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Chaos in Physiological Control Systems: Health or Disease?

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ABSTRACT During the nineties, the Rössler's have reported in their famous book "Chaos in Physiology," that "physiology is the mother of Chaos." Moreover, several researchers have proved that Chaos is a generic characteristic of systems in physiology. In the context of disease, like for example growth of cancer cell populations, Chaos often refers to irregular and unpredictable patterns. In such cases, Chaos signatures can be used to prove the existence of some pathologies. However, for other physiological behaviors, Chaos is a form of order disguised as disorder and can be a signature of healthy physiological functions. This is for example the case of human brain behavior. As the boundary between health and disease is not always clear-cut in chaotic systems in physiology, some conditions may involve transitions between ordered and chaotic states. Understanding these transitions and identifying critical points can be crucial for predicting Healthy vs. pathological Chaos. Using recent advances in physiological Chaos and disease dynamics, this survey paper tries to answer the crucial question: when Chaos be a sign of health or disease?

KEYWORDS
Modelling in physiology
Homeostasis
Physiological chaos
Chaos in disease
Pathological chaos
Healthy chaotic patterns

INTRODUCTION

In Chaos theory, Chaos dynamics refer to a complex, unpredictable, and random behavior within a system. The concept of Chaos is often associated with nonlinear and complex dynamics showing inherent sensitivity to initial conditions where small effects lead to large and unexpected consequences (Sprott 2003; Lassoued and Boubaker 2016; Devaney 2018; Lozi 2023). While in the vast literature, Chaos theory and its applications to various fields, including mathematics, physics, engineering and so on have been extensively discussed (Boubaker and Jafari 2018), its application in medicine remains both intriguing and challenging. Figure 1 shows the production per year as well as the production by country or territory for a literature review done in January 2024 via the Scopus database using the keyword "Chaos".

The investigation shows the considerable number of journal papers published in the field. It is found 40.169 journal papers written in English with a peak of production in 2023. The search also reveals that China, United States and India are the three countries with the highest production in the field. Figure 2 presents the classification of production by subject area. It is noticed that mathematics, physics, and engineering are the fields with the highest production. To my surprise, among this considerable number of papers dedicated to Chaos theory, I found only 883 articles devoted for medicine and 638 documents for neurosciences. This little production stands for simply 3.8% of the total. The production per year related to these two categories is shown in Figure 3 and Figure 4, respectively. In the opposite way, it is important to note here that the most cited paper in all categories presented in Figure 2 is the paper titled "Approximate entropy as a measure of system complexity," published in 1991 by Pincus presenting an application of Chaos theory to the analysis of heart rate data, and its effectively discriminated between healthy and sick groups of neonates (Pincus 1991).

This observation is consistent with the statements of Rössler in his famous book "Chaos in Physiology" published in 1994 in which he has reported that "the physiology is the mother of Chaos" and that "It appears that physiology has a particularly high affinity to Chaos" (Rossler and Rossler 1994). It was during the nineties that researchers have proved that Chaos is a regular characteristic for systems in physiology (Mackey and An Der Heiden 1984; Mpitsos *et al.* 1988; Glass *et al.* 1988; da Silva 1991; Goldberger *et al.* 1990; Elbert *et al.* 1994)

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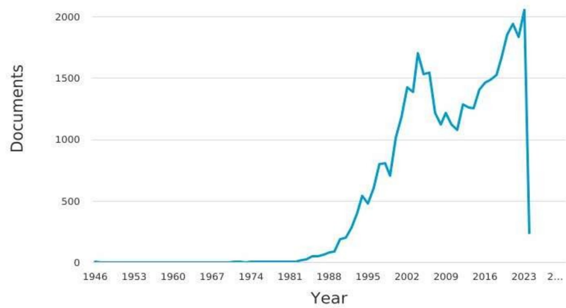
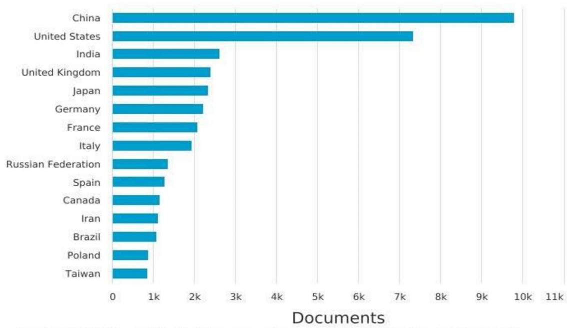


(a)



(b)

Figure 1 Data from Scopus database. Query: KEY (Chaos) AND (LIMIT-TO (SRCTYPE, «j»)) AND (LIMIT-TO (LANGUAGE, «English»)). (a)Production per year, (b) Production by country or territory.

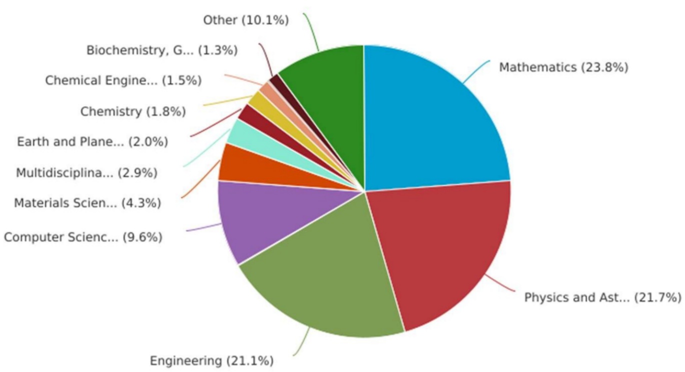


Figure 2 Data from Scopus database: Documents by subject area. Query: KEY (Chaos) AND (LIMIT-TO (SRCTYPE, «j»)) AND (LIMIT-TO (LANGUAGE, «English»)). The category "Other (10.1%)" includes medicine and neurosciences with 3.7%.

In this framework, I should note that cardiovascular system, with a specific focus on heart rate variability (HRV), was the pioneering area of application of Chaos theory in physiology recognizing that the heart rate does not exhibit a constant rhythm over time (Leaning *et al.* 1983; Pincus and Goldberger 1994; Mansier *et al.* 1996). Early investigations within Chaos in physiological control systems had also considered respiratory control model (Flower *et al.* 1993), blood pressure regulation (Persson 1996; Wagner *et al.* 1996), autonomic nervous system dynamics (Korn and Faure 2003) and neuroendocrine system (Lipsitz and Goldberger 1992). Let us recognize here that the study of Chaos in physiology is a complex and evolving field, and the understanding of its implications in medicine is continually expanding. Researchers use mathematical models, computational simulations, and empirical observations to explore the dynamic nature of physiological systems and their relationship to human health (Lassoued and Boubaker 2020).

