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

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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.

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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.

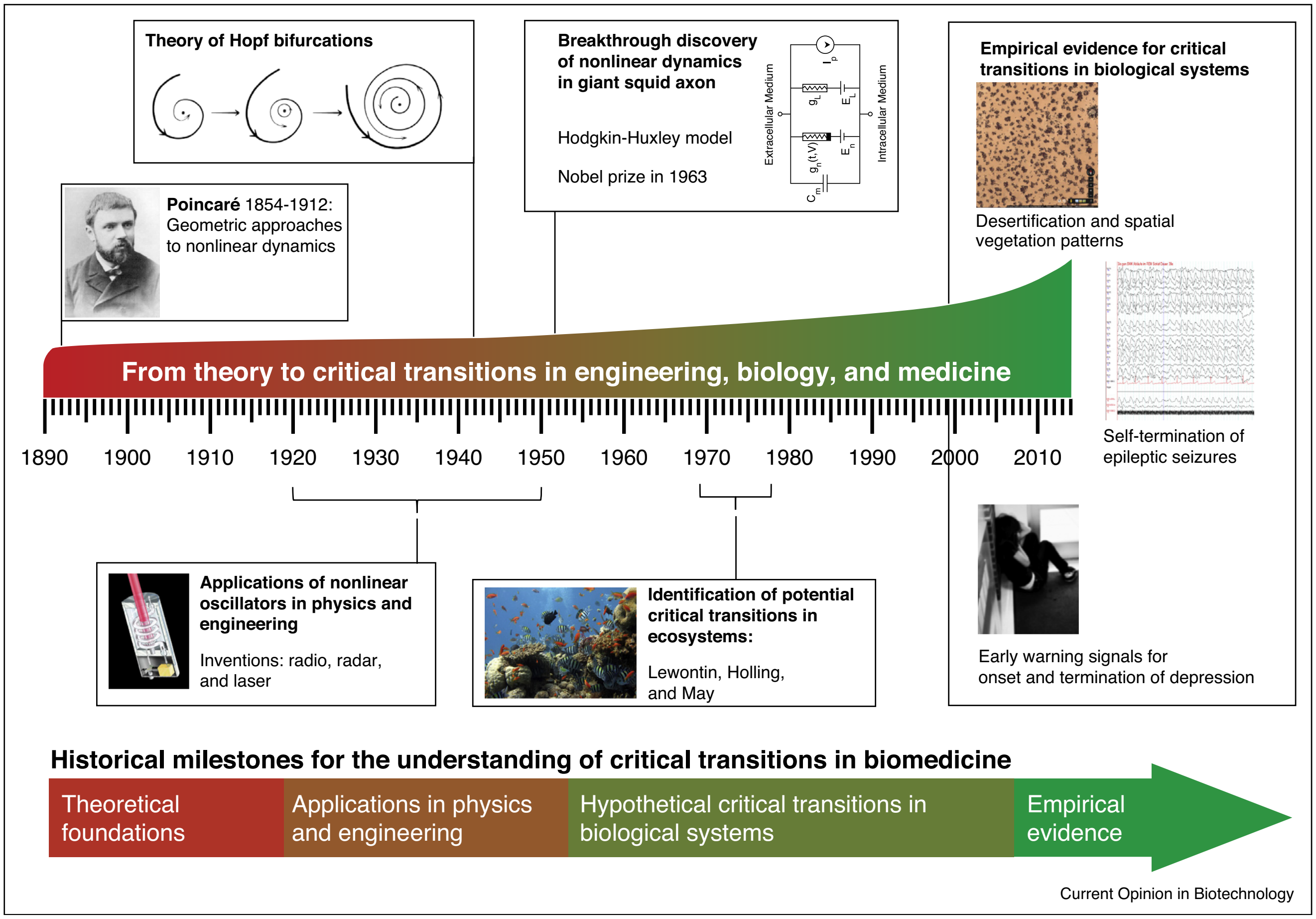
Examples of clinical relevance in the context of critical transitions

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

Figure 1



History of critical transitions. From theory to applications in medicine. Copyrights: Desertification: Google, Map data: DigitalGlobe. All other images were reproduced with written consent or found in the public domain. Hopf bifurcation freely adapted from [5].

