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Review

Changing complexity in human behavior and physiology through aging and disease

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Abstract

Lipsitz and Goldberger [47] proposed that there is a loss in the complexity of physiological and behavioral systems with aging and disease. Here, we show that this unidirectional view of the change in system complexity is too narrow in its consideration of the *actual* changes that occur with aging and disease. An increase or decrease in the complexity of a behavioral or physiological system output can occur and the direction of change is dependent on the confluence of constraints that channel the system dynamics. It is postulated that the observed increase or decrease in complexity with aging and disease is dependent on the nature of both the intrinsic dynamics of the system *and* the short-term change required to realize a local task demand.

Keywords: Aging; Disease; Complexity; Dynamics; Endocrinology; Motor control; Cardiovascular physiology; Neurophysiology

1. Introduction

Behavioral and physiological changes that occur with aging and disease emerge from multiple factors at a variety of levels of analysis of the organism-environment interaction [3,18,50,78]. For example, a reduction in nerve conduction velocity, a loss of high frequency sound, and a reduction in force expiratory volume can all be related to aging and disease [48,53,82]. In most cases, however, it is the interaction of multiple physiological control systems that affects each particular marker of age and disease. For instance, the loss of high frequency sound (presbycusis) in the human inner ear may be caused by alterations in sound receptors, their neurons, the blood supply, or in the structural changes of the basilar membrane in the inner ear [3].

The changes that occur with age and disease are consequences of the alterations in the structural and functional properties of the multiple macro and micro systems of the organism. These changes reduce the capacity of the system to adapt to various forms of stressors that can potentially provide different time-varying constraints. The reduced capacity to adapt to stress has been hypothesized to result from a loss of complexity with aging and disease [47]. This hypothesis holds that the loss of complexity of a physiological control system results from either a reduction in the number of individual structural components with age/disease or an alteration in the coupling function between these components. In many respects, the loss of complexity hypothesis is a subset of the broader concept of dynamics in disease [21] and aging [91–93], in which behavioral and physiological systems change due to aberrations in the temporal organization of the evolving dynamics.

We show that the pathway of change in behavior and physiology with age and disease is not limited to a decrease in complexity as proposed by Lipsitz and Goldberger [47]. Rather, there can be either an increase or decrease in the complexity of the respective macro or micro system's output. The specific direction of the change in complexity is dependent on the nature of the intrinsic dynamics of the system and the short-term adaptive change required to meet an immediate task demand.

Initially, in this article we outline the essence of the Lipsitz and Goldberger [47] perspective on the loss of complexity hypothesis with aging and disease. The empirical evidence that pertains to the loss of complexity hypoth-

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esis is then reviewed in relation to experimental data from both behavioral and physiological systems. Finally, a new postulate of the complexity and aging/disease relation is advanced that is elaborated from a dynamical systems physical biology approach to aging [92,93].

2. Conceptions of complexity

The concepts of thermodynamics and self-organization have motivated several efforts to develop a physical biology approach to physiology and behavior [21,43,70,91]. One outgrowth of this emerging theoretical framework is the examination of the complexity of biologic systems, including the behavior and physiology of aging [91–93], using the tools of nonlinear dynamics [22,28,36,63]. The concept of complexity is inherently linked to several other concepts in physics and biology, including entropy, randomness, and information theory [24,75,79,80] and this has produced a multitude of working definitions of complexity [20]. For the most part, the prevailing definitions of complexity are driven by the operational consideration of the number of system elements and their functional interactions. A particular experimental focus of this orientation has been the identification of the deterministic and stochastic properties that influence system complexity.

One standard approach to determining the complexity of a system examines the number of independent variables that is needed to reproduce or predict the output of the system. For example, the fiber type expression in skeletal muscle is dependent on the genetic, hormonal, neuronal, cardiovascular, and activity-related influences that affect the slow or fast myosin isoform expressed in muscle [51,71]. Since there are several variables that influence the phenotype of skeletal muscle fibers this physiological system resembles a highly complex system. A reductionistic model does not capture the rich dynamics that affect the phenotype of muscle fibers, and a systems model is invoked to understand the complex behavior of the system output.

In the expression,

$$X = f(\alpha_i, \beta_j, \delta_k, \ldots, \lambda_l) \quad (1)$$

the output of the system X is a function of several variables. The function f may be a linear or non-linear function of the variables that make up the system. As an example, X may be representative of the phenotype of the muscle fiber, and the variables in the function f represent the genetic, hormonal, neuronal, cardiovascular, and activity-related influences on muscle. It should also be noted that each variable has its own time scale of change, which introduces multiple time scales and correlated structure on the dynamics of the measured variable X [31,59]. Changing the number of variables or the parameters of the variables in function f would alter the complexity of the system output [37].

A second approach to altering the complexity of a system output would be to change the stochastic inputs to the system [65]. In Eq. (1), there are no stochastic inputs that might alter the system output. However,

$$X = f(\alpha_i, \beta_j, \delta_k, \ldots, \lambda_l) + \xi \quad (2)$$

Eq. (2) has an added component, ξ, which provides a stochastic input into the system. The stochastic input reduces the predictability of X, and this results in a more complex output of the system. The predictability of a system is based on the behavior of the system in the past, along with the initial conditions of the system. The greater influence from stochastic properties the less predictable the output of the system [37,65]. Thus, the complexity of a system is determined by both the deterministic and stochastic inputs that influence the state of the system.

A third approach to changing the complexity of a system is to alter the properties of the coupling function that relates the variables and parameters of the system. For instance, in Eq. (1) the coupling function, f, may change with age and disease although the structural components of the system are not altered. An example of this type of change can be observed in elderly humans' ability to perform reaching movements to a target. When an individual reaches quickly to a target with their hand, the agonist muscle burst accelerates the limb to the target and the antagonist muscle burst is activated at a time delay to decelerate the limb as it approaches the target. In the deceleration phase, the agonist and antagonist burst co-activate more in aging humans than young adult control subjects [74]. This finding illustrates that although elderly subjects have two effective structural components (i.e. agonist and antagonist muscle groups) the coupling function between these muscle groups is compromised with age. More generally, this example indicates that the complexity of a system output can be altered by changes in the coupling function.

Multiple factors influence an observed behavioral or physiological signal and the complexity of a system's output has been examined using multiple methods. The main theoretical focus for measures of complexity has been derived from the tools of nonlinear dynamics [36] together with the operational instantiation of information theory [75]. The methods used to assess physiological and behavioral complexity include but are not limited to: correlation dimension [24], approximate entropy [63], detrended fluctuation analysis [27], spectral analysis [33], Lyapunov exponent [8], false nearest neighbors [40], recurrence plot analysis [13,87], and pointwise correlation dimension [76]. Each of these methods captures to varying degrees a different aspect of the system dynamics. A major goal of complexity research in aging and disease has been to apply combinations of these tools to: a) reveal the relative contribution of deterministic and stochastic influences to the change in system output; and b) isolate the class of dynamic model that could be supporting the complexity of the system output.

