Loss of 'Complexity' and AgingPotential Applications of Fractals and Chaos Theory to Senescence

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Loss of 'Complexity' and Aging

Potential Applications of Fractals and Chaos Theory to Senescence

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The concept of "complexity," derived from the field of nonlinear dynamics, can be adapted to measure the output of physiologic processes that generate highly variable fluctuations resembling "chaos." We review data suggesting that physiologic aging is associated with a generalized loss of such complexity in the dynamics of healthy organ system function and hypothesize that such loss of complexity leads to an impaired ability to adapt to physiologic stress. This hypothesis is supported by observations showing an age-related loss of complex variability in multiple physiologic processes including cardiovascular control, pulsatile hormone release, and electroencephalographic potentials. If further research supports this hypothesis, measures of complexity based on chaos theory and the related geometric concept of fractals may provide new ways to monitor senescence and test the efficacy of specific interventions to modify the age-related decline in adaptive capacity.

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HEALTHY physiologic function is characterized by a complex interaction of multiple control mechanisms that enable an individual to adapt to the exigencies and unpredictable changes of everyday life. The aging process appears to be marked by a progressive impairment in these mechanisms, resulting in a loss of dynamic range in physiologic function and, consequently, a reduced capacity to adapt to stress.

A key question is how to quantitate physiologic aging. Previous investigations have focused primarily on age-related declines in the mean value of discrete physiologic variables such as creatinine clearance,[1] forced expiratory volume,[2] nerve conduction velocity,[3] and insulin sensitivity.[4] However, the wide interindividual variance of such measures with increasing age, as well as their dependence on factors such as genetic background, diet, and activity,[5] severely limits their utility as universal markers of aging. Furthermore, the evaluation of only mean changes in a given variable over time (or in response to a stimulus) ignores the dynamic nature of physiologic processes (Fig 1).[6]

This article briefly reviews the concepts of fractals and chaos derived from the field of nonlinear dynamics and suggests how these concepts might provide a new framework for understanding, quantitating, and eventually modeling physiologic aging. Since the basic science discipline of nonlinear dynamics has only recently been applied to medicine and physiology,[7-11] much of the work in this area is necessarily preliminary.

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NONLINEAR DYNAMICS, FRACTALS, AND CHAOS

As implied by its name, nonlinear dynamics studies systems, such as those in physiology, in which output is not proportional to input. Two central concepts in nonlinear dynamics are fractals and chaos.

The term *fractal* is a structural (geometric) concept that applies to a wide class of complex shapes that are not simply lines, rectangles, or cubes.[7-12] Instead, fractals are irregular, but their irregularity has an underlying pattern. The key feature of this fractal pattern is called self-similarity. The more closely a fractal object is inspected the more structure is revealed. Furthermore, the details seen under magnification resemble the outline of a larger structure (Fig 2).[10] Of physiologic interest is the fractal-like (self-similar) branching architecture of many anatomies, including certain nerve networks, His-Purkinje fibers, gastrointestinal folds, and vascular systems.[8,13]

The term *chaos* describes an apparently unpredictable behavior that may arise from the internal feedback loops of certain nonlinear systems.[7-12] Just as a fractal does not have a characteristic or single scale of length, a chaotic process generates complex fluctuations that do not have a single or characteristic scale of time. Instead, chaos produces a "noisy-looking" signal that varies in an erratic and unpredictable fashion. A counterintuitive finding has been that chaotic-like behavior characterizes the output of a number of different physiologic systems that have until now been thought of as being relatively periodic.[12] For example, Fig 1 shows that the normal sinus rhythm heartbeat in a healthy young subject at rest is not strictly regular but instead shows a complex type of variability ("constrained randomness") reminiscent of chaos.[9,12] One way of defining the complexity of a process, such as phys-

