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Complexity and network dynamics in physiological adaptation: An integrated view

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ABSTRACT

Living organisms constantly interact with their surroundings and sustain internal stability against perturbations. This dynamic process follows three fundamental strategies (restore, explore, and abandon) articulated in historical concepts of physiological adaptation such as homeostasis, allostasis, and the general adaptation syndrome. These strategies correspond to elementary forms of behavior (ordered, chaotic, and static) in complex adaptive systems and invite a network-based analysis of the operational characteristics, allowing us to propose an integrated framework of physiological adaptation from a complex network perspective. Applicability of this concept is illustrated by analyzing molecular and cellular mechanisms of adaptation in response to the pervasive challenge of obesity, a chronic condition resulting from sustained nutrient excess that prompts chaotic exploration for system stability associated with tradeoffs and a risk of adverse outcomes such as diabetes, cardiovascular disease, and cancer. Deconstruction of this complexity holds the promise of gaining novel insights into physiological adaptation in health and disease.

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1. Introduction

Living organisms safeguard their integrity and survival against internal and external challenges through adaptation. This dynamic process involves monitoring deviations from the norm, developing appropriate responses to correct the impact of perturbations, and verifying outcomes by sampling internal parameters [1–4]. Adaptation has been extensively studied at successive organizational levels of the biosphere, ranging from unicellular organisms to human society [5–7]. Adaptation may occur at different time scales. Evolutionary adaptation pertains to changes in heritable (i.e., genetic and epigenetic) components of a species or population that accumulate and transfer over many generations [8,9], while physiological adaptation describes how individual organisms, enabled (and limited) to do so by their unique genome, respond to a variety of day-to-day challenges within a lifetime [3,4]. Thus, the primary goal of evolutionary adaptation is to maintain reproductive fitness, while physiological adaptation is more concerned with maintaining energy efficiency and finding the best possible answer to lifetime encounters. Nevertheless, evolutionary and physiological adaptations share many features and complement each other as natural selection acts through individuals.

Since the pioneering work of Claude Bernard [10], our understanding of adaptation in biological systems has benefited from a large body of observational and experimental work. Physiologists, neuroendocrinologists, and behavioral and social scientists developed new theories to interpret the ways by which adaptation may take place in individual organisms. However, a century and a half after Bernard introduced his groundbreaking concepts, there is still an ongoing dispute about the framework of physiological adaptation and how to best apply this knowledge in medicine that primarily aims to prevent and cure dysfunction of this process manifesting as disease [11–15].

In parallel with these efforts, the basic operational principles of life as a dissipative system have been defined by mathematical and thermodynamic reasoning [16,17]. More recently, complex network science has provided new tools to study human physiology and offered new opportunities on disease definition, outcome prediction, and personalized therapy [18,19]. Here we aim to integrate the advances in three major fields of biomedical research to define a comprehensive framework of physiological adaptation. First, we review parallel and competing concepts of physiological adaptation providing the fundamental principles of regulating the integrity of living systems. Second, we evaluate these theories in the context of life as a complex adaptive system. Third, we analyze physiological adaptation from a network perspective to describe common structural elements, operational patterns, and regulatory circuitries. Throughout the paper, we use obesity as a prototype of chronic complex diseases to demonstrate the relevance and utility of this integrative approach.

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2. Historical concepts of physiological adaptation

2.1. Homeostasis

Claude Bernard was the first to recognize the importance of constant dialogue between organism and environment [10]. Bernard's key legacy is the notion of *milieu intérieur* or internal environment, which is in a dynamic equilibrium that must be preserved in all living systems [10]. Based on these principles, Cannon introduced the term homeostasis as the ability to sustain various physiological parameters in a steady state (stabilized around a set point) amidst wide fluctuations in external conditions [20]. Although Cannon illustrated homeostasis by relatively simple examples, such as regulation of thirst and acid–base balance, he intended to use the concept in a broader sense [5]. Indeed, the paradigm of homeostasis contains many conceptual elements on which we may continue to improve our view of physiological integrity and development of disease [12].

2.2. Stress and the general adaptation syndrome

An interesting aspect of physiological adaptation was highlighted by the work of Selye, who found that experimental animals responded with surprisingly similar clinical symptoms to a wide range of acute physical, chemical, biological, or psychological stimuli, and this response uniformly included activation of the hypothalamic–pituitary–adrenal axis [21,22]. Selye chose the term 'stress' for this consistent reaction and 'stressors' for the noxious stimuli. He subsequently observed that patients with different diseases exhibited common symptoms of stress and introduced the concept of general adaptation syndrome [23]. In his concept, Selye distinguished the stages of alarm, resistance, and exhaustion to describe how prolonged stress becomes a major challenge to homeostasis with failing adaptation that may culminate in all-consuming disease [23]. The ability of each individual to tailor the magnitude and outcome of this generic response to stress, however, remained difficult to predict.

