Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Biotechnology

Critical transitions in chronic disease: transferring concepts from ecology to systems medicine

Christophe Trefois[1], Paul MA Antony[1], Jorge Goncalves[2], Alexander Skupin[3,4] and Rudi Balling[1]

Ecosystems and biological systems are known to be inherently complex and to exhibit nonlinear dynamics. Diseases such as microbiome dysregulation or depression can be seen as complex systems as well and were shown to exhibit patterns of nonlinearity in their response to perturbations. These nonlinearities can be revealed by a sudden shift in system states, for instance from health to disease. The identification and characterization of early warning signals which could predict upcoming critical transitions is of primordial interest as prevention of disease onset is a major aim in health care. In this review, we focus on recent evidence for critical transitions in diseases and discuss the potential of such studies for therapeutic applications.

Addresses
[1] Experimental Neurobiology Group, Luxembourg Centre for Systems Biomedicine (LCSB), University of Luxembourg, Campus Belval, 7 Avenue des Hauts-Fourneaux, L-4362 Esch-sur-Alzette, Luxembourg
[2] Systems Control Group, Luxembourg Centre for Systems Biomedicine (LCSB), University of Luxembourg, Campus Belval, 7 Avenue des Hauts-Fourneaux, L-4362 Esch-sur-Alzette, Luxembourg
[3] National Center for Microscopy and Imaging Research, University of California San Diego, 9500 Gilman Drive, La Jolla, CA, United States
[4] Integrative Cell Signalling Group, Luxembourg Centre for Systems Biomedicine (LCSB), University of Luxembourg, Campus Belval, 7 Avenue des Hauts-Fourneaux, L-4362 Esch-sur-Alzette, Luxembourg

Corresponding author: Balling, Rudi (rudi.balling@uni.lu)

Current Opinion in Biotechnology 2015, **34**:48–55

This review comes from a themed issue on **Systems biology**

Edited by **Sarah Maria Fendt** and **Costas D Maranas**

http://dx.doi.org/10.1016/j.copbio.2014.11.020

Critical transitions in complex systems

Biological systems are complex, characterized by emerging behavior and often obey nonlinear dynamics (Box 1). In many cases this nonlinear behavior of biological systems leads to tipping points where the equilibrium state (Box 1) of the system abruptly changes from one stable state to another (Box 1). This change is also called critical transition (Box 1) or regime shift [1]. Although sudden state transitions such as phase transitions or exothermal reactions are established concepts in physics and chemistry, increasing awareness rises that also complex biological systems can exhibit abrupt changes in their dynamics. The idea that natural systems might exhibit sudden changes in their dynamical states originated mostly from theoretical models over 50 years ago [2–4] and are based on mathematical catastrophic bifurcation theory [5]. These studies, motivated by descriptions of magnetic systems, laid the concept that natural systems might have alternative stable states and thereby undergo critical transitions (Box 1), typically without obvious warning signals (Figure 1). At that time, these theories lacked robust empirical evidence [6].

Only in the last decade, several studies provided evidence for the existence of critical transitions in natural and societal systems. In ecology [7], there are examples of the desertification of Mediterranean arid ecosystems [8] or the tree abundance in tropical forest and savannah [9]. Critical transitions have also been associated with the eutrophication of lakes [10], collapse of fish populations due to overfishing [11] and algae overgrowth in Caribbean coral reefs [12]. On larger scale such as the earth's climate system, reduction of Greenland ice sheets or melting of arctic sea-ice has been associated with a potential transition in the global climate system, which may or may not be reversible [13]. Similar to ecological systems, humans have complex traits. When considered as complex systems, both present positive and negative feedback loops, inherent nonlinearity and hysteresis (Box 1) [14]. Here, we show how concepts first developed in physics are now increasingly used to describe complex systems in the context of health and disease.

Critical transitions in medicine

Recently the concept of critical transitions and tipping points has been applied to clinical questions and systems medicine. We are convinced that a detailed understanding of critical transitions in disease onset and progression will provide broad applications in health care. The identification of early warning signals (Box 1) for example, can be expected to leverage prevention strategies. Already identified sudden transitions in the medical context have been associated with gut microbiome dysregulation [15••], pulmonary disease [16], depression [17•], type 1 and 2 diabetes [18,19], inflammation [20], start [21] and termination [22•] of epileptic seizures [23], cancer [24], and cardiovascular events [25]. Examples will be elaborated in more details in the section *Examples of clinical relevance in the context of critical transitions.*

Box 1 Stable state—A stable state of a dynamical (phenotype) system does not change its average phenotypic trait when being exposed to small random perturbations.