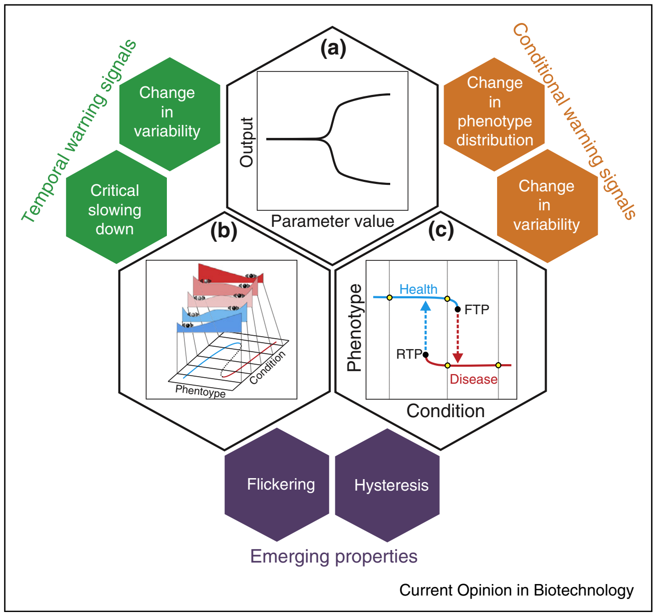
upcoming transitions from a normal to a depressed state or vice versa.

Diabetes mellitus has two major sub-types. In type 1 diabetes, patients cannot produce enough insulin and in type 2 diabetes the produced insulin is not used efficiently [50]. Both sub-types can be categorized into multiple disease stages ranging from pre-disease to full onset with clinical diagnosis often occurring only at the latter stage. Dynamical network biomarkers were found to be early warning signals for critical transitions from a pre-disease to a disease state for type 1 [18,51] and type 2 [19] diabetes in mice. On the scale of cellular interactions, critical transitions were identified in insulin-producing pancreatic-cell islets [52]. In this system, a critical amount of β-cell death at which pancreatic islets lose connectivity in the islet network results in systemic failure.

Dynamics of certain pro-inflammatory cytokines play a pivotal role in the unfolding of inflammation [53]. For instance, Interleukin-6 (IL-6) dynamics in pig blood revealed that variations of this cytokine over time could potentially serve as an early warning signal [20]. Scheff *et al.* showed on a mathematical model that under gradually increasing inflammatory conditions, the state of the system remains stable until a critical threshold at which it evolves from a healthy to an inflammatory state [54]. A mathematical model was created from experimental data where humans underwent an endotoxin application to simulate chronic inflammation. More generally, it has been proposed that early warning signals could predict upcoming epidemic infectious inflammatory disease occurrences in populations [55].

Epileptic seizures start and terminate suddenly and diminish quality of life in patients [56]. Increased variance in spiking patterns of individual neurons has been proposed as an early warning signal to detect the onset of a sudden epilepsy seizure [57]. Further, the mechanism leading to the unfolding of a seizure, when considering groups rather than single neurons, was attributable to a Hopf bifurcation. Recently, Kramer and colleagues

Figure 2



Critical transitions and their characteristics in biomedicine. The general basis of critical transitions is the existence of multistability of the underlying dynamic systems. **(a)** Such a multistability can occur by bifurcations where, for instance, a single stable state is turned into two stable states in dependence on a system parameter during a pitchfork bifurcation. **(b)** Under the assumption of equilibrated systems, the dynamics can be visualized by quasi-energy potentials or stability landscapes where the state of the system describing the phenotype corresponds to a ball in the potential. Changing the condition adiabatically will lead to a modification of the potential and can induce multistability (potentials with grey and black ball) from a single stable point (potentials with only black ball) by imperfect bifurcations. In this regime, the system can perform either induced or spontaneous state transitions by jumping from one well to another. The stability landscapes are projected on the underlying bifurcation diagram. Freely adapted from [7]. **(c)** A typical bifurcation diagram of a bistable system exhibiting hysteresis. The point where a system is switching from one phenotype to another one like in a health-to-disease transition is called the forward tipping point (FTP). The reverse tipping point (RTP) indicates the state where the system can return to the alternative one. For many nonlinear systems the FTP and RTP are not identical and this is known as hysteresis. The area between FTP and RTP corresponds to the regime of coexistence where critical transitions occur which can induce bimodality in populations. These properties may lead to system specific warning signals and emerging properties.

presented evidence of the existence of a critical transition between the ictal and post-ictal states of a seizure, representing alternative stable states [22•]. This critical transition was preceded by critical slowing down, increased autocorrelation and flickering.

Outlook: cross-sectional and longitudinal monitoring of health states

A potential application of using some of the described early warning signals for upcoming critical transitions could be in the generation of a population reference profile and the longitudinal monitoring of healthy people and patients. Similar to the human reference genome, a population reference profile would represent the variation of some of the early warning signals, in time and specific conditions from a representative healthy population. Due to the expected variability between individuals, longitudinal studies are expected to provide clearer signals than studies across populations. Such unique patient reference profiles could, for instance, be obtained during regular visits at the clinic. At each point of sample extraction, the current profile could be compared to the reference profile. The difference between the profiles would then be indicative of disease progression. At a certain threshold, the clinician could take appropriate measures to prevent a critical transition from a healthy to a disease state in individual patients.