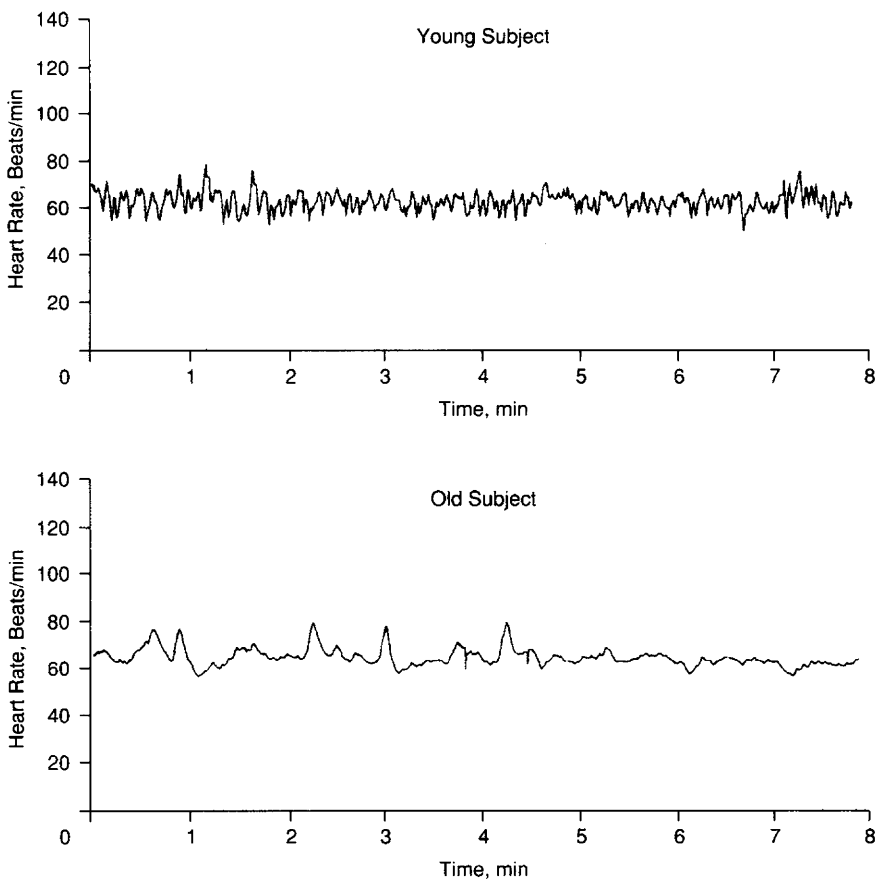

Fig 1.—Heart rate time series for a 22-year-old female subject (top panel) and a 73-year-old male subject (bottom panel). The mean heart beats per minute for the young subject was 64.7; SD, 3.9; and approximate entropy, 1.09. The mean heart beats per minute for the old subject was 64.5; SD, 3.8; and approximate entropy, 0.48. Approximate entropy is a measure of "nonlinear complexity."[8] Despite the nearly identical means and SDs of heart rate for the two time series, the "complexity" of the signal from the older subject is markedly reduced.

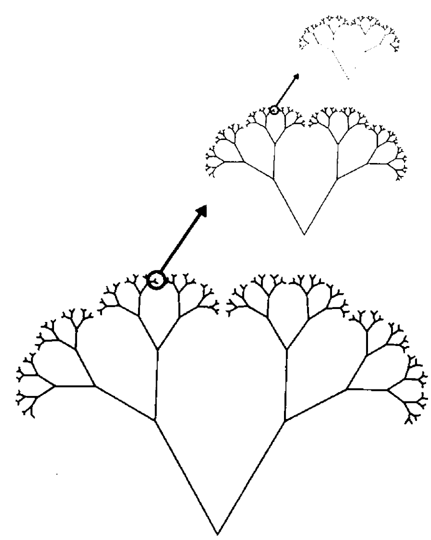

Fig 2.—An example of a computer-generated fractal structure, illustrating self-similarity on multiple scales (adapted from West and Goldberger[10]).

iologic control of heart rate, is the extent to which that process generates aperiodic fluctuations that resemble nonlinear chaos.

HOW CAN THE COMPLEXITY OF NONLINEAR STRUCTURES AND PROCESSES BE MEASURED?

In view of observations that many anatomic structures have a complex fractal-like morphology and that physiologic processes show complex variability, it is important to have measures that adequately capture these nonlinear features. Conventional measurements such as length, area, and volume (with integer dimensions of one, two, and three, respectively) are not sufficient to characterize fractal structures. Fractal objects have noninteger dimensions because they show structure on multiple scales of length. Fractal structure can be quantitated by computing a so-called fractal dimension.[10] This measurement provides an index of how much space a particular object fills. Intuitively, a relatively sparse branching structure would appear to have a lower fractal dimension than that of a more complex, "bushier" object.