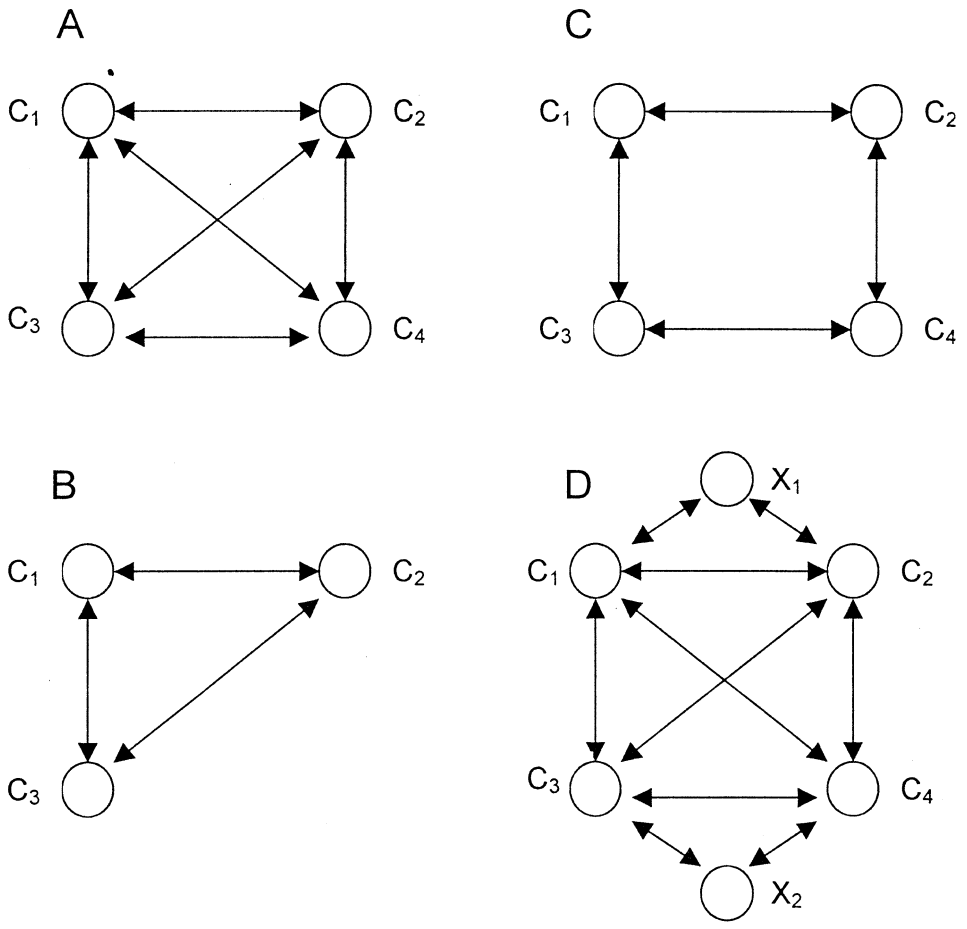

Fig. 1. Schematic of the loss of complexity hypothesis in a four-component system. **A**, the four circles represent the four components of the system and the arrows represent the coupling between the components. **B**, shows the loss of complexity by the loss of a structural component from the system. **C**, illustrates an age/disease related change in the coupling between the components of the system. The reduction in the number of arrows represents an alteration in the coupling function between structural components. **D**, demonstrates an increase in the number of structural components of the system.

3. The loss of complexity hypothesis

Lipsitz and Goldberger [47] proposed that there is a reduction in the complexity of a physiological or behavioral control system with age and disease. They postulated that the reduced complexity reflects the underlying structural (component) and functional (coupling) changes in the organization of the system. Generally, a loss of system complexity reflects: 1) a loss or impairment of functional components; and/or 2) altered nonlinear coupling between the components. This idea is illustrated in Fig. 1A where each circle represents a component of a system and the arrows reflect the coupling between components. For simplicity, a system with only four components is shown. The components could be taken as reflecting the structural aspects of a physiological system. For example, this scheme could reflect the motor units at the neuromuscular junction, sinus node cells of the heart, or the number of dopamine receptors in the striatum.

Fig. 1B shows there may be a loss in the number of structural components with age or disease that contributes to reducing the complexity of a system's output. The loss of a structural component shown in Fig. 1B is analogous to losing a component variable of function *f* from Eq. (1). An example of this type of change in dynamics is the progressive loss of dopaminergic cells in the substantia nigra compacta of the basal ganglia that occurs with age and Parkinson's disease. In Parkinson's disease, approximately 80% of the dopaminergic cells die before most of the behavioral symptoms of Parkinson's disease are observed [89]. A reduction in the dopamine cells reduces the outflow from internal globus pallidus of the basal ganglia and this is related to the loss of complexity that is observed in the tremor output of individuals with Parkinson's disease [84, 85].

Other examples of a reduction in the number of structural components with age include: i) estrogen hormone activity in females [16]; ii) collagen fibers per unit of surface area in skin tissue [41]; iii) sinus node cells in the heart [88]; and iv) the number of alveoli of the lungs [3,90]. It should also be noted that the number of structural components might increase with age (Fig. 1D). For example, the growth and proliferation of cancer cells represents an increase in the number of structural components and this can create a

deleterious effect on the health of an individual. These age-related changes in the number of structural components of physiological systems provide a primary mechanism for the altered complexity of the physiological or behavioral systems output.

The second mechanism that Lipsitz and Goldberger [47] proposed to account for a loss of complexity was that the coupling between components was altered with aging and disease processes. A change in coupling is illustrated schematically in Fig. 1C, which shows the same number of structural components as Figs. 1A and B, but the number of arrows connecting each structural component is altered. It is also possible for the time scales of the couplings between the components to change with age and disease.

An example of the influence on system complexity of a change in the coupling between structural components could be in the synchronization between motor units [15, 19]. The motor unit includes the nerve, muscle fibers, and the neuromuscular junction where the nerve and muscle fibers communicate [11,51]. While there are structural changes in motor units with age [45], there could, in principle be changes in the coupling between motor units. Changes in motor unit synchrony would represent the altered coupling between structural components of the nervous system.

4. Decreases in complexity with age and disease

Lipsitz and Goldberger [47] reported data from only a few experiments that supported the loss of complexity hypothesis. Since the time of this publication several more studies have been reported in both the physiological and behavioral literatures that provide additional evidence for the hypothesis. Here, by way of example, we highlight some recent experimental examinations of the loss of complexity in physiology and behavior.

4.1. Decreases in complexity: behavioral systems

To illustrate the loss of complexity hypothesis in behavioral systems, we emphasize some recent experimental work on human upright standing posture, pathological tremor, and mood disorders in bipolar patients. These macro level system behaviors are usually considered in an independent light, although as we show, they all similarly exhibit a loss of complexity with age and/or disease.

During the maintenance of upright standing posture—a fundamental motor act that provides the basis for locomotion and most other movement tasks—the position of the global ground reaction force (center of pressure), is measured to provide an index of postural stability. The x and y position of the center of pressure is derived from the linear forces and rotational moments that are measured from a force platform. It is generally thought that the center of pressure trajectory fluctuates around an equilibrium point during upright quiet standing [10].