Recently, wearable devices such as Fitbit® devices [58], and automated voice recording devices [59,60] have been proposed to be able to provide easy-use monitoring of specific activities in patients. For instance, symptoms such as tiredness, anxiety or speech difficulties, contributing to wearing-off in Parkinson's disease patients are difficult to assess during brief clinic visits [61,62]. Wearing-off means that specific symptoms make a re-appearance before the next scheduled administration of the therapeutic drugs. Wearing-off could become one way to assess critical transitions in Parkinson's disease from a clinical point of view. One could compute variables such as the number of wearing-off occurrences during the day or the time interval between the beginning of wearing-off and the next scheduled drug intake. Consequently, indicators as discussed throughout this review could be

Table 1

Potential indicators for early warning.

Early warning signal	Definition	Observed system variable
Variance	Scatter of data	Phosphorus concentration in lake [10] Pollutant across multiple regions [31] Interleukin-6 levels [20] Spiking patterns in neurons [57]
Coefficient of variation	Standard deviation normalized by the mean	Population density [32] Spatial heterogeneity of ventilation [16] Infectious population dynamics [55] Ozone levels [49•]
Lag-1 autocorrelation	Correlation of data with itself shifted by one time point	Rate of resource harvesting [33•] Connected population density [32]
Flickering	System states are driven back and forth between alternate stable states by intrinsic noise	Sediment diatom composition [35•] Ice conductivity [34] Phosphorus dynamics [36] Invasive electrocorticogram recordings [22•]
Skewness	Third standardized moment of the distribution of system states	Vegetation biomass [37] Phosphorus density [37]
Dynamical network biomarkers	Evolution over time of difference in molecular networks	Gene expression profiles [18,19,38,51]
Critical slowing down	Recovery rates tend to zero after small external perturbation	Calcium carbonate levels [41] Cyanobacteria population density [42•] Nutrient cycling in lakes [39] Macrophyte cover [39] Vegetation growth [40] Mood dynamics [17•]
Spatial distribution	Non-random distribution of elements in a biological entity	Vegetation patchiness [8]
Conditional heteroscedasticity	Variance is conditional on past time points	*E. coli* population growth [28] Chlorophyll-*a* concentration [43]

determined and used to assess the progression of the disease and classify the patient's disease states. Such predictors could allow clinicians to modify treatments accordingly and thereby increase patients' quality of life.

Conclusions

Although a large number of theoretical studies and computational simulations have been carried out to provide evidence for catastrophic shifts, there are still only a few biological and medical studies experimentally or empirically validating the predictions and the relevance of the critical transition concept for medical applications.

Furthermore, error rate estimations for false positive and false negative rates of the models underlying the predictions are rarely available. In order to prevent or revert critical system states this will become more important [63••]. In some disciplines, replicate experiments are often not possible, for example, when analyzing the occurrence of ice-ages, the sudden collapse of fish-populations or catastrophic transitions in the financial markets, as has been witnessed a few years ago. Biological systems and disease pathogenesis however might be studied in depth in animal models, patients with identical or closely related clinical symptoms or adverse responses to specific drug treatments. Due to this feasibility and their importance, biological and biomedical applications might play a driver role in our attempts to experimentally dissect and understand complex nonlinear natural systems. The development of system specific mathematical models and machine learning tools, integrating a wide range of omics and clinical data, and prior knowledge, for example, from literature, public databases and modern media, will become a central domain in systems medicine.

A note of caution

Critical slowing down might only occur in specific situations. Catastrophic collapse can occur without prior early warning signals in autocorrelation or variance [64••]. Therefore these early warning signals are not always globally applicable and it was suggested that in fact each system might have a characteristic subset of early warning signals [65]. This individuality is based on the intricate interplay of the underlying dynamics which are typically nonlinear and include intrinsic random forces originating, for example, from the stochastic nature of molecular interactions. The existence or occurrence of multiple stable states corresponds to inducible systems many of which exhibit excitable dynamics. Many natural systems exhibit such excitable dynamics like neuron spiking [66] or laser pulsing [67]. Driving such nonlinear dynamics by random perturbations can induce state transitions with a mathematically strictly defined transition rate [68] and lead to non-trivial effects like stochastic and coherence resonance [69,70].

Stochastic resonance describes the scenario where a weak periodic input signal of an excitable nonlinear system is amplified by intrinsic noise. Although first used to describe ice-age periodicity [71] stochastic resonance was subsequently found in a variety of natural and biological systems [72]. In general, stochastic resonance is characterized by a maximum in the signal-to-noise ratio in dependence on the noise intensity and corresponds to a minimum in the coefficient of variation. Similarly, coherence resonance occurs in excitable systems only driven by inherent noise and is also characterized by minimal values of coefficient of variations for optimal random perturbations [70]. These mechanisms can interfere with the general assumptions that critical transitions are accompanied by an increase of variability.

These prominent examples demonstrate that noisy nonlinear systems like those found in biology can obey unintuitive dynamics. The resulting complex behavior including noise induced effects question the general application of the early warning signals mentioned above but emphasize the need to complement experimental investigations with mechanistic theoretical models to fully characterize critical transitions.

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