Chaotic behavior in physiology was often associated within certain pathological conditions and may be linked to disease (Cross and Cotton 1994). For example, for the glucose-insulin regulatory system numerous anomalies are perceived in form of chaotic dynamics such as hypoglycemia, hyperinsulinemia, and type 2 diabetes (Rajagopal *et al.* 2020). The chaotic pathological signatures of migraine headache (Bayani *et al.* 2018), the epileptic seizures (Panahi *et al.* 2017, 2019) and the attention deficit hyperactivity disorder (Ansarinasab *et al.* 2023) are recently considered. Complex dynamics for type 1 diabetes (Ginoux *et al.* 2018) and cancer model (Xuan *et al.* 2022) are also studied.

On another side, Chaos can be a normal and healthy aspect of certain physiological processes like for example the heartbeat, the respiratory patterns, and the neural activity which often show complex irregular patterns falling under the umbrella of Chaos dynamics. These dynamics can contribute to the adaptability and resilience of the organism (Golbin and Umantsev 2006; Goldberger and West 1987). As physiological systems are highly interconnected and dynamic, Chaos theory can help us appreciate the complexity of these interactions, perturbations, or changes. Some complex dynamics of the system can lead to unpredictable consequences, which may have implications for health or disease.

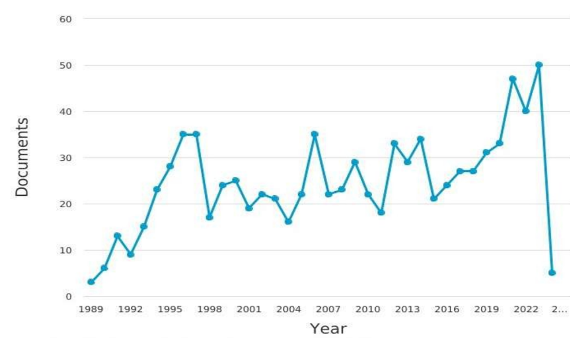


Figure 3 Data from Scopus database: Production per year in the field of medicine. Query: KEY (Chaos) AND (LIMIT-TO (SRCTYPE, «j»)) AND (LIMIT-TO (LANGUAGE, «English»)) AND (LIMIT-TO (SUBJAREA, «MEDI»))

In this paper, after reviewing the fundamental basics in modeling and control in physiology, I will try to answer the three following key questions:

1. How does manifest pathological Chaos in physiological control systems and what are the motivation behind studying these dynamics?

2. What are the control systems in physiology showing healthy chaotic patterns?

3. How can we distinguish between healthy and pathological Chaos?

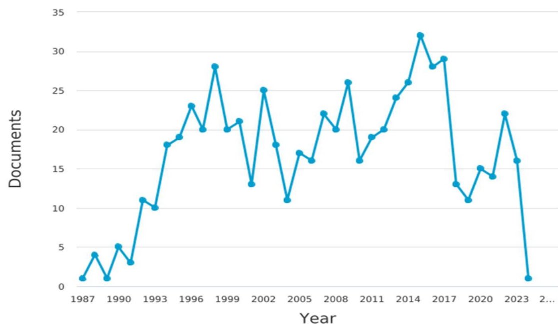


Figure 4 Data from Scopus database: Production per year in the field of neurosciences. Query: KEY (Chaos) AND (LIMIT-TO (SRCTYPE, «j»)) AND (LIMIT-TO (LANGUAGE, «English»)) AND (LIMIT-TO (SUBJAREA, «NEUR»))

This paper is organized as follows: the following section introduces fundamentals in modeling and control in physiology. In section 3, main pathological and healthy chaotic systems are reviewed and discussed. Finally, general principles and approaches to help differentiate between healthy and pathological chaotic dynamics are exposed.

FUNDAMENTALS IN MODELING AND CONTROL IN PHYSIOLOGY

This section will expose motivations and used approaches for modelling dynamic systems in physiology. It also introduces the importance of the principle of Homeostasis in controlling physiological systems.

Motivations

Modeling and controlling complex physiological systems is a new research area compared to other applications in control systems like robotics, aeronautics, and industrial systems. The results of this new research field are of huge importance as they can be used to understand the complexity of physiological systems, to establish a diagnosis and to forecast the dynamics of some diseases (Lassoued and Boubaker 2020). Furthermore, in many cases, certain failures in the body process require external control laws to normalize the performances of the body (Boubaker 2020) or use of artificial organs and robotic assistive technologies (Boubaker 2023).

Modelling in physiology

Modelling in physiology can be organized via three main approaches: the compartment modelling approach, the equivalent modeling approach and the data driven modelling approach (see (Lassoued and Boubaker 2020) and related references).

Compartmental modeling approachy It is one of the oldest approaches used for modelling physiological systems (Enderle and Bronzino 2012). The related basic equations are expressed as follows (Lassoued and Boubaker 2020):

$$\frac{dx_i}{dt} = f_{i0} + \sum_{\substack{j=1 \\ j\neq i}}^{n} (f_{ij} - f_{ji}) - f_{0i} \quad ; \quad x_i(0) = x_{0i} \quad ; \quad i = 1,2,\ldots,n \tag{1}$$

where x_i denotes the amount of material in compartment i and x_{i0} represents the related initial value. f_{ji} is the mass flow rate of compartment j from compartment i. Figure 5 shows its arrangement. The index zero represents the environment of the physiological system (Lassoued and Boubaker 2020). Applications of this approach can be found in (Alvarez-Arenas *et al.* 2019; Yousefnezhad *et al.* 2021; Rajeswari and Vijayakumar 2023; Giakoumi *et al.* 2023; Boudin *et al.* 2023; McKnight *et al.* 2013). Figure 6 describes the example of the insulin-independent two-compartment model.

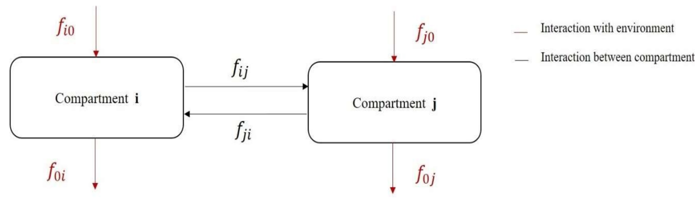


Figure 5 Basics in compartmental modelling approach (Lassoued and Boubaker 2020).