The complexity of the center of pressure trajectory was examined in children (3 and 5 years), young adult (18–25 years), and elderly (60–75 years) subjects during an upright quiet standing task with the eyes open and closed [55]. ApEn[1] was used to index the complexity of the center of pressure trajectory [63]. There was an increase in the complexity (increased ApEn) from the 3- to the 5-year-olds to the young adult subjects and a decline in complexity (decreased ApEn) from the young adult to the elderly subjects (at ApEn values that were similar to the 3 year old subjects). These findings are consistent with the hypothesis that the complexity of the postural system output takes the form of an inverted U-shaped function across the life-span with increases in complexity during child development to adulthood and decreases in complexity as a function of old age [55]. The life-span changes in the complexity of upright standing posture parallel other findings in the analysis of both physiological and pathological tremor.

Tremor is defined as the involuntary, rhythmic, approximately sinusoidal oscillation of a body segment [14]. Tremor is one of the cardinal signs of Parkinson's disease and results from a reduction in the level of dopaminergic neurons present in the substantia nigra of the basal ganglia. There is a reduction in the spectral bandwidth of the 8–12 Hz physiological tremor in healthy subjects to a 4–6 Hz tremor in individuals with Parkinson's disease [17,44]. The decrease in bandwidth of tremor spectrum reflects a reduction in the complexity of the tremor output in Parkinson's disease.

A direct examination of the complexity of resting tremor, finger tremor, and postural tremor has been reported in mild to moderate Parkinson's disease patients using ApEn and spectral analysis techniques [84]. It was found that the patients have a reduction in the complexity of their tremor output even though the modal frequency and amplitude of the tremor is not different than that of age-matched controls. Moreover, the relation between the Unified Parkinson's Disease Rating Scale and measures of complexity during a force production task has been examined when subjects were required to match a constant force level over 5%, 25%, and 50% of their maximal voluntary contraction under a vision and no vision condition [85]. The Unified Parkinson's Disease Rating Scale had a strong negative correlation with the ApEn measure of complexity ($r = -0.84$) over all force and vision conditions indicating a strong inverse relation between the severity of Parkinson's disease and the complexity of motor output. These findings reveal the power of dynamical techniques in the assessment of Parkinson's disease tremor and show that progressions in the disease state are characterized by a reduction in complexity of the motor output.

In tardive dyskinesia, tremor and other superfluous movements of the limbs also demonstrate a reduction in complexity. Tardive dyskinesia is a movement disorder that

arises from prolonged intake of neuroleptic medication [2] and has a high prevalence in mental retardation and schizophrenia [35]. The complexity of finger tremor in tardive dyskinesia patients has a reduced correlation dimension [24] when compared to the dimension of the matched control subjects [57]. Similarly, in an examination of upright standing posture a dimension estimate of 2.2 was reported for the center of pressure in normal healthy subjects and a lower estimate of 1.3 for the age-matched individuals with tardive dyskinesia [60]. Neuroleptic medication has also been shown to reduce the complexity of lip motion kinematics in patients with tardive dyskinesia over the course of a drug withdrawal protocol [58].

In bipolar disorder the patients' mood can change repeatedly and exhibit varying degrees of complexity compared to control subjects. In an examination of complexity in biopolar disorder, patients with at least four mood-changing episodes in the previous 12 months were selected and measurements of their self-reported mood index were taken [23]. The mood index was measured on a quantitative one-dimensional scale that ranged from the 'best to the worst I have ever felt'. A log-log transform was applied to the power spectrum of the mood index and the linear slope of the frequency and power axes was examined. The bipolar patients had a slope of -1.24 and the control subjects had a slope of -0.69 suggesting that a higher level of complexity in the mood index of control subjects compared to the bipolar patients. Indeed, dimensional analysis of the mood index revealed a D_2 of 3.2 for the bipolar patients and an unbounded, noisy D_2 for the control subjects.

These data on bipolar disorder, pathological tremor and postural control all reveal a reduction in the behavioral complexity of the macro level systems output with age and disease. The findings of these studies are consistent with the hypothesis that there is a loss of complexity with age and disease [47]. It should be noted that these different task paradigms all require the subjects to maintain a constant mean state such that the behavioral variability manifests from fluctuations around a stationary mean (see Section 6 for more detail on the importance of a stationary mean).

4.2. Decreases in complexity: physiological systems

The study of the complexity of physiological systems originated with the examination of cardiovascular dynamics in elderly individuals and patients with a variety of different cardiovascular complications. Kaplan and colleagues [37] were the first to directly examine the complexity of heart rate variability and systolic blood pressure from the radial artery in young (21–35 years) and elderly (62–90 years) adults. The subjects were required to breathe in synchrony with a metronome (0.25 Hz), breathe in a normal spontaneous rhythm while lying supine, and breathe in a normal spontaneous rhythm with the body tilted 60° in a head up position. Complexity of output was assessed by using approximate entropy [63] and approximate dimension, which is a modified version of the correlation dimension [24].

The authors found that in the R-R heart beat intervals and blood pressure concentration variability, the elderly subjects had a reduction in complexity in both the metronome and quiet breathing conditions compared to controls [37]. These differences in system complexity can be attributed to changes in the physiological control of the cardiovascular system that occur with advancing age. The reduction in the complexity of R-R heart beat intervals has also been shown to decrease from young adults ($<$40 years) to middle aged (40–60 years) to old age ($>$60 years) individuals [62].

There are several disease-related changes in heart rate complexity that are similar to the decrease in the complexity of heart rate variability with age. For instance, using a recurrence plot analysis procedure [13,87] the complexity of heart rate variability in diabetic patients was found to be lower than that of healthy control subjects [52]. Additionally, the Ewing score (standard diagnostic test for neuropathy) correlated strongly ($r = -0.60$) with the longest length index of the recurrence plot analysis indicating that the cardiovascular system of diabetic patients was under more stringent control with increases in the severity of the diabetic neuropathy. Furthermore, infants at risk of sudden infant death syndrome (SIDS) have reduced heart rate complexity compared to control infants [64] and heart transplant patients have reduced heart rate complexity compared to control subjects [42,94].

Di Mascio and others [12] examined the interspike intervals of midbrain dopaminergic neurons recorded in vivo, in anesthetized rats. They found that the complexity of the interspike interval decreased as a function of age. Similarly, the complexity of the electroencephalogram (EEG) has been shown in several studies to exhibit less complex dynamics with age and pathology. For example, the range of EEG frequencies elicited in response to light, sound, and other sensory stimuli decline with age in both animals and humans [18]. In addition, it has been shown that approximately 11 min before epileptic patients have a seizure the complexity of the EEG is decreased [46]. The reduction in dimension (complexity) is taken to represent the increased synchronization between discharging seizure-related neurons. The complexity of the EEG has also been shown to decrease as a function of Alzheimer's disease when subjects were required to rest quietly with the eyes closed, resting with the eyes open, and while performing mental arithmetic [6,32,34].