Just as fractal structures cannot be characterized with conventional geometric measurements, complex, chaotic-like behavior cannot be adequately measured with statistics based simply on mean and variance. As shown in Fig 1, it is possible for two processes to have outputs with nearly identical means and variances but very different dynamics. A number of techniques have been devised that do allow physiologists and clinicians to measure the complexity of biologic signals, independent of their mean and variance.[14,15]

One traditional approach is to measure the frequency components of a signal using standard Fourier analysis, which decomposes the signal into its constituent frequencies.[16,17] If the output is perfectly periodic (ie, a sine wave), it will have only one frequency component. For chaotic processes, the frequency spectrum is quite broad, comprising a wide range of low-through-high frequencies. In general, more complex signals have a broader frequency pattern. Conversely, loss of complexity is usually accompanied by a narrowing of the frequency spectrum. (Compare a pure-tone generator and a symphony orchestra.) Typically, for physiologic processes, the loss of complexity is also characterized by relative reduction in the high-frequency components and corresponding increase in the relative contribution of lower-frequency components.[9,17] An example is the selective loss of high-frequency auditory responsiveness with aging (presbycusis).[18]

However, spectral analysis, a technique based on linear mathematics, is of limited value in assessing the complexity of nonlinear systems. Other, more direct measures of complexity have been recently devised based on concepts from chaos theory.[6,14,15,19,20] One method of measuring the complexity of a process uses the concept of the dimension of a nonlinear system. For complex systems, the dimension is related to the number of dynamic variables required to reproduce the output of that system. The higher the dimension, the greater the number of variables and the more complex the signal. A strictly periodic process has a dimension of one (ie, only one variable is required).

Another way to measure complexity is to calculate the so-called entropy of the system.[6,19] (The conceptual approach to senescence described herein differs fundamentally from the intuitive view that aging increases the degree of disorder or thermodynamic entropy.[21,22]) Nonlinear entropy (a concept only indirectly related to classical thermodynamic entropy) is a measure of the amount of information needed to predict the future state of the system. The more complex the dynamics are, the larger the entropy and the less predictable the system. Recently, techniques have been devised that allow approximations of nonlinear dimension and entropy to be performed on relatively short-term samples of data, comprising, for example, only 1000 points[6,19] (Fig 1). These measurements permit comparison of data sets from different individuals, as well as examination of the effects of various interventions on the complexity of a dynamic system.[20]

Fig 3.—Age-related loss of fractal structure in the dendritic arbor of the giant pyramidal Betz cell of the motor cortex. Left, The complex, branching, fractal-like architecture of the dendritic arbor in a young adult man. Right, suggestion of the loss of "complexity" (fractal dimensionality) in the structure of the dendritic arbor in a 65-year-old man (reprinted with permission from WB Saunders Co[28]).

Examples of Decreased Structural (Anatomic) and Functional (Physiologic) 'Complexity' in Advanced Age

	Measure of Complexity	Age Effect
Anatomic structures Neuronal dendrites[28]	Branching arbor	Dendrite loss and reduced branching
Bone trabeculae[42]	Meshwork	Trabecular loss, disconnection
Physiologic systems Heart rate variability[18,20]	Dimension, entropy	Decrease
Blood pressure variability[20]	Dimension, entropy	Decrease
Pulsatile thyrotropin release[33]	SD of interpulse interval	Decrease
Electroencephalographic evoked potentials[27]	Range of frequencies evoked	Decrease
Auditory[17]	Range of audible frequencies	High-frequency loss

AGING AND LOSS OF COMPLEXITY

We propose that aging can be defined by a progressive loss of complexity in the dynamics of all physiologic systems. This loss of complexity in physiologic function may be due mechanistically to (1) a loss or impairment of functional components, and/or (2) altered nonlinear coupling between these components. For example, the age-related decline in heart rate variability discussed below is likely due to dropout of sinus node cells,[23] altered β-adrenoceptor responsiveness,[23] and an apparent reduction in parasympathetic tone.[17] Together, these structural and functional changes reduce the complexity of physiologic heart rate control, impairing the aged individual's ability to adapt to stresses such as hypotension.[24]

This hypothesis relating aging to loss of complexity suggests new ways to monitor the physiologic aging process based on measurements such as nonlinear entropy described above, and to test the efficacy of specific interventions (eg, exercise or pharmacologic agents) that may modify the age-related decline in adaptive capacity. Furthermore, physiologic models designed to simulate the aging process should account for loss of complexity in the dynamics or structure of the system being studied.