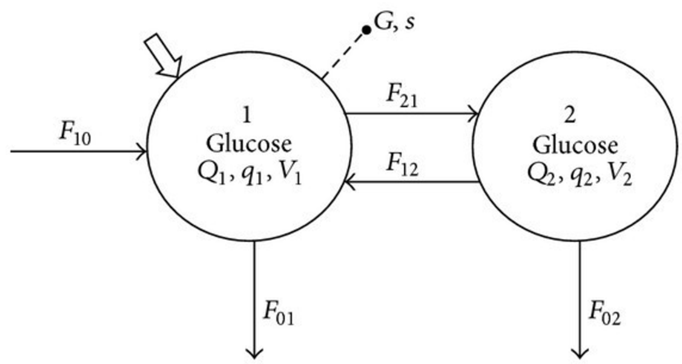


Figure 6 Insulin-independent two-compartment model for describing glucose kinetics. First compartment holds the vascular space. Arrowed solid lines are flows, hollow arrow is glucose application (infusion or dose), and broken line sampling (McKnight *et al.* 2013).

Equivalent modeling approach By such an approach, physiological variables are modelled via physical mechanisms such as electrical or mechanical components (see Table.1). Figure 7. shows an example of an equivalent electronic circuit of blood-vessels system (Lassoued and Boubaker 2020). Figure 8. shows an example of the equivalent electronic circuit for a short segment of squid giant axon proposed by Hodgkin and Huxley (Hodgkin and Huxley 1952). Furthermore, an example of a physiological system modelled by an equivalent electronic circuit for the cardiovascular system is found in (Ismail *et al.* 2018; Zhang *et al.* 2020).

Data driven modeling approach It is here an empirical approach that does not imply mathematical modelling derived from physical systems but machine learning and deep learning modeling approaches using time series data. Applications of such an approach can be found in many recent papers (see for example (Dutta *et al.* 2018; Paoletti *et al.* 2019) for diabetes management, (Fong *et al.* 2018; Yoo *et al.* 2022) for immune system modelling, (Dritsas and Trigka 2023) for cardiovascular disease modelling and (Khan *et al.* 2022) for brain disease modelling).

Classification of mathematical models Dynamical systems in physiology can be described using lumped models described by

Table 1 Physical, mechanical, and electrical analogues (Lassoued and Boubaker 2020).

Physiological measurements	Mechanical analogues			Electrical analogues		
	Name	Notation	Symbol	Name	Notation	Symbol
Pressure	Force	F	-	Voltage	V	-
Volume	Displacement	x	-	Charge	q	-
Flow	Velocity	$v = \frac{dx}{dt}$	-	Current	$I = \frac{dq}{dt}$	-
Viscous drag	Viscous resistance	$B = \frac{F}{v}$		Resistance	$R = \frac{V}{I}$	
Compliance	Compliance	$C' = \frac{x}{F}$		Capacitance	$C = \frac{q}{V}$	

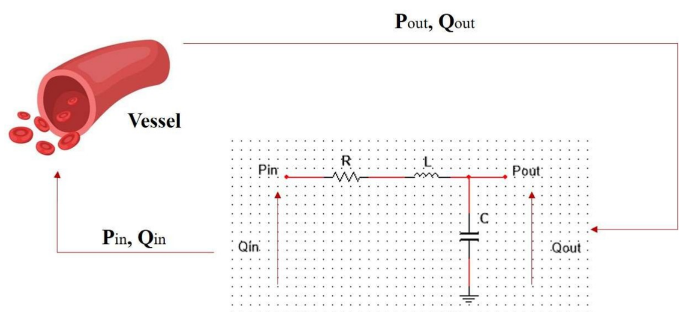


Figure 7 Equivalent electronic circuit of blood-vessels system (Lassoued and Boubaker 2020).

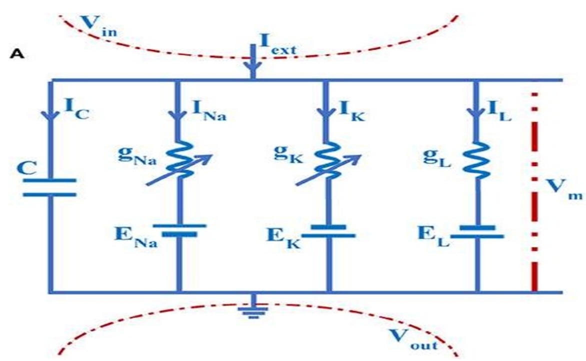


Figure 8 Electrical equivalent circuit for a short segment of squid giant axon proposed by Hodgkin and Huxley. The capacitor represents the capacitance of the cell membrane; the two variable resistors represent voltage-dependent Na+ and K + conductance, the fixed resistor represents a voltage-independent leakage conductance, and the three batteries represent reversal potentials for the corresponding conductance (Fang and Wang 2021).

ordinary differential equations or distributed parameter models described by partial differential equations (Shi *et al.* 2011). They can be also described by deterministic or stochastic models, continuous-time, or discrete-time models or by, parametric or non-parametric models.

Many recent papers have described physiological systems using fractional-order derivatives. Some other papers have included time-delays in mathematical models. In fact, "fractional calculus is recognized as one suitable option to increase the accuracy of the mathematical models and to provides a memory effect into the time evolution of the system since its future solutions will depend on all past times and not only from recent event" (Fernández-Carreón *et al.* 2022).

Homeostasis principle

"In physiology, control refers to the process of stabilizing a physiological variable to a specified set point, either by reversing perturbations via negative feedback closed loops or via anticipatory open loops. In the human body, the control process is designed by Homeostasis" (Lassoued and Boubaker 2020). Homeostasis principle was discovered by Walter Bradford Cannon in 1929 (Cannon 1929). A literature survey of this principle can be found in (Chapelot and Charlot 2019). "The Homeostasis principle is the property of a physiological system to regulate its internal environment to a given set point in presence of a specific stimulus producing changes in that variable" (Lassoued and Boubaker 2020).

As shown by Figure 9, the control activity in the body is guaranteed by the arrangement of the control center (composed by nervous and endocrine systems), sensors and effectors. Figure 10 gives several examples of Homeostasis. The example of temperature regulation in the human body is described by Figure 11. As reported in (Houk 1988), three basic control strategies guarantying Homeostasis exist: negative feedback, feedforward, and adaptive control. These approaches are summarized in Figure 12. Figure 13 and Figure 14 present the two examples of postural balance homeostasis and glucose homeostasis, respectively, using feedback control laws. For further examples of physiological systems using feedforward and adaptive control, the reader can refer to (Lassoued and Boubaker 2020).