In summary, these studies of the physiology of the cardiovascular system and brain processes, together with the work from behavioral systems such as pathological tremor and upright standing posture, provide support for the hypothesis of Lipsitz and Goldberger [47] that there is a reduction in the complexity of system output with age and disease. However, there is also evidence that the loss of complexity hypothesis is not a universal principle specifying change in physiology and behavior with age and disease

in that there are several empirical examples that are directly counter to the loss of complexity hypothesis. In the next section we turn to some relevant examples from physiology and behavior that show an *increase* in complexity with age and disease.

5. Increases in complexity with age and disease

5.1. Increases in complexity: behavioral systems

During locomotion there is an altered fractal scaling in the timing of the gait cycle over long walking intervals with age and Huntington's disease. The gait patterns of young (24.6 ± 1.9 years), elderly (>70 years), and Huntington's disease (34.5 ± 13.4 years) subjects were examined while walking at their self-determined pace on flat ground for about 5–6 min [26]. The stride interval (heel strike to the next heel strike) was measured and the detrended fluctuation analysis (DFA) method was applied to the stride interval data. DFA is an analysis procedure that examines the short-range and long-range correlation structure and distinguishes between white, brown, and 1/f type noise [4]. The slope, α, of the DFA method assesses the degree of long-range fractal correlations within the signal. It was found that the Huntington's disease subjects had the lowest slope ($\alpha = .60$) followed by the elderly ($\alpha = .68$) and young ($\alpha = .87$) subject groups. The closer the slope, α, is to 0.5 the less predictability in the stride interval gait cycle. Thus, there was less correlated structure (less predictability) in the stride interval of Huntington's disease patients compared to control subjects which is counter to the Lipsitz and Goldberger [47] idea that the predictability in physiological output increases with age and disease.

An increase in the complexity of a behavioral systems output has also been shown in the bimanual finger movements of schizophrenic patients [38]. The study required subjects to oscillate their index fingers in an anti-phase movement pattern at increasing frequencies in horizontal and vertical conditions. It was found that the schizophrenic patients had a higher point wise dimension (i.e. increased dimension from the algorithm of Skinner et al. 1994) in the horizontal and vertical movement pattern compared to the control subjects. This finding demonstrates that rhythmic bimanual coordination is more complex in schizophrenic patients.

Finally, in the study of a choice task paradigm, schizophrenic and control subjects were required to guess the direction (left or right) that a randomly presented stimulus would appear on a computer monitor [61]. Complexity of the behavioral responses was assessed through a measure of dynamical entropy. It was found that the schizophrenic patients displayed extreme levels of both increases and decreases in the complexity of their responses compared to control subjects. The findings demonstrated that there is not a universal directionally specific change in the complexity of schizophrenic patients' behavior in a choice task paradigm, but rather that their behavior was at the extremes of highly regular and highly complex behavioral output.

5.2. Increases in complexity: physiological systems

Most of the support from physiology for an increase in the complexity with age and disease comes from the endocrine system. For instance, growth hormone (GH) is produced by somatotropic cells and promotes protein synthesis by encouraging the metabolism of fats for energy. During acromegaly—a disease characterized by enlarged extremities—there are excessive amounts of GH used for protein synthesis by the bones and skeletal system. Indeed, the GH release pattern over a 24-h period has a diurnal cycle with the highest levels during the evening and lower levels during the day. Individuals with acromegaly have a reduction in the orderliness (increased ApEn) of the 24-h GH release pattern compared to control subjects [25], revealing that with acromegaly there is an increase in the complexity of GH over time.

In an investigation of the hypothalamo-pituitary-testicular axis, an important component in the reproductive capacity of males, the complexity of the hormone secretion aids in the understanding of how this system maintains reproductive function. Pincus and others [67] examined serum concentration levels of luteinizing hormone (LH) and testosterone (T) of the hypothalamo-pituitary-testicular axis in a group of young (21–34 years) and elderly (62–74 years) adults. They calculated the approximate entropy of each hormone time-series and the cross-approximate entropy [68] between the LH and T time-series. The LH and T concentrations were more irregular (more complex) in the elderly subjects compared to the matched controls. Moreover, the cross-approximate entropy was more asynchronous between the LH and T concentration levels indicating that the level of LH and T synchrony decreases with age. The decreased synchrony with age was proposed to result from the decreased feedback signal strength from the hypothalamic gonadotropin-releasing hormone neuronal network or a decreased responsiveness to the feedback signal. Thus, these experiments show that the LH and T concentration levels increase in complexity as a function of age.

The data from the changes in the complexity of reproductive hormones correspond to the changes in adrenocorticotropin (ACTH) and cortisol concentration levels of Cushing's disease and matched control subjects. ACTH is a hormone that is activated by corticotropin releasing hormone and stimulates the adrenal cortex to release corticosteroid hormones, such as cortisol. Cortisol is the primary glucocorticoid that aids in the metabolism of most body cells and provides resistance to stressors. In Cushing's disease there is an ACTH-releasing tumor of the pituitary or by a glucocortidoid-releasing tumor of the adrenal cortex that causes persistent hyperglycemia and several other disabling symptoms.

Van den Berg and others [86] examined the complexity of ACTH and cortisol concentration levels in Cushing's disease and control subjects by withdrawing blood samples at 10-min intervals for a 24-h period. It was found that Cushing's disease patients had greater ApEn values for ACTH (Cushing's = 1.38; Control = 0.83) and cortisol (Cushing's = 1.45; Control = 0.86) concentration levels indicating that there was greater complexity in the 24-h hormone patterns of the Cushing's disease patients. Furthermore, the joint synchrony (assessed by cross-ApEn) [68] between ACTH and cortisol levels is more asynchronous in Cushing's disease patients implying an erosion of the feedback control processes regulating hormone release patterns [66,69].

6. Attractor dynamics and the change in complexity

The synthesis in Sections 4 and 5 indicates that a physiological or behavioral system can reveal either a decrease or increase in complexity of output as a function of age or disease. This potential bi-directional change of complexity in biologic systems invites at least two related questions. First, why is there an increase in the complexity of certain systems with age/disease and a decrease in the complexity of others? Second, is the directional change in system complexity due to a particular dynamic property of the respective system?

To approach these questions we consider the loss of complexity hypothesis of Lipsitz and Goldberger [47] in a broader dynamical systems perspective to aging and disease [73,91–93]. This theoretical perspective considers individuals as part of a broader living open eco-system in which the principles of thermodynamics organize the energy exchanges together with the resultant and emerging entropy of an aging system [7]. This dynamical perspective affords a coherent framework for the consideration of aging and disease in the context of nonlinear dynamics and the concepts of stability, variability, and fluctuations in system output.

A dynamical system perspective also provides a theoretical background for principles about the direction of change in the dynamical degrees of freedom (dimension) of a system over time [56]. This theoretical framework affords a resolution to the apparent paradox of there being potentially either an increase or decrease in complexity of a physiological or behavioral systems output. A key feature is the nature of the adaptive change required of the intrinsic dynamics to realize a particular system's environmental demands.

