, despite the vast knowledge about p53, its specific contribution to the cell in disease and in health remains enigmatic [7, Fig. 1].

Biological systems (including the nucleus and the mitochondria) that portray self-organized characteristics also exhibit fractal geometry of self-similarity and repeating patterns and the interactions between these systems have non-linear properties [8–11]. Moreover, in these systems temporal and spatial scale spectra cannot be linked in the large temporal, spatial and/or topological scales of self-organized structures due to the difference in time scale. The time scale in small self-organized systems processes is significantly shorter than in large self-organized systems processes with their long lifetime dynamics of metastable states [9,11,12].

A possible way to describe the physical background of these dynamics is the chaos theory. In this field of study of non-linear dynamics, systems are investigated by deterministic equations. Edward Lorenz stated that these systems are sensitive to their initial conditions and their future behavior can be determined by searching for these conditions. Thus, when dealing with this kind of

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[1] Nuclear DNA (nDNA) is linear while mitochondrial DNA (mtDNA) is circular (1).

[2] nDNA is ~3x109 bp while mtDNA is ~16,569 bp (1).

http://dx.doi.org/10.1016/j.chaos.2016.12.013
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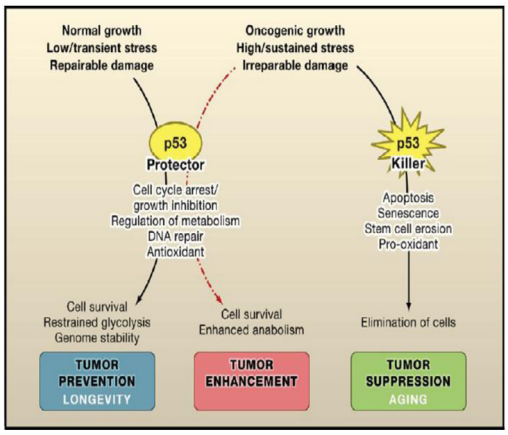

Fig. 1. The p53 paradox. In different environmental requirements, cell conditions and concentrations, p53 can promote the repair and survival of damaged cells or permanent removal of damaged cells though death or senescence. In the first case, p53 can contribute to tumor development without proper regulation (red dashed arrow), or with proper regulation enhance longevity. In the latter case, p53 can promote aging. Vousden and Prives et al. 2009. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

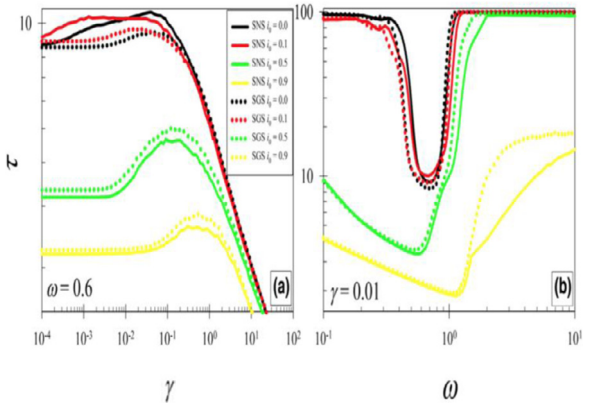

Fig. 2. The importance of frequency and environment in self-organized systems. In normal Josephson junction (SNS) and in a superconductor (SGS) with different currents, a periodic change is observed in accordance to frequency (ω) and fixed noise intensity (γ). This may hinder on the great importance of noise and frequency in self-organized systems. Spagnolo et al. 2015.

systems, we need to look for the Lorenz attractor's dynamics in order to understand their chaotic behavior [12]. In the perspective of a biologist, this theory may determine the entropy or the overall behavior of biological systems.

2. The frequency theory and its biological significance

Previous research in non-linear dynamics emphasized the importance of frequency in biological systems [13–15, Fig. 2]. In the famous experiment performed by Joshua Lederberg and Salvador Luria in 1943 the rate of mutations in bacteria in each generation was defined as $\sim 4.7 \times 10^{-9}$ [16]. Ten years later William Hayes defined the rate of conjugation as $\sim 10^{-1}$ in each generation [17]. However, the current definition of frequency is not sufficient in order to explain the dynamics in biological systems. Thus, I would like to suggest a different approach to the definition of frequency. Instead of the number of times a biological behavior repeats itself in a certain interval of time, frequency is the rate of self-organized systems with hereditary material in accordance to the change of environment and the individual systems' demands, or what is termed in non-linear physics as noise [9–11,15,18,19].

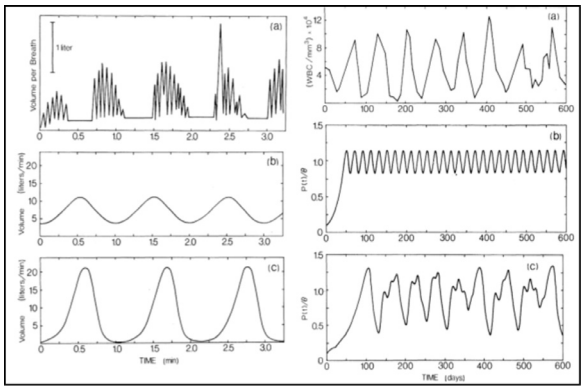

Fig. 3. Oscillatory behavior can indicate on physiological conditions. (Left) Adults with Cheyne-Stockes syndrome exhibit periodic change in respiration (liters of air) over time (min). (Right) A similar phenomenon is observed in peripheral white blood cells count in chronic granolitic leukemia (production of white blood cell over time, population) over time (days). Source: Mackey and Glass 1977.

Observing the behavior of common biological systems (such as fluctuation of metabolites or electrochemical signals), we can see that most of them have a repetitive variation around a central value- an oscillatory behavior [20–26]. The possible meaning of a single oscillation is accordance with the second law of thermodynamics [25,26]:

1. Rise to a peak in oscillation is the advantage of the system over its environment by having momentarily more enthalpy force to overcome the overall entropy (termed: *growth*).
2. Decline is the advantage of the environment over the system increasing the entropy even further than the initial state (termed: *decay*).

Ideally, the decay and the growth are both symmetrical to one another and, therefore, balanced. However, there are cases that the balance is broken in favor of one of the forces, observed in the system's oscillation [24, Fig. 3].

Another aspect of oscillation worth further observation in the context of biological systems is how more than one oscillation behaves and what can it tell us about between the system and its environment. In order to further investigate this behavior in means of non-linear dynamics, we need to return back to what may be the key process that started it- transcription. The dynamics of transcription processes were previously quantified by the oscillation of the concentrations of RNA [20] or of TFs [21–23]. Let us differentiate two types of groups of oscillations: common and different angular frequency oscillations. In the first group TFs might differ in the time of start, wavelength or amplitude of oscillation, but their purpose in the cell is common or at least parallel [27]. In the second group TFs cannot differ in any parameter except the angular frequency. If there is a difference in the wavelength or amplitude, quantification can only be applied when TF oscillatory behavior is coupled to the counter actor. In the biological perspective, both the TF groups have the same target, but opposite roles for it.[3] Each TF can exhibit common or different angular frequency oscillations depending on the TF to which it is compared to [7,27].

Various articles have tried to use oscillatory behavior as means of quantifying chaotic dynamics, especially in biological systems [18,24,28,29]. However, at least in biological systems, I postulate that quantifying oscillatory behavior is not the end point in understanding the chaotic dynamics of a system. The amplitude and the rate of oscillation can allude to the state of the cell. In this sense, the state of the cell is dynamic and repetitive at the same time

[3] Such as PKA and PKB that function oppositely in multiple cellular processes.