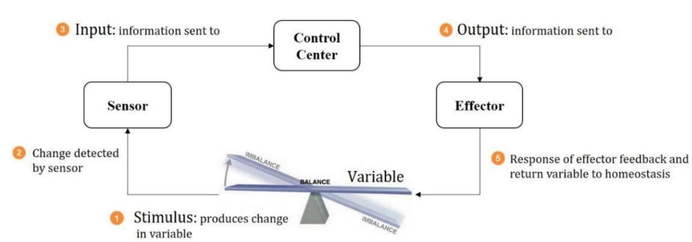


Figure 9 Homeostasis principle (Lassoued and Boubaker 2020).

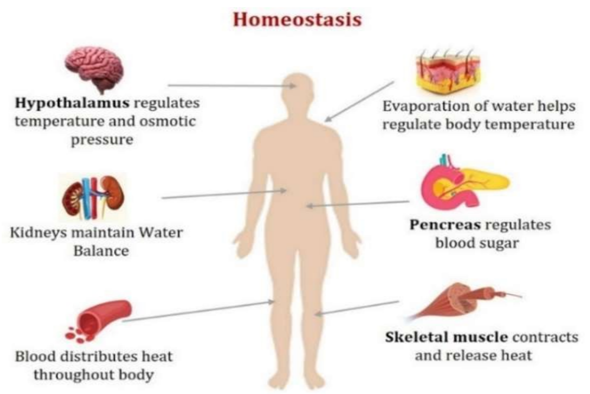


Figure 10 Homeostasis examples including energy and fluid balances (Lassoued and Boubaker 2020).

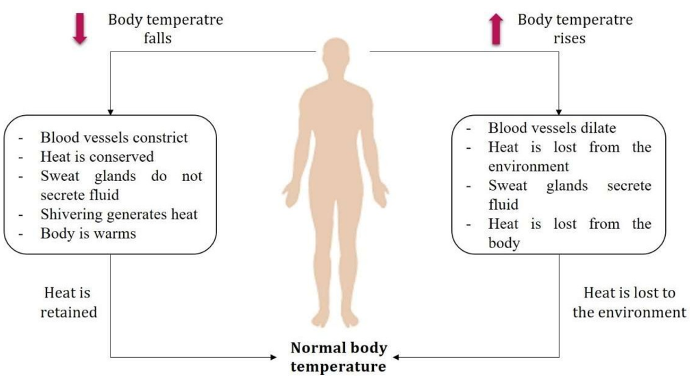


Figure 11 Human temperature Homeostasis (Lassoued and Boubaker 2020).

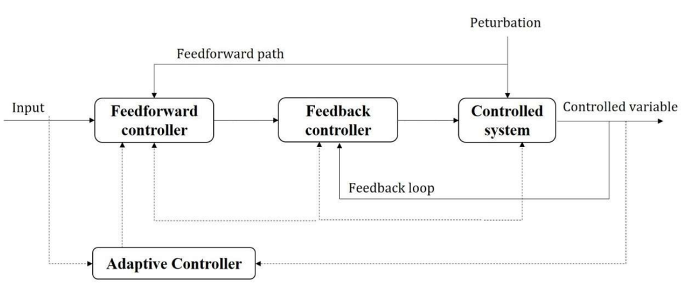


Figure 12 Basic control strategies in Homeostasis principle (Lassoued and Boubaker 2020).

CHAOS IN PHYSIOLOGY

According to classical concepts of physiological control, healthy systems are self-regulated to reduce variability and keep physiological constancy. However, contrary to the predictions of homeostasis, the output of a wide range of systems fluctuates in a complex manner that is underpinned by non-linear mechanisms and the low dimensional dynamics of Chaos. Chaos supplies new concepts and methods of analysis that help to understand the dynamics of neural networks in both health and disease that complement existing approaches and may lead to new investigative opportunities (Kernick 2005).

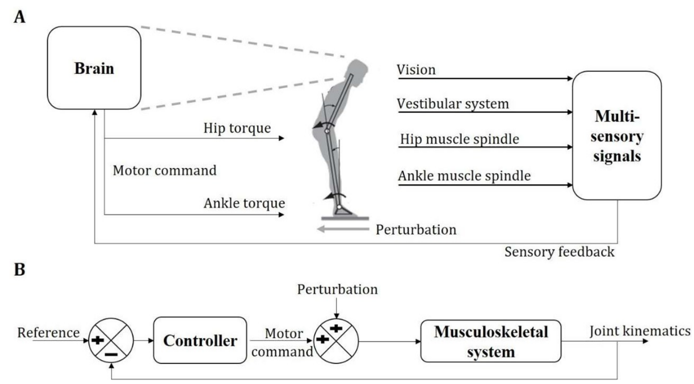


Figure 13 Postural balance via feedback control laws; (A) schematic model (B) Block diagram (Lassoued and Boubaker 2020).

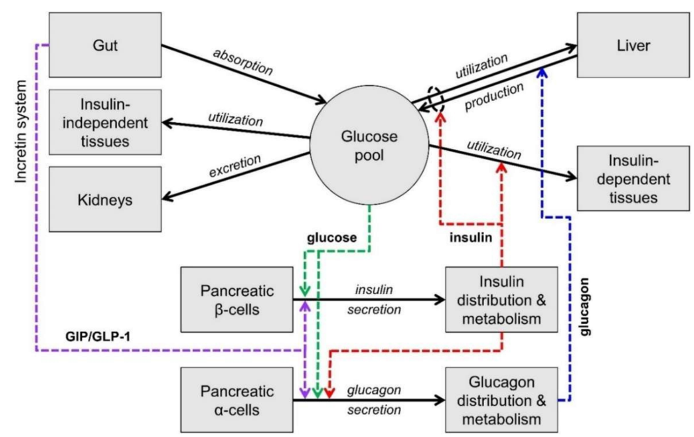


Figure 14 Scheme of the main mechanisms of glucose homeostasis. Colored dashed arrows are control signals (glucose or hormone concentrations) that regulate glucose fluxes or insulin and glucagon secretion. The scheme does not show adaptive control mechanisms (e.g., insulin secretion upregulation with insulin resistance) (Mari *et al.* 2020).

Really, Peng et al. were between the first researchers claiming that the classical theory of homeostasis, according to which stable physiological processes seek to maintain constancy and its more recently proposed modifications under the rubric of hemodynamics, need to be revised and extended to account explicitly for this far from equilibrium behavior (Peng *et al.* 1994).

Nonlinear dynamics in physiology

In (Goldberger *et al.* 2002), Goldberger et al., have given an exhaustive list of nonlinear dynamics that a physiological system can generate. These complex behaviors include abrupt changes (like bifurcations, bistability and multistability), hysteresis, nonlinear oscillations (including limit cycles, phase-resetting, entrainment…), scale invariant (including fractal and multi-fractal scaling, long range correlation, self-organized criticality), nonlinear waves (like spirals, scrolls, solitons) and deterministic Chaos.