The increase and decrease in complexity depends on the intrinsic dynamics of the respective system. The intrinsic dynamic refers to the natural operating properties of a behavioral or physiological system operating within an environment that has nonspecific task demands [39]. In other words, the intrinsic dynamic is the qualitative organization of the state space that the system returns to following a perturbation from internal or external demands. Mathematically, the intrinsic dynamic refers to the set of points R where a point in the vicinity of R approaches R as t approaches infinity. For instance, blood pressure regulation occurs about a fixed-point intrinsic dynamic (homeostatic process) in that the cardiovascular and endocrine systems regulate the blood pressure levels around a fixed, steady state.

Here, we outline how three factors interact to influence the directional change in the complexity of system output with age and disease: 1) the dimension of the relevant intrinsic dynamic; 2) the nature of the change required from the intrinsic dynamic to realize a particular task or environmental demand; and 3) the changes in the intrinsic dynamic over short- and long-term time scales. These factors are discussed in relation to theory and the relevant empirical evidence for the directional change in the complexity of system output with age and disease.

The output of a behavioral or physiological system can fluctuate around a stationary or a non-stationary attractor. For instance, the notion of homeostasis in physiology holds that a system operates around a steady state or fixed-point attractor whereby the mean output of the system is stationary and the system output fluctuates about the fixed point [5,9]. As discussed in Section 3 the number of heart beats per minute (measured by ECG) fluctuates around an individually and relatively fixed heart rate of $70-80$ beats per minute that is set by the sinoatrial node (the pacemaker) located in the right atrial wall. The heart beat rate rises due to stressors and then resonates back to steady state levels where it fluctuates around the fixed point. In this example, the heart beat dynamics fluctuate around a fixed-point attractor with zero dimension.

An alternative intrinsic dynamic for a behavioral or physiological system is a rhythmical attractor, such as a limit cycle oscillator [21]. In a limit cycle attractor the output of the system is sinusoidal with time and when a perturbation is delivered to the system, its output will usually return back to the limit cycle attractor. In physiology, this type of process has been termed a homeodynamic process [92]. The dimension of a limit cycle oscillator equals one. An example of a limit cycle oscillator from behavior is locomotion in human walking. Here, the leg swing from the hip can be modeled as a hanging pendulum with a limit cycle oscillation [1,29]. Although there are few examples, an intrinsic dynamic could be more complex and reflect a strange or chaotic attractor with a higher dimension.

We postulate that the directional change of the complexity of a physiological or behavioral system with aging or disease covaries with the dimension of the intrinsic dynamic that organizes the system output. Fig. 2A illustrates the first part of this postulate by showing that with a fixed-point intrinsic dynamic the complexity decreases with age and disease. More generally, in physiological and behavioral systems where the intrinsic dynamic is a dimension of zero (fixed-point attractor) there will be a decrease in complexity

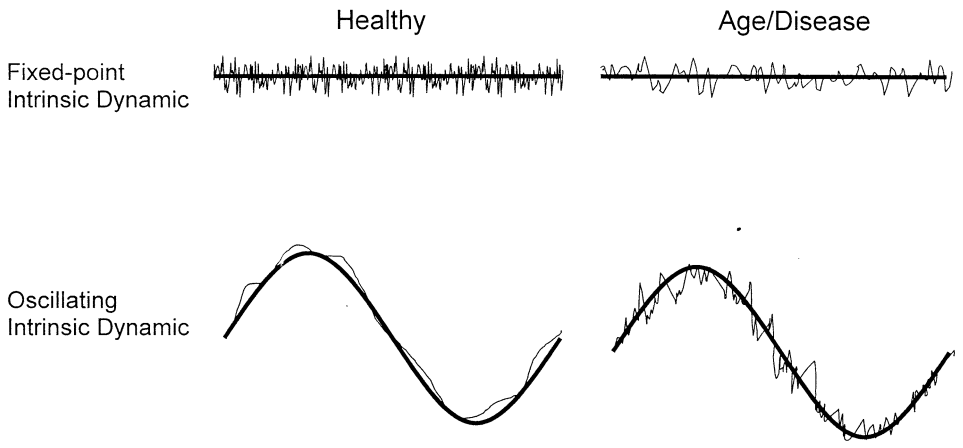

Fig. 2. Schematic illustrating the fixed-point and rhythmical intrinsic dynamic postulate. **A**, the fixed-point intrinsic dynamic is consistent with homeostatic models in physiology and behavior where the system attempts to regulate output around a constant mean state. **B**, the rhythmical intrinsic dynamic is consistent with a limit cycle or higher dimensional attractor where the mean output changes over time. This is consistent with the notion of a homeodynamic physiological process [92].

with age and disease. For instance, in control systems where the intrinsic dynamic is a fixed point, equilibrium is maintained through negative feedback from the receptors and efferent pathways that regulate the systems output around the fixed point.

A system with an intrinsic dynamic having a dimension of zero requires more complexity in the output of the system to maintain optimal performance. When the system does not maintain optimal performance (e.g. with age and disease) there is a reduction in the complexity of the system with poorer performance. The nature of the fixed-point model specifies this relation and the resultant decrease in complexity. As a control system maintains the output of the system within a threshold of the desired fixed point, the system must minimize the contribution of high amplitude, dominant rhythms and introduce multiple rhythms that effectively dampen the output fluctuations around the fixed point. The introduction of multiple rhythms increases the dimension of the systems output and enhances the performance of the system by maintaining the output close to the fixed point.

An example of this type of behavior is seen [see Fig. 3, 77] when subjects produced isometric force while viewing their force output on a computer monitor under varying frequencies of visual feedback. With increases in the frequency of visual feedback, there were higher frequency oscillations in the power spectrum and this resulted in a greater complexity (increased ApEn) in force output. Greater complexity in force output was highly correlated with enhanced performance (decreased force output variability) in the force control task.

The reduction in complexity within a fixed-point intrinsic dynamic is amplified when considering the work from pathological tremor and blood pressure regulation. First, pathological tremor is traditionally examined when the limb maintains a constant joint angle in a resting or postural task. Any fluctuations away from the fixed-point (constant joint angle) require the subject to voluntarily correct or rely on involuntarily reflexes to compensate for a departure from the fixed-point [83]. The tremor of the limb represents the fluctuations about the fixed-point. As stated in Section 3, the tremor of individuals with Parkinson's disease and tardive dyskinesia shows a reduction in complexity consistent with the fixed-point hypothesis [57,84]. Second, blood pressure levels increase and decrease due to internal and external demands, but at rest blood pressure levels are consistently around 110–140 mm Hg for systolic blood pressure and 75–80 mm Hg for diastolic blood pressure in healthy adults. When a stressor in the environment, such as a walking up a hill, is encountered several neural and chemical factors respond to accommodate the stressor and then bring the blood pressure level back down to fixed-point levels. This negative feedback system helps to adjust the blood pressure levels around the fixed-point intrinsic dynamic and the blood pressure levels decrease in complexity with age and disease [37].