2.3. Complementary models of physiological adaptation

The following decades have seen an expansion of interest in the physiology of adaptation and resulted in parallel growth of related concepts. This trend highlighted some important aspects that were not fully elaborated within the original homeostasis theory [12]. Waddington used the term homeorhesis to describe the goal of physiological control as a trajectory rather than a set point [24]. Selye added heterostasis to distinguish adaptation that reaches a new equilibrium from one that reestablishes original physiological parameters [25]. Moore-Ede proposed a distinction between reactive and predictive homeostasis to emphasize the difference between adaptive strategies that occur in the wake of perturbations as opposed to those initiated in anticipation of predictable changes [26].

2.4. Allostasis and allostatic load

The concept of allostasis was proposed in 1988 as a comprehensive effort to address some of the perceived limitations of homeostasis [27]. Allostasis is defined as a way to maintain stability through changes by adapting to both predictable and unpredictable events [28]. Key elements of allostasis include shifting set points, alternative pathways, and coordination across multiple regulatory systems orchestrated by the brain [29,30]. Allostasis has proven to be a useful framework to assess the impact of neurobehavioral and psychosocial factors in areas where anticipatory physiological regulation is essential such as developmental changes, reproductive cycles, diurnal variations, and in adverse situations such as addiction and post-traumatic stress disorder [30–32].

While the utility of allostasis as yet another term of physiological adaptation remains debated [11,12,14], allostatic load has been introduced to address long-term consequences of adaptation, combining relevant elements of homeostasis and chronic stress [33]. Allostatic load refers to the aggregate impact of physiological adaptation over the lifespan of an individual, corresponding to a summary effect of tradeoffs, compromises, and collateral damage [33]. Allostatic load may accumulate faster than expected if sustained activation of regulatory networks exceeds optimal operating ranges either because of excessive duration, frequency, or intensity of perturbations [34]. This accelerated process has been designated as allostatic overload and proposed to correlate with increased vulnerability and risk for development of disease [28]. However, prediction of an individual's ability to limit the accumulation of allostatic load and identification of the specific components that do so remain difficult.

2.5. Inflammation as an adaptation response

An intriguing concept was recently introduced by Okin and Medzhitov to redefine the role of inflammation within the context of physiological adaptation [35]. Accordingly, full-scale biological performance in specialized tissues depends on accessory cells originating in the immune system. Due to their mobility and ability to connect various tissues, these accessory cells are the 'common currency' that brings similar operational principles to these sites [35]. Normally, resident 'client' cells successfully cope with perturbations to maintain homeostasis. If this level of physiological adaptation becomes insufficient, accessory cells are recruited to initiate inflammation for a heightened level of tissue adaptation that dominates over homeostasis and involves collateral damage [35]. In this sense, inflammation can be defined as a mechanism of allostasis.

Inflammation is particularly relevant to obesity and its associated adverse health conditions, such as type 2 diabetes, cardiovascular disease, and cancer [36–38]. Aiming at accommodating sustained nutrient excess, adipose tissue growth and remodeling is central to the pathogenesis of obesity, featuring macrophage infiltration and secretion of pro-inflammatory adipokines such as leptin, resistin, tumor necrosis factor [TNF]-alpha, and interleukin [IL]-6 [36]. The ensuing systemic low-grade inflammation promotes a multitude of pathological and self-perpetuating events, such as insulin resistance, endothelial dysfunction, and activation of oncogenic pathways [36,39]. As discussed further below, obesity is an important example of how environmental factors can create unprecedented challenges for physiological adaptation.

2.6. Strategies of physiological adaptation in historical concepts

Three distinct strategies of physiological adaptation can be inferred from the concepts discussed above. First, when the status quo is indispensable or remains preferable over change, biological systems *restore* current parameters to values that preceded the perturbation. This is the dominant strategy of homeostasis. Second, biological systems may *explore* alternative states to find a new balance (set point) with the environment, in particular if the perturbation has excessive duration, frequency, or intensity. There may be anticipatory elements in this process as living organisms tend to track variations or even alter the environment (e.g., niche construction) to secure physiological integrity and survival [4]. In many situations, this may be a preferable strategy (e.g., inflammation) even if there are compromises and collateral damage involved, as outlined in the concepts of general adaptation syndrome and allostasis. Third, physiological adaptation may require the organism to *abandon* some of its functions or components (e.g., removing a group of cells by apoptosis) and avoid the spread of system disruption, which may ultimately result in death. Essentially all concepts related to physiological integrity are based on one or more of these distinct adaptation strategies (Table 1).

3. Chaos and complexity in physiological adaptation

Biological systems acquire free energy and substances from the environment that are subsequently returned in a degraded form. This