Even controlled via Homeostasis principle, it is proved in many other research papers that physiological controlled systems are, at least, capable of the four kinds of behaviors described by Figure 15 (Lassoued and Boubaker 2020; Uthamacumaran 2021). These dynamics can include fixed point, limit cycle, limit torus and strange attractor behavior. It is important to note that the term Chaos in physiology does not imply randomness in the traditional sense but rather a complex and often nonlinear behavior that deviates from typical physiological patterns (Kernick 2005; Coffey 1998). Studying these chaotic dynamics is crucial for understanding diseases mechanisms and developing targeted interventions.

Healthy chaotic patterns

Chaotic physiological systems in healthy organisms refer to systems that show complex, unpredictable behavior despite being in a state of normal health. It is important to note that Chaos in physiological systems does not always imply dysfunction; rather, it reflects the inherent complexity and dynamic nature of these systems. It is important to emphasize that Chaos in these systems is often related to their adaptability and responsiveness to changing internal and external conditions as healthy and stable living systems are set up as chaotic and fractal in nature (Golbin and Umantsev 2006; Goldberger and West 1987; Korolj *et al.* 2019). While Chaos might be present in healthy physiological systems, it is typically controlled and contributes to the overall stability and resilience of the organism. It is proved in many research papers that a healthy dose of Chaos is always necessary (Korolj *et al.* 2019). I give below some examples.

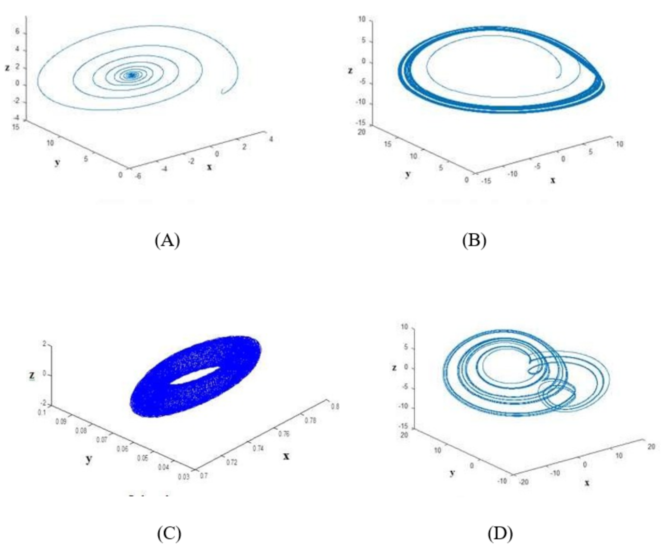


Figure 15 Various behaviors shown by complex systems in physiology (Lassoued and Boubaker 2020). (A) Fixed point; (B) Limit Cycle; (C) Limit Torus; (D) Strange attractor.

Chaos in healthy cardiovascular and respiratory systems The cardiovascular system is composed of the heart and vessels. Its main function is to pump the blood in the body in order to supply all tissues and organs with oxygen and other nutrients (Formaggia *et al.* 2010). The earliest model of this system was proposed in (Grodins 1959). The modeling of this system was then determined via different point of view (Golbin and Umantsev 2006; Gois and Savi 2009; Noble *et al.* 2012; Cheffer *et al.* 2021; Yadav and Jadhav 2021). For example, in (Golbin and Umantsev 2006), the authors prove via the cardiac Hodgkin– Huxley equation that hearts are poised near the edge of Chaos. They find that the potassium ion-channel and the sodium ion-channel are memristors.

In (Zhang *et al.* 2020; Coffey 1998), the authors prove that cardiac Chaos is prevalent in healthy heart, and a decrease in such Chaos may be indicative of congestive heart failure. Let us note that during intense physical exercise, the interaction between the cardiovascular and respiratory systems can also show chaotic behavior. This complexity is often seen as a normal adaptive response to the increased demands on the body (Golbin and Umantsev 2006; Goldberger and West 1987). The HRV may show a more irregular pattern during exercise, and this variability is often considered a sign of a healthy cardiovascular system (Pincus and Goldberger 1994; Mansier *et al.* 1996).

Chaos in healthy neural activity in the brain Neural networks in the brain often display complex patterns of activity (Poon and Merrill 1997). Some level of Chaos in neural activity is considered healthy and necessary for cognitive function. Indeed, neuronal firing patterns and the interactions between different brain regions contribute to the complexity of brain function. This complexity is not only normal but is also thought to be essential for cognitive processes such as learning, memory, information processing and adaptability (Xuan *et al.* 2022; Pritchard and Duke 1995; Breakspear 2017; Kavakci 2021). The concept of Chaos in neural dynamics is often explored through the study of brain waves. For example, it is proved that the EEG frequencies of aging subjects show a loss of low-voltage fast waves and an increase in slow waves with diffusion of slow periodicity. Measures of complexity using fractals and Chaos theory always help to assess age-related anatomic and physiologic changes and predict pathologies (Goldberger *et al.* 2002).

Healthy Chaos in gait and locomotion system Human movement and locomotion involve a complex interplay of muscles, joints, and neural signals. Walking, for example, is not a perfectly regular and predictable activity. Gait patterns show variability and chaotic dynamics, allowing individuals to adapt to changes in terrain and keep balance. This variability is considered a sign of a healthy and adaptable motor control system (Müller *et al.* 2017).

Healthy chaos in immune system According to (Heltberg *et al.* 2019), Chaos in bodily regulation can optimize our immune system and can have of great significance for avoiding serious diseases such as cancer and diabetes.

Heltberg *et al.* (2019) show how chaotic dynamics create a heterogeneous population of cell states and describe how this can be beneficial in multi-toxic environments. The dynamics of the transcription factor of the immune system when driven by an external periodic signal and exhibiting chaotic signals are described by Figure 16.

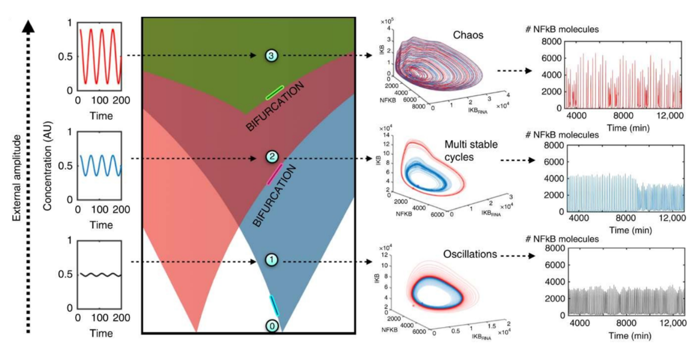


Figure 16 Dynamics emerging from a transcription factor of the immune system when driven by a periodic tumor necrosis factor (TNF) signal exhibiting chaotic output signals when amplitude of external signals increase (Heltberg *et al.* 2019).