In contrast to the reduction in complexity with age and disease found in systems with a fixed-point intrinsic dynamic, we postulate that there is an increase in complexity with age and disease in systems where the intrinsic dynamic is oscillatory. Fig. 2B illustrates this postulate by showing the hypothetical example of a healthy individual's output more closely following the properties of the intrinsic dynamic; hence, there is a limited increase in the system complexity. However, with age and disease the system fluctuates more around the intrinsic dynamic, which leads to an increase in system complexity.

An example of this postulated directional change in complexity is the circadian rhythm, which affects the long-term behavior of several physiological systems. In the endocrine system the 24-h ACTH concentration levels have a diurnal rhythm rather than a constant, fixed-point resting level. The fact that the intrinsic dynamic is rhythmical rather than constant specifies that the complexity of the system in-

creases with age and disease. In other words, when the regular low-dimensional ACTH pattern is disrupted with a more irregular, high-dimensional pattern, then this increases the complexity of the ACTH release process and impairs the release of corticosteroids from the adrenal cortex [67]. The irregularity of ACTH levels is related to hyperglycemia and has been shown to be an important characteristic of Cushing's disease [69].

Enhanced variability in a rhythmical intrinsic dynamic is observed in human locomotion. Since the walking gait cycle is consistent with an oscillating pendulum [1,29] the behavior is inherently rhythmical. This rhythmical intrinsic dynamic specifies the increase in complexity found in the non optimal performance that is observed with age and disease. As discussed in Section 4, the stride interval complexity of elderly subjects is higher than younger subjects and is also higher in Huntington's disease patients when compared to their matched controls [26]. It appears that departures from the rhythmical pattern of the intrinsic dynamic increase the complexity of the limb kinematics.

Thus, task and environmental factors can induce either an increase or decrease in complexity with age and disease. The hypothesis that rhythmical motor output will induce a reduction in complexity with optimal performance and that motor output operating in a fixed-point mode will induce an increase in complexity with optimal performance was directly tested [54]. Healthy, adult subjects learned to maintain force with their index finger in an isometric force task by matching their force output to a target on the computer monitor. The target was either a sinewave (rhythmical condition) or a constant force level (the fixed-point condition). The study examined complexity using ApEn and correlation dimension and showed that in the constant force task, maximal performance was obtained by increasing the complexity of force output, whereas in the sinewave task maximal performance was obtained by decreasing the complexity of force output. Although comparing increases and decreases in complexity with changes in force output variability is not a direct assessment of the fixed-point and rhythmical hypothesis with age, the findings on the direction of change in complexity as a function of adaptation are consistent with the current postulate in regard to the potential bi-directional change in complexity in elderly and disease populations.

Finally, it should be noted that the time scale over which the system output is measured is another important factor that influences the intrinsic dynamic of system behavior. There may exist multiple time scales that operate locally and globally that influence the directional change in the complexity with age and disease. For instance, over short time scales the intrinsic dynamic of blood pressure regulation operates around a fixed point attractor to maintain homeostasis; however, over a 24-h period there is a circadian rhythm to blood pressure with an increase in blood pressure during the day and decrease in blood pressure at night [49].

An example of the effects that the measurement period has on the directional change in complexity can also be observed in the cardiovascular system. Long-range correlations of the cardiac sinus rhythm were examined in young (21–34 yrs) and elderly (68–81 yrs) individuals [30]. The ECG recording was made over a period of 2-h and the interbeat interval time series was assessed by the detrended fluctuation analysis method. In both elderly and young subjects a short- and long-term correlation component of the DFA plot was identified. Over the short-term young subjects had a lower slope ($\alpha = .90$) compared to the elderly ($\alpha = 1.12$); however, the long-term correlations were reversed such that the slope of the young ($\alpha = .99$) was higher than the slope of the elderly ($\alpha = .75$) subjects. This indicates that over the short-term there was a reduction in complexity of the cardiac inter-beat intervals for the elderly group (slope more distal from $\alpha = .5$) and an increase in complexity over the long-term for the elderly group (slope more proximal to $\alpha = .5$). Thus, over the short-term a system may appear to operate around a fixed-point intrinsic dynamic but over the long-term the output of the system changes with time consistent with a rhythmical intrinsic dynamic. In summary, the dimensionality of the intrinsic dynamic together with the direction of the nature of the adaptation determines the directional change in the complexity with age and disease.

7. Conclusions and future directions

The present paper outlined a new postulate to the relations between age, disease, and complexity in behavior and physiology. The postulate states that there is not a universal increase or decrease in complexity with age and disease. Rather, the directional change in complexity is dependent on the dimension of the intrinsic dynamic of the behavioral or physiological system. In order to test this postulate, future investigations of complexity in behavior and physiology should find examples where the output of the system organizes around a fixed-point or rhythmical attractor. Moreover, the intrinsic dynamic could be more complex and reflect a strange or chaotic attractor with a higher dimension, and these relations should be examined in the context of age and disease. Since the literature on complexity in age and disease has theoretical and clinical implications in a variety of different settings (e.g. cardiovascular physiology, endocrinology, respiratory physiology, neuroscience) then understanding the factors that influence the directional change in complexity would seem an important area for future inquiry.

Notes

1. Approximate entropy (ApEn) is a measure that examines regular and irregular patterns in time series data [63]. Typically, the ApEn algorithm returns a value tending toward 2 for highly irregular signals, and approaches 0 for highly regular signals. One limitation

of ApEn is that it does not directly distinguish between the contribution of deterministic and stochastic processes to the observed regularity. Surrogate data tests should be used to rule out the possibility that the regularity in the time series data are not merely a reflection of random noise [72,81].