Alternative stable states—Distinct stable states of a dynamical system for the same set of environmental conditions. These alternative stable states are separated by a metastable state.

Equilibrium state—The state in which a system stays when no additional external perturbations are applied.

Critical transition—Sudden shift from one stable state to an alternative one where the actual transition can be triggered by small perturbations.

Tipping point—A threshold point at which a system will undergo a critical transition when exposed to perturbations.

Hysteresis—Current system state is depended on both the input and the history of the system.

Nonlinearity—A dynamical system is nonlinear if the set of underlying differential equations exhibit products of variables in at least one equation. Note that systems can obey linear dynamics even if the outcome has a nonlinear form like it is the case of exponential growth.

Early warning signal—An observable variable whose dynamics change considerably before a critical transition occurs.

Emergence—A phenotype that is exhibited at the system level but does not exist when studying the system components individually.

Early warning signals to detect upcoming critical transitions

A critical transition is usually detectable after the transition [26] and difficult to anticipate [27]. Before the critical forward transition, the system's equilibrium state might stay relatively unchanged until the forward tipping point is reached (Figure 2c) [28]. Consequently, static observations might not provide enough information to detect upcoming abrupt transitions [29]. By contrast, changing system dynamics have been suggested as early warning signals (EWS) for critical transitions [30•]. A general challenge for data analysis is the intrinsic noise in biological systems which originates from the stochastic nature of molecular interactions and heterogeneity of individual entities like cells or organisms. A brief explanation for the most commonly used early warning signals can be found in Table 1.

The influence of the random behavior is amplified in the vicinity of tipping points because small perturbations in the vulnerable regime of the system can have large effects (Figure 2). Due to this amplified heterogeneity, an increase in variance [10,31] or coefficient of variation [32] has been associated with upcoming critical transitions. Further, an increase or decrease of lag-1 autocorrelation may indicate the unfolding of an abrupt shift [6,33•]. An increase of flickering activity [34] has been identified as EWS for critical transitions in lake eutrophication [35•,36]. Changing skewness in the distribution of time-series climate data, could be used as a robust indicator for some complex natural systems [37]. Dynamical network biomarkers are a new approach to predict upcoming transitions and showed promising results for liver cancer [38]. Critical slowing down is found in some ecological systems when approaching a tipping point [39–41,42•]. A transition from vegetation to desertification was preceded by changes in the spatial distribution of vegetative patches [8]. Finally, significant heteroscedasticity [43] was observed one year before a critical transition in a lake [44]. This multitude of early warning signals to detect critical transitions shows that the nonlinearity in different systems are not always accompanied by the same EWS.

Examples of clinical relevance in the context of critical transitions

A recent example of alternative stable states was found in the context of microbiome dysregulation in human intestines. A highly diverse and dynamically evolving microbial ecosystem, mainly including bacteria from the *Firmicutes*, *Actinobacteria* and *Bacteroidetes* phyla, is living in the human gut and its dysregulation can have stark consequences on health [45]. It is thought that certain diseases such as obesity and irritable bowel syndrome might unfold due to transitions in microbial composition [46]. Recently, the question whether these transitions are linear or rather abrupt and nonlinear was raised [47]. Alternative stable states with high resilience were identified in human individuals after repeated prolonged exposure to an antibiotic (Figure 2) [47]. Such alternative stable states of bacterial ecosystems were confirmed in a study covering 1000 individuals [15••].

Acute asthma attacks are characterized by a constriction of the bronchioles which ultimately leads to patchiness in lung ventilation [16] and difficulties to breathe [48]. Such patch clusters can potentially lead to critical transitions via an interaction of feedback mechanisms [16]. One study developed a model of a bronchial tree and simulated incremental airway smooth muscle stimulation [16]. At a stimulation threshold, the system underwent a critical transition and showed severe ventilation defects [48]. In environmental epidemiology, early warning signals in the forms of changing variance and skewness were found for the deterioration of lung activity in humans after exposure to ozone [49•].

Clinical depression is characterized by a wide array of symptoms such as inability to sleep, low mood, loss of interest and suicidal tendencies. Onset and remission of clinical depression can occur suddenly. A recent study suggests that critical slowing down could be an early warning signal for onset and termination of depression [17•]. During the study, subjects were logging their mood states by self-assessment on an emotional scale at random intervals during the day. In follow-up assessments, subjects were re-evaluated using the same scales. Interestingly, existence of critical slowing down based on the collected mood states was confirmed and was indicative of