Chaos in disease

Chaos in the context of disease often refers to irregular and unpredictable patterns or behaviors within physiological systems (Cross and Cotton 1994). There are diverse ways in which chaotic dynamics contribute to the complexity and unpredictability of various diseases across different physiological systems. Understanding these chaotic patterns is essential for developing effective diagnostic and therapeutic strategies. Here are examples where chaotic dynamics may be seen in the context of various diseases.

Cardiovascular and respiratory disorders Cardiac fibrillation, with its complex and disordered patterns, can be seen as a manifestation of Chaos in space and time within the heart muscle (Garfinkel *et al.* 1997; Cheffer *et al.* 2021). The chaotic electrical activity can disrupt the normal pumping function of the heart, leading to compromised blood circulation (Gupta *et al.* 2020, 2021; Gupta 2023). On the other hand, other studies focusing on chronic obstructive pulmonary disease, and asthma have shown the chaotic behavior within these diseases. In this framework, (Mansour *et al.* 2023) have proposed a new chaotic system that investigates the connection between weather patterns and respiratory illness.

Cancer progression Cancers are complex systems, consisting of groups of adaptive malignant cells that self- organize in time and space, far from thermodynamic equilibrium (Uthamacumaran 2021). They are considered as of the most curious physiologic problems in these last years. The growth and spread of cancer cells can show chaotic patterns (Fong *et al.* 2018; Yoo *et al.* 2022; Sedivy and Mader 1997; Debbouche *et al.* 2022; Uthamacumaran 2020; Naik *et al.* 2020). Tumor growth is influenced by complex interactions between cancer cells, the immune system, and the surrounding microenvironment, resulting in unpredictable disease progression (Russo *et al.* 2021). Several mathematical models were proposed to predict the evolution of this disease. They are based on the Volterra–Lotka type prey– predator models. One of the most interesting models was proposed by Itik and Banks in (Itik and Banks 2010). The non-dimensional model considering a three-cell population is described by:

$$\begin{aligned}\frac{dx_1}{dt} &= x_1(1-x_1) - a_1x_1x_2 - a_2x_1x_3\\ \frac{dx_2}{dt} &= a_3x_2(1-x_2) - a_4x_1x_2\\ \frac{dx_3}{dt} &= \frac{a_5x_1x_3}{x_1+a_6} - a_7x_1x_3 - a_8x_3\end{aligned} \tag{2}$$

where x_1 represents the number of tumor cells, x_2 indicates the number of host cells, x_3 refers to the number of effectors cells in the single tumor compartment and a_i ($i = 1, ..., 8$) are system's parameters. Let us note that a patient is healthy when the effector cells are equal to zero, more precisely when the chaotic-cancer system converges to an equilibrium point. Several papers have proved that entropy in individual cells change with cancer induction and increasing anaplasticity (See (Uthamacumaran 2021) and related papers).

Recent works in this field have considered fractional-order differential systems to describe cancer models. The most recent model is described by (Karaca 2023):

$$\begin{aligned}D_t^\gamma x_1 &= x_1(1-x_1) - a_1x_1x_2 - a_2x_1x_3\\ D_t^\gamma x_2 &= a_3x_2(1-x_2) - a_4x_1x_2\\ D_t^\gamma x_3 &= \frac{a_5x_1x_3}{x_1+a_6} - a_7x_1x_3 - a_8x_3\end{aligned} \tag{3}$$

where D_t^γ is the Caputo-Fabrizio-Caputo fractional derivative and $0 < \gamma \leq 1$ is the fractional order. Figure 17 describes the numerical simulation for the model (3).

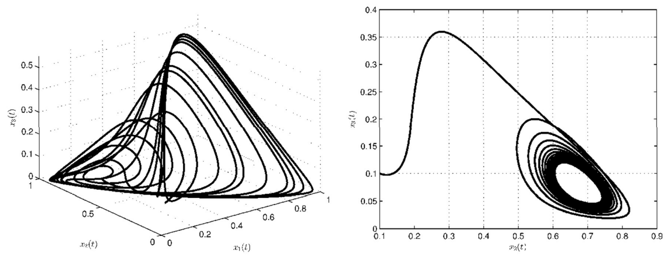


Figure 17 Numerical simulation for cancer model via Atangana-Baleanu-Caputo fractional operator. (A): Simulation in the three dimensional-space; (B): projected onto x_2(t)-x_3(t) planes, respectively (Karaca 2023).

Metabolic disorders It was proved through several research works that metabolic disorders including obesity, hyperglycemia, hypertension, dyslipidemia, hypercholesterolemia, hypertriglyceridemia, non- alcoholic fatty liver disease and type I and type II diabetes have complex dynamic patterns. Diabetes involves dysregulation of blood glucose levels, and the metabolic Chaos associated with insulin resistance and impaired insulin secretion can lead to erratic fluctuations in blood sugar levels (Ginoux *et al.* 2018; Rajeswari and Vijayakumar 2023; Dutta *et al.* 2018; Paoletti *et al.* 2019; Shabestari *et al.* 2019; Borah *et al.* 2021).

One of the most interesting integer-order models for human glucose-insulin regulatory system is described by (Shabestari *et al.* 2019):

$$\begin{aligned}\frac{dx_1}{dt} &= a_1x_2(t-\tau_1)x_3(t-\tau) - a_2x_1 + a_3x_3(t-\tau_1)\\ \frac{dx_2}{dt} &= \frac{a_4}{x_3} - a_5x_1(t-\tau_2) + a_6\\ \frac{dx_3}{dt} &= a_7(x_2-\hat{x_2})(T-x_3) + a_8x_3(T-x_3) - a_9x_3\end{aligned} \tag{4}$$

where x_1, x_2, x_3 and $\hat{x_2}$ are the insulin level, glucose level, beta-cells number and the glucose metabolism considering its basal state, respectively. τ_1 is the delay for the insulin production, because of blood glucose level rising. The delay between augmented insulin level and glucose reduction is τ_2. Figure 18. Shows the bifurcation diagrams for the glucose-insulin system (4) depending on the bifurcation delays τ_1 and τ_2 and showing routes to Chaos.