Neuroendocrine Function

Normal brain function produces apparently chaotic electroencephalographic (EEG) fluctuations with changes related to the state of consciousness.[25] The EEG frequencies of aging subjects show a loss of low-voltage fast waves and an increase in slow waves with diffuse slow periodicity.[26] Furthermore, the latency, amplitude, and range of EEG frequencies elicited in response to light, sound, hyperventilation, and other sensory stimuli decline with age in animals and humans.[27] This loss of dynamic range has been attributed to a decrease in neuron number, impaired cerebral energy metabolism, reduced cerebral perfusion, altered transmitter metabolism, and disrupted internal connections.[27] With aging, the branching pattern of Betz cells in the frontal cortex, spiny cells in the caudate, and anterior horn cells in the spinal cord becomes less complex (Fig 3).[28] Although actual measurements of fractal dimensions of anatomic structures have been reported recently,[15,29,30] changes with age have not yet been quantitated.

A loss of complexity in the regulation of anterior pituitary hormone secretion is also apparent in aging humans. Pulsatile release of growth hormone,[31] luteinizing hormone,[32] and thyrotropin[33] is attenuated with healthy aging. The SD of the mean interval between thyrotropin pulses is smaller in healthy elderly subjects compared with healthy young ones,[33] suggesting a less complex pattern of hormonal secretion. This finding reflects a narrowing of regulatory control of thyrotropin secretion, probably due in part to alterations in dopaminergic modulation of pulsatile thyroid-stimulating hormone release.[33]

Cardiovascular Function

Studies of heart rate variability using traditional methods such as the ratio of expiratory to inspiratory R-R intervals,[34-36] as well as spectral analysis,[17,37,38] consistently demonstrate a decline in heart rate variability with aging. Of note, a decline in heart rate variability is a marker of increased susceptibility to sudden death[39,40] and mortality following myocardial infarction.[41] Using the measurements of nonlinear entropy and dimension described above, we have also shown a reduction in the complexity of heart rate and blood pressure variability in healthy elderly subjects compared with healthy young subjects.[20]

Data for a number of different anatomic structures and physiologic systems consistent with the hypothesized loss of complexity with aging are summarized in the Table.[16,17,20,27,28,42]

FUTURE DIRECTIONS

If these new dynamic measures of physiologic complexity are useful in quantitating the effects of normal aging, various interventions may be tested for their efficacy in preventing disease or modifying its progression. For example, measurements of the complexity of EEG responses to cognitive tasks in healthy aging and dementia may prove useful in distinguishing these conditions and in testing the effect of specific drugs on cognitive function or behavior. If the complexity of heart rate and blood pressure dynamics serve as biomarkers of cardiovascular aging, the effects of exercise or nutrition on cardiovascular senescence can be more readily quantitated. Measurement of the degree to which an individual's adaptive capacity is reduced by aging or disease may also prove useful in predicting adverse effects of drugs, surgery, or other stressors. The loss of physiologic complexity in cardiac interbeat interval variability in sinus rhythm may have value in identifying syncope patients at risk of sudden death, determining the seriousness of intermittent cardiac arrhythmias, predicting mortality following myocardial infarction, and assessing the severity of congestive heart failure.[39-41,43]

CONCLUSION

Measures of complexity derived from the field of nonlinear dynamics (fractals and chaos theory) may help assess age-related anatomic and physiologic changes and possibly predict pathology. We hypothesize that physiologic aging is characterized by a generalized loss of complexity in the dynamics of healthy organ system function. This dynamical concept of aging is intended to stimulate further analyses of continuously recorded time series (Fig 1) as well as the construction of nonlinear models of basic mechanisms.

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