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References

[1] Alexander RMcN. Energy-saving mechanisms in walking and running. J Exp Biol 1991;160:55–69.
[2] American Psychiatric Association Task Force on Tardive Dyskinesia. Tardive dyskinesia: a task force report of the American Psychiatric Association. Washington, DC: American Psychiatric Association, 1992.
[3] Arking R. Biology of aging: observations and principles. Massachusetts: Sinauer Associates, 1998.
[4] Bassingthwaighte JB, Liebovitch LS, West BJ. Fractal physiology. New York: Oxford University Press, 1994.
[5] Bernard C. Introduction a l'étude de la mèdicine experimentale. Paris: J.B. Ballière et Fils, 1965.
[6] Besthorn C, Sattel H, Geiger-Kabisch C, Zerfass R, Forstl H. Parameters of EEG dimensional complexity in Alzheimer's disease. Electroencephalogr Clin Neurophysiol 1995;95:84–9.
[7] Bortz WM. Aging as entropy. Experimental Gerontology 1986;21: 321–8.
[8] Briggs K. An improved method for estimating Lyapunov exponents of chaotic time series. Physics Letters A 1990;151:27–32.
[9] Cannon WB. The wisdom of the body. New York: W.W. Norton & Co., Inc, 1960.
[10] Collins JJ, De Luca CJ. Open-loop and closed-loop control of posture: a random-walk analysis of center-of-pressure trajectories. Exp Brain Res 1993;95:308–18.
[11] Connelly DM, Rice CL, Roos MR, Vandervoort AA. Motor unit firing rates and contractile properties in tibialis anterior of young and old men. J Appl Physiol 1999;87:843–52.
[12] Di Mascio M, Di Giovanni G, Di Matteo V, Esposito E. Reduced chaos of interspike interval of midbrain dopaminergic neurons in aged rats. Neuroscience 1999;89:1003–8.
[13] Eckmann JP, Kamphorst SO, Ruelle D. Recurrence plots of dynamical systems. Europhys Lett 1987;4:973–7.
[14] Elble RJ, Koller WC. Tremor. Baltimore: Johns Hopkins University Press, 1990.
[15] Erim Z, Beg MF, Burke DT, De Luca CJ. Effects of aging on motor-unit control properties. J Neurophysiol 1999;82:2081–91.
[16] Finch CE, Gosden RG. Animal models for the human menopause. In: Mastroianni L, Paulsen CA, editors. Aging, reproduction and the climacteric. New York: Plenum, 1986.
[17] Findley LJ, Gresty MA, Halmagyi GM. Tremor, the cogwheel phenomenon and clonus in Parkinson's disease. J Neurol Neurosurg Psychiatry 1981;44:534–46.
[18] Frolkis VV, Bezrukov VV. Aging of the central nervous system. Interdisciplinary Top Gerontol 1979;16:87–9.
[19] Galganski ME, Fuglevand AJ, Enoka RM. Reduced control of motor output in a human hand muscle of elderly subjects during submaximal contractions. J Neurophysiol 1993;69:2108–15.
[20] Gell-Mann M. What is Complexity? Complexity 1995;1(1):16–9.
[21] Glass L, Mackey MC. From clocks to chaos. New Jersey: Princeton University Press, 1988.
[22] Goldberger AL, West BJ. Fractals in physiology and medicine. Yale J Biol Med 1987;60:421–35.
[23] Gottschalk A, Bauer MS, Whybrow PC. Evidence of chaotic mood variation in bipolar disorder. Arch Gen Psychiatry 1995;52:947–59.
[24] Grassberger P, Procaccia I. Measuring the strangeness of strange attractors. Physica D 1987;9:189–208.
[25] Hartman ML, Pincus SM, Johnson ML, Matthews DH, Faunt LM, Vance ML. Enhanced basal and disorderly growth hormone (GH) secretion distinguish acromegalic from normal pulsatile GH release. J Clin Invest 1994;94:1277–88.
[26] Hausdorff JM, Mitchell SL, Firtion R, Peng CK, Cudkowicz ME, Wei JY, Goldberger AL. Altered fractal dynamics of gait: reduced stride interval correlations with aging and Huntington's disease. J Appl Physiol 1997;82:262–9.
[27] Hausdorff JM, Peng CK, Ladin Z, Wei JY, Goldberger AL. Is walking a random walk? Evidence for long-range correlations in stride interval of human gait. J Appl Physiol 1994;78:349–58.
[28] Heath RA. Nonlinear dynamics: techniques and applications to psychology. Mahwah, NJ: Lawrence Erlbaum Associates, 2000.
[29] Holt KG, Hamill J, Andres RO. The force-driven harmonic oscillator as a model for human locomotion. Hum Mov Sci 1990;9:55–68.
[30] Iyengar N, Peng CK, Raymond M, Goldberger AL, Lipsitz LA. Age-related alterations in the fractal scaling of cardiac interbeat interval dynamics. Am J Physiol 1996;40:R1078–R1084.
[31] Ivanov PC, Amaral LA, Goldberger AL, Havlin S, Rosenblum MG, Struzik ZR, Stanley HE. Multifractality in human heartbeat dynamics. Nature 1999;399:461–5.
[32] Jelles B, van Birgelen JH, Slaets JP, Hekster RE, Jonkman EJ, Stam CJ. Decrease in non-linear structure in the EEG of Alzheimer patients compared to healthy controls. Clin Neurophysiol 1999;110:1159–67.
[33] Jenkins GM, Watts DG. Spectral analysis and its applications. London: Holden-Day, 1968.
[34] Jeong J, Kim SY, Han SH. Non-linear dynamical analysis of the EEG in Alzheimer's disease with optimal embedding dimension. Electroencephalogr Clin Neurophysiol 1998;106:220–8.
[35] Kalachnik JE. Tardive dyskinesia and the mentally retarded: a review. In: Bruening SB, editor. Advances in mental retardation and developmental disabilities. Greenwich, CT: JAI, 1984.
[36] Kaplan D, Glass L. Understanding nonlinear dynamics. New York: Springer-Verlag, 1995.
[37] Kaplan DT, Furman MI, Pincus SM, Ryan SM, Lipsitz LA, Goldberger AL. Aging and the complexity of cardiovascular dynamics. Biophys J 1991;59:945–9.
[38] Keil A, Elbert T, Rockstroh B, Ray WJ. Dynamical aspects of motor and perceptual processes in schizophrenic patients and healthy controls. Schizophr Res 1998;33:169–78.
[39] Kelso JAS. Dynamic patterns: the self-organization of brain and behavior. Cambridge: MIT Press, 1995.
[40] Kennel MB, Brown R, Abarbanel HDI. Determining embedding dimension for phase space reconstruction using a geometrical construction. Physical Review A 1992;45:3403–11.
[41] Kligman AM, Grove GL, Balin AK. Aging of human skin. In: Finch CE, Schneider EL, editors. Handbook of the biology of aging. New York: Van Nostrand Reinhold, 1985.
[42] Kresh JY, Izrailtyan I. Evolution in functional complexity of heart rate dynamics: a measure of cardiac allograft adaptability. Am J Physiol 1998;275:R720–7.
[43] Kugler PN, Turvey MT. Information, natural law, and the self-assembly of rhythmic movement. New Jersey: L. Erlbaum Associates, 1987.