Fractional-order modelling of glucose-insulin biological systems was also considered by some researchers (see for example (Rajagopal *et al.* 2020; Munoz-Pacheco *et al.* 2020; Fernández-Carreón *et al.* 2022)). In (Fernández-Carreón *et al.* 2022), the authors derived the fractional-order model corresponding to the integer-order model (5) as follow:

$$\begin{aligned}D_t^\gamma x_1 &= a_1x_2(t-\tau_1)x_3(t-\tau) - a_2x_1 + a_3x_3(t-\tau_1)\\ D_t^\gamma x_2 &= \frac{a_4}{x_3} - a_5x_1(t-\tau_2) + a_6\\ D_t^\gamma x_3 &= a_7(x_2-\hat{x_2})(T-x_3) + a_8x_3(T-x_3) - a_9x_3\end{aligned} \tag{5}$$

By using the fractional-order operator and representing the phase portraits and bifurcations diagrams, the authors conclude that numerical simulations remain in good agreement with the theoretical findings and that a memory profile, can provide improved accuracy of the physiological disorders. Furthermore, in (Munoz-Pacheco *et al.* 2020), the authors who proposed an electronic realization of the fractional glucose-insulin regulatory model confirm that the use of fractional-order modelling for chaotic systems is more interesting for embedded technologies.

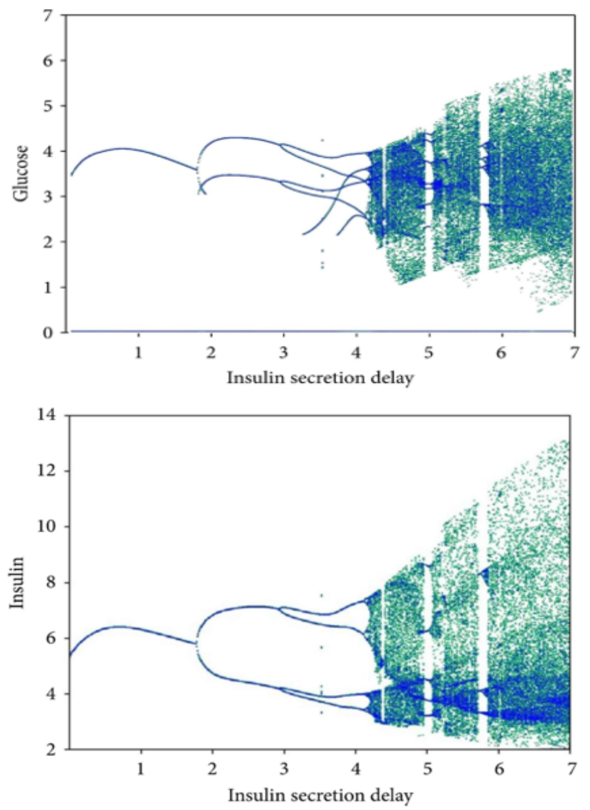


Figure 18 Bifurcation diagram for the glucose-insulin system (5) depending on the bifurcation delays τ_1 and τ_2 and showing routes to Chaos (Shabestari *et al.* 2019).

Neurological disorder Neurological disorders are conditions that affect the nervous system, which includes the brain, spinal cord, and peripheral nerves. These disorders can result from abnormalities in the structure, function, or chemistry of the nervous system and often lead to a variety of symptoms affecting movement, sensation, cognition, or other functions. Examples of specific neurological disorders showing chaotic patterns, contributing to the characteristic motor symptoms are Alzheimer's disease (Khan *et al.* 2022), neurodegenerative diseases like Parkinson's disease and Huntington's disease (Yulmetyev *et al.* 2006; Borah *et al.* 2021; Shabestari *et al.* 2019) and Epilepsy (Panahi *et al.* 2017, 2019; Sarbadhikari and Chakrabarty 2001).

However, the application of chaos theory to these diseases is still an area of ongoing research, and the nature of the dynamics may vary between individuals. Between neurological diseases I can also cite migraines attacks involving severe headaches often accompanied by nausea, sensitivity to light, and sound. The triggers and the unpredictable nature of migraine attacks are also examples of chaotic behavior in the nervous system (Bayani *et al.* 2018; Kernick 2005; Khan *et al.* 2022). Other examples of neuronal diseases can also be cited such as the chaotic model of memristive nature of autapsis when an axon is injured. This involves poisoning in ion channels or heterogeneity in a local area of the axon for which signal transmission may be interrupted or blocked during neuronal communication (Muni *et al.* 2022).

Viral diseases impacting the immune system There are many fatal diseases impacting the immune system like HIV/AIDS, Hepatitis C (HCV) and Herpes Simplex Virus (HSV) which are caused by virus. For example, HIV-1 infection is a hazardous disease that can lead to cancer, AIDS, and other serious illnesses. The progression of HIV to AIDS involves chaotic dynamics in the immune system. The virus attacks and depletes CD4 T cells, disrupting the body's ability to mount an effective immune response (Borah *et al.* 2021; Ye *et al.* 2009; Duarte *et al.* 2018). The related model can be described by (Naik *et al.* 2020):

$$
\begin{aligned}
\frac{dx_1}{dt} &= x_1[a_1\left(1-\frac{x_1+x_2+x_3}{a_2}\right)-a_3x_2] \\
\frac{dx_2}{dt} &= x_2[a_4\left(1-\frac{x_1+x_2+x_3}{a_2}\right)-a_5x_1-a_6x_3] \\
\frac{dx_3}{dt} &= a_6x_2x_3-a_7x_3
\end{aligned}
\tag{6}
$$

where x_1 is the population number of cancer cells, x_2 represents the number of healthy cells, x_3 refers to the number of HIV-infected cells a_i $(i = 1, ..., 7)$ are system's parameters. Once again, stability investigations and results obtained in (Naik *et al.* 2020) indicate that fractional models are better predictors, among others.

HOW DISTINGUISHING BETWEEN HEALTHY AND DISEASE CHAOS?

Distinguishing between healthy Chaos and chaotic patterns associated with disease is a complex task that often requires a thorough understanding of the specific physiological system under consideration. Interdisciplinary collaboration, combining ability from clinicians, researchers, and data scientists, is essential for a comprehensive assessment of chaotic dynamics in physiological systems. This collaborative approach enables a more nuanced interpretation of Chaos, considering both the specific characteristics of the system under study and the broader clinical context. Here are some general principles and approaches to help differentiate between healthy and pathological chaotic dynamics.

Temporal Patterns

In physiology, there are several types of physiological signals that can be collected. They include the electroencephalogram (EEG) measuring the electrical activity of the brain, the electrocardiogram (ECG) recording the electrical activity of the heart, Electromyogram (EMG) recording the electrical activity of muscles, the Electrodermal Activity (EDA) measuring the electrical activity of the skin, the Oxygen Saturation (SpO2) measuring the percentage of oxygen in the blood, the body Temperature, the respiratory rate, the blood pressure, the blood glucose, the bioelectrical impedance analysis (BIA), the Capnography measuring the concentration of carbon dioxide in exhaled air and so on (Shirmohammadi *et al.* 2016). Examining the temporal patterns and dynamics of physiological systems over time is especially important (Stam 2005).

We should recognize that time series often hold "hidden information" including chaotic signals for a wide range of physiological systems. Healthy Chaos often shows short-term dynamics within a stable overall pattern. In contrast, chaotic patterns associated with disease may be characterized by sustained instability, irregularities, or a lack of right regulation (Goldberger *et al.* 2002). Nonlinear analysis of time series of physiological signals such as EEG and HRV signals can be used to support the diagnosis of many diseases like cardiovascular diseases (Poon and Merrill 1997).

Integration of multiple parameters

Combining information from multiple physiological parameters can supply a more comprehensive understanding. Examining the interactions between different systems and their chaotic patterns can reveal insights into overall health or the presence of disease (Poon and Merrill 1997; Borah *et al.* 2021; Stam 2005; Garland 2013; Cashin and Yorke 2016).

Using quantitative measures

Employing quantitative measures can supply objective assessments of Chaos. Analyzing specific parameters, such as largest Lyapunov exponent, fractal dimensions, Hausdorff dimension D, correlation dimension D2, wavelet transform modulus maxima, time asymmetry/irreversibility parameters, Renyi's entropy (REN), Shannon spectral, entropy and so on can offer insights into the nature of chaotic behavior and whether it aligns with healthy or pathological patterns (Faust and Bairy 2012; Müller *et al.* 2017; Pereda *et al.* 2005).

Integration of imaging techniques

Utilizing advanced imaging techniques (Choquet *et al.* 2021), such as functional magnetic resonance imaging (MRI) and electroencephalography (EEG), can supply insights into the spatial and temporal patterns of chaotic behavior within the body. It can enhance the understanding of Chaos dynamics within a physiological system. Recent advancements in deep learning, particularly convolutional networks, have rapidly become the preferred methodology for analyzing medical images, facilitating tasks like disease segmentation, classification, and pattern quantification of a range of diseases including Alzheimer's, breast cancer, brain tumors, glaucoma, heart murmurs, retinal microaneurysms, colorectal liver metastases, and more (Rasool and Bhat 2023).

Baseline variability, population-based Comparisons, and genetic factors

Healthy physiological systems often show a certain degree of variability or Chaos within a defined range. Understanding the normal range of variability for a given parameter, such as heart rate, neural activity, or hormone levels, is crucial. Deviations that fall outside the normal range may show pathology. Furthermore, comparing individual physiological patterns to population-based norms can be informative (Poon and Merrill 1997).

Deviations that are consistent with a healthy range in the population may suggest adaptive Chaos, while patterns that diverge significantly may show disease-related Chaos. Genetic and epigenetic factors play a role in deciding the baseline characteristics of physiological systems. Understanding how genetic and epigenetic factors influence chaotic patterns can contribute to distinguishing between healthy and pathological dynamics (Sedivy and Mader 1997).

Adaptability and responsiveness to interventions

Healthy chaotic patterns are often associated with adaptability and responsiveness to internal and external stimuli (Cross and Cotton 1994). Interventions or modifications, such as lifestyle changes, medications, or therapeutic approaches, can supply valuable information. These adaptive responses contribute to the system's ability to support homeostasis. In contrast, chaotic patterns in disease may be maladaptive, resulting in dysfunction or failure to respond appropriately to challenges (Golbin and Umantsev 2006). Indeed, healthy systems often have a reserve ability that allows them to adapt to stressors and challenges. Assessing the functional reserve ability of a physiological system can help distinguish between adaptive, healthy Chaos and dysfunction. Showing specific associated with healthy or pathological chaotic patterns can be useful. Certain biomarkers may say adaptive responses in a healthy context or dysregulation in the presence of disease.

Contextual understanding, functional outcome, and clinical symptoms

Understanding the purpose and context of chaos within a system is important. For example, chaotic neural activity during certain cognitive processes is normal (Tsuda 2015), but chaotic patterns in neural activity associated with seizures may say pathology (Tsatsaris *et al.* 2016; Kavakci 2021). Furthermore, symptoms and signs associated with disease should not be overlooked. The presence of abnormal clinical symptoms, in conjunction with chaotic physiological patterns, may say pathology. Assessing the functional outcome of chaotic dynamics is crucial. Healthy chaotic behavior contributes to the proper functioning of physiological systems, supporting best performance. Chaotic patterns associated with disease may lead to impaired function, symptoms, and negative health outcomes.

Examining network analysis

Utilizing network analysis techniques can help understand the connectivity and interactions within a physiological system. Indeed Healthy and stable living systems are proved as chaotic and fractal in nature. A few of the most accessible examples include neurons and neural networks, heart rate variability, and the branching vasculature (Korolj *et al.* 2019). Healthy chaotic networks often exhibit organized complexity, while aging and disease-related may disrupt normal network dynamics (Alves *et al.* 2017). Lets' note for example that physiologic aging is associated with a generalized loss of such complexity in the network showing loss of complex variability in multiple physiologic processes including cardiovascular control, pulsatile hormone release, and electroencephalographic potentials and leading to an impaired ability to adapt to physiologic stress (Peng *et al.* 1994; Alves *et al.* 2017; Goldberger *et al.* 2002; Uthamacumaran 2021).

CONCLUSION

In this paper, after reviewing basics in modeling and control in physiology, I have examined through a state of art pathological vs healthy chaotic patterns in physiological systems. I have listed a number of principles and approaches to help differentiate between healthy and pathological chaotic dynamics. In all examples, the presence of chaos does not always show dysfunction or disease. Instead, it can reflect the intrinsic adaptability of physiological systems. Researchers have studied these chaotic dynamics to better understand the baseline behavior of healthy systems, which can provide valuable insights for distinguishing normal variations from patterns associated with pathology. Several prospectives can be suggested for this complex research domain including improving the performance of disease diagnostic models and exploring a new paradigm for intelligent assisted disease diagnosis (Liu *et al.* 2024; Rasool and Bhat 2023), diseases prediction (Mansour *et al.* 2023) and disease's optimal control (Mohammadi and Hejazi 2023).

Availability of data and material

Not applicable.

Conflicts of interest

The author declares that there is no conflict of interest regarding the publication of this paper.

Ethical standard

The author has no relevant financial or non-financial interests to disclose.

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