[44] Lance JW, Schwab RS, Peterson EA. Action tremor and the cogwheel phenomenon in Parkinson's disease. Brain 1963;86:95–110.
[45] Larsson L, Sjodin B, Karlsson J. Histochemical and biochemical changes in human skeletal muscle with age in sedentary males, age 22–65 years. Acta Physiol Scand 1977;103:31–9.
[46] Lehnertz K, Elger CE. Can epileptic seizures be predicted? Evidence from nonlinear time series analysis of brain electrical activity. Phys Rev Lett 1998;80:5019–22.
[47] Lipsitz LA, Goldberger AL. Loss of 'complexity' and aging: potential applications of fractals and chaos theory to senescence. JAMA 1992; 267:1806–9.
[48] Mader S. Hearing impairment in elderly persons. J Am Geriatr Soc 1984;32:548–53.
[49] Marieb EN. Human anatomy and physiology. California: Benjamin/ Cummings Science Publishing, 1998.
[50] McClearn GE. Biogerontologic theories. Experimental Gerontology 1997;32:3–10.
[51] McComas AJ. Skeletal muscle: form and function. Champaign, IL: Human Kinetics, 1996.
[52] Mestivier D, Chau NP, Chanudet X, Bauduceau B, Larroque P. Relationship between diabetic autonomic dysfunction and heart rate variability assessed by recurrence plot. Am J Physiol 1997;272: H1094–9.
[53] Munsat TL. Aging of the neuromuscular system. In: Albert ML, editor. Clinical neurology of aging. New York: Oxford University Press, 1984.
[54] Newell KM, Broderick MP, Handly K, Slifkin AB. Task constraints and change in the dynamical degrees of freedom with motor learning. Manuscript under review, 2000.
[55] Newell KM. Degrees of freedom and the development of postural center of pressure profiles. In: Newell KM, Molenaar PCM, editors. Applications of nonlinear dynamics to developmental process modeling. New Jersey: Lawrence Erlbaum Associates, 1998.
[56] Newell KM, Vaillancourt DE. Dimensional change in motor learning. Human Movement Science, in press.
[57] Newell KM, Gao F, Sprague RL. The dynamics of finger tremor in tardive dyskinesia. Chaos 1995;5:43–7.
[58] Newell KM, Bodfish JW, Mahorney SL, Sprague RL. Dynamics of lip dyskinesia associated with neuroleptic withdrawal. Am J Mental Retardation 2000;15:260–8.
[59] Newell KM, Liu Y-T, Mayer-Kress G. Time scales in motor learning and development. Psych Review 2001;108:57–82.
[60] Newell KM, van Emmerik REA, Lee D, Sprague RL. On postural stability and variability. Gait Posture 1993;4:225–30.
[61] Paulus MP, Geyer MA, Braff DL. Use of methods from chaos theory to quantify a fundamental dysfunction in the behavioral organization of schizophrenic patients. Am J Psychiatry 1996;153:714–7.
[62] Pikkujamsa SM, Makikallio TH, Sourander LB, Raiha I,J, Puukka P, Skytta J, Peng CK, Goldberger AL, Huikuri HV. Cardiac interbeat interval dynamics from childhood to senescence: comparison of conventional and new measures based on fractals and chaos theory. Circulation 1999;100:393–9.
[63] Pincus SM. Approximate entropy as a measure of system complexity. Proc Natl Acad Sci USA 1991;88:2297–301.
[64] Pincus SM, Cummins TR, Haddad GG. Heart rate control in normal and aborted-SIDS infants. Am J Physiol 1993;264:R638–R646.
[65] Pincus SM, Goldberger AL. Physiological time-series analysis: what does regularity quantify? Am J Physiol 1994;266:H1643–H1656.
[66] Pincus SM, Hartman ML, Roelfsema F, Thorner MO, Veldhuis JD. Hormone pulsatility discrimination via coarse and short time sampling. Am J Physiol 1999;40:E948–E957.
[67] Pincus SM, Mulligan T, Iranmanesh A, Gheorghiu S, Godschalk M, Veldhuis JD. Older males secrete luteinizing hormone and testosterone more irregularly, and joinly more asynchronously, than younger males. Proc Natl Acad Sci USA 1996;93:14100–5.
[68] Pincus SM, Singer BH. Randomness and degrees of irregularity. Proc Natl Acad Sci USA 1996;93:2087–8.
[69] Roelfsema F, Pincus SM, Veldhuis JD. Patients with Cushing's disease secrete adrenocortiotropin and cortisol jointly more asynchronously than healthy subjects. J Clin Endocrinol Metab 1998;83:688–92.
[70] Rosen R. Fundamentals of measurement and representation of natural systems. New York: North-Holland, 1978.
[71] Schiaffino S, Reggiani C. Myosin isoforms in mammalian skeletal muscle. J Appl Physiol 1996;77:493–501.
[72] Schreiber T, Schmitz A. Surrogate time series. Phys Rev Lett 2000; 142:346–82.
[73] Schroots JJF, Yates FE. On the dynamics of development and aging. In: Bengtson VL, Schaie KW, editors. Handbook of theories of aging. New York: Springer Publishing, 1999.
[74] Seidler-Dobrin RD, He J, Stelmach GE. Coactivation to reduce variability in the elderly. Motor Control 1998;2:314–30.
[75] Shannon CE, Weaver W. The mathematical theory of communication. Urbana-Champaign: University of Illinois Press, 1949.
[76] Skinner JE, Molnar M, Tomberg C. The point correlation dimension: performance with nonstationary surrogate data and noise. Integr Physiol Behav Sci 1994;29:217–34.
[77] Slifkin AB, Vaillancourt DE, Newell KM. Intermittency in the control of continuous force production. J Neurophysiol 2000;84:1708–18.
[78] Spirduso WW. Physical dimensions of aging. Champaign, IL: Human Kinetics, 1995.
[79] Takens F. Detecting strange attractors in turbulence. In: Rand DA, Young L-S, editors. Dynamical systems and turbulence. Berlin: Springer, 1981.
[80] Tashman LJ, Lamborn KR. The ways and means of statistics. New York: Harcourt Brace Jovanovich, 1979.
[81] Theiler J, Eubank S, Longtin A, Galdrikian B, Farmer JD. Testing for nonlinearity in time series: the method of surrogate data. Physica D 1992;58:77–94.
[82] Tobin JD. Physiological indices of aging. In: Danon D, Shock NW, Marois M, editors. Aging: a challenge to science and society: biology. New York: Oxford University Press, 1981.
[83] Vaillancourt DE, Newell KM. Amplitude changes in the 8–12 Hz, 20–25 Hz and 40 Hz oscillations of finger tremor. Clin Neurophysiol 2000a;111:1792–801.
[84] Vaillancourt DE, Newell KM. The dynamics of resting and postural tremor in Parkinson's disease. Clin Neurophysiol 2000b;111:2042–52.
[85] Vaillancourt DE, Slifkin AB, Newell KM. Time regularity of force tremor in Parkinson's disease, in press. Clinical Neurophysiol.
[86] Van den Berg G, Pincus SM, Veldhuis JD, Frölich M, Roelfsema F. Greater disorderliness of ACTH and cortisol release accompanies pituitary-dependent Cushing's disease. Euro J Endocrinol 1997;136: 394–400.
[87] Webber CL, Zbilut JP. Assessing deterministic structures in physiological systems using recurrence plot strategies. In: Khoo MCK, editor. Bioengineering approaches to pulmonary physiology and medicine. New York: Plenum Press, 1996.
[88] Wei JY, Gersh BJ. Heart disease in the elderly. Curr Probl Cardiol 1987;12:7–65.
[89] Weiner WJ, Lang AE. Movement disorders: a comprehensive survey. New York: Futura Publishing Company, 1989.
[90] Whitbourne SK. The aging body: physiological changes and psychological consequences. New York: Springer-Verlag, 1985.
[91] Yates FE. Self-organizing systems: the emergence of order. New York: Plenum Press, 1987.
[92] Yates FE. The dynamics of aging and time: how physical action implies social action. In: Birren JE, Bengtson VL, editors. Emergent theories of aging. New York: Springer, 1988.
[93] Yates FE. The dynamics of adaptation in living systems. In: Selfridge OG, Rissland EL, Arbib MA, editors. Adaptive control of ill-defined systems. New York: Plenum Press, 1984.
[94] Zbilut JB, Mayer-Kress G, Geist K. Dimensional analysis of heart rate variability in heart transplant patients. Math Biosci 1988;90:49–70.