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Phase Transitions and Resilience in Physical and Psychological Health

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5.1. INTRODUCTION

To explain the usefulness of complexity science in medicine and clinical psychology, we will start with answering the golden *why*. Why do we need complex systems theory in studying diseases? Thereafter, we will discuss *how* this complexity thinking affects medicine, and *what* specific tools from complexity science can be applied. Both will be detailed in an in-depth description of our understanding of resilience and the dynamics of tipping points (TPs) that are often met in clinical practice. This will be followed by a methodological description of how the complexity and resilience of human physiological and psychological systems can be studied and quantified in medicine and psychology. We will end this chapter picturing the horizon of the next stage of application of complexity science in patient care and medical science.

5.1.1 The Why of Complex Systems for Complex Patients

The adjective "complex" for patients describes them in abstract ways as a multicomponent system (1), with many (feedback) interactions (2), that are at least partly nonlinear (3), history and environment dependent (4), and of different temporal and spatial scales (5).[1] The components can be organs, but also components in the environment (e.g., the patient's family) that impact the patient's physical and psychological health. In the following sections, we will discuss examples in which the complexity lens in medicine and psychology is helpful

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in understanding and forecasting critical transitions between different disease states.

5.1.2. Complexity in Older Persons

Many examples of transitions and cascades of change can be seen in older people, who repeatedly have to adapt to changing conditions due to social change (e.g., retirement, loss of spouse) or incident chronic diseases (e.g., heart failure, dementia) against the background of the physiology of aging that involves diminishing physical and cognitive reserve capacity. The underlying multimorbidity dominantly presents in almost all older persons, and their multiform interactions (between the multiple disease causes, the symptoms, the medicines, and the other treatment components such as exercise and diet) reflect the multiple-agent condition in humans.[2] In these clinical scenarios, it is widely recognized that the linearly organized medical practice, fueled by the science of single disease management, is insufficient to understand, study, and handle such complex multimorbidity conditions.[3,4]

Many other patient problems may also profit from enriching the classical medical and psychological knowledge base by using a complexity science perspective. This holds true within the single disease domain, be it for complex chronic diseases such as depression, diabetes, or Alzheimer's disease or for infectious diseases such as HIV. All show similar complex phenomena in pathophysiology: They have multiple etiological and interacting components, multiple factors determining nonlinear spread, multiple organs involved in different historical time lines, and thus different consecutive stages and emerging stage-transitions in their patient's journeys.[5,6] This warrants a complexity science perspective in healthcare sciences as well as in psychological and medical sciences.

5.1.3 How Complexity Thinking Affects Medicine

The paths to improved understanding of many human diseases, including cancer, diabetes, chronic inflammatory diseases, and neurodegenerative disorders, lie in understanding the changed functioning (and malfunctioning) of interactions between biological components.[7] Often malfunctioning of a single organ (or organ part) does not cause serious problems due to redundancy in the physiological networks, but the combined effects of multiple malfunctioning components of an interacting network of organs are substantial and life threatening. For example, hippocampal and prefrontal cortex atrophy are often seen together with white matter lesions as malfunctioning components or nodes, of which only the summed pathophysiology in the neuronal network causes cognition and functional performance to deteriorate in daily living so that dementia must be diagnosed. An understanding of how individual (sub)components function is helpful, but not enough to understand the whole disease severity and the individually emerging disease presentations. This means that reducing the research focus to smaller and smaller components, which is the traditional scientific approach, has limits in understanding individual patients and the huge variation present in clinical practice. Precision medicine, with a focus on genetic, proteomic and metabolomic phenotyping, will not be able to forecast treatment effects in complex diseases that are further determined by relevant interactions at a higher level of scale (e.g., increasing amyloid-beta knowledge in Alzheimer's disease did not result in a single trial with positive effects on cognition and daily functioning nor in accurate predictions of Alzheimer disease trajectories). This requires multiscale modeling and predictors at a higher level, integrating not only molecular, cellular, and organ but also individual and group pathophysiological factors (e.g., also white matter lesions, sleep quality, loneliness, and caregiver support probably highly determine Alzheimer treatment effect and prognosis).[8]

5.1.4 Tools for Investigating HUMAN complexity

There are three modes of investigation of human physiology when working within complexity science: *theoretical, computational, and experimental*. These modes increasingly include quantitative, realistic, and even predictive models, bringing together statistical data analysis, modeling efforts, analytical approaches, and laboratory experiments.

As evidenced by the growing literature on complexity and TPs in medicine and psychology,[9,10] these constructs are already being applied in medical research and clinical practice. This may lead to an exciting time where our current, more static concepts of chronic diseases are likely to change, in favor of highly dynamic concepts with multiple scales taken into account in understanding and influencing health and disease.[10]

Complexity science perspectives in medicine and psychology demand attitudes quite different from those in physics, chemistry, and mathematics, where one may successfully search for fundamental laws, true for all conditions. Biological complex systems are different, as they also experience evolution, degeneration, and loss of entropy by added energy and human behavior, in contrast with the second law of thermodynamics that predicts stability of entropy in closed systems in equilibrium state and increase of entropy in open natural processes. Thus, there probably are no general laws for complexity in the domain of human physiology. Nevertheless, we may sharpen our reasoning on human complexity in health and disease by learning how complexity science tools were applied and helped to explain complex behaviors in other solid matter, biological and social systems. In the following section, we will discuss some of these tools, including (indicators of) TPs and resilience in the context of medicine and clinical psychology.

5.2. TIPPING POINTS, TRANSITIONS, AND RESILIENCE

It is becoming increasingly evident that many complex systems have critical thresholds, or TPs, during which the system shifts abruptly from one state to another. In clinical practice we often meet such unpredicted TPs, which therefore probably are the most undisputed phenomena that fit better with complexity than with deterministic theory. Well-known examples of TPs include acute transition toward delirium episodes, heart failure crises, recurrent falls, migraine attacks, epileptic seizures, and other acute severity states. In the psychological domain, the TPs in bipolar disorder are also studied using complexity science methods. The common denominator of complex systems in which these TPs for acute and theoretically reversible changes are observed is that they all rely on one or more positive feedback mechanisms. These can accelerate change and propel the system over the TP and into a different and less preferable, but stable, diseased state.

Within dynamic systems theory, the mathematical catastrophe model helps to understand how changes in a patients' systemic resilience act as risk markers of increased likelihood of passing TPs. In this model, TPs are known as catastrophic bifurcations. These bifurcations can be easily imagined for the equilibrium state of an older patient that can respond with either recovery or severe complications to stressors such as surgery or chemotherapy. Although some older patients (the "systems") with sufficient *resilience* may respond well, change can also be dramatic in patients with low resilience, causing a complication to pass a TP. The situation in which critical transitions occur, for example, toward delirium, a syncope (fall due to insufficient cerebral perfusion), or a stroke, can be modeled by an equilibrium curve that is acutely "folded." Notably, when a patient is close to such a "fold," or TP bifurcation, a minor stressor can already push his system across the safe boundary. Although declining systemic resilience may seemingly have little effect on older (or intensive care) patients when they are not meeting (anymore) stressors, they may be in a situation where even small (additional) stressors may push these patients over a TP, which shows lack of resilience. The concept of systemic resilience is therefore closely connected to the TP theory. However, it is in fact not obvious that a single overarching resilience property for the whole system exists that might determine the risk of passing through and recovering from TPs for the most important disease states in older adults. In principle, the acute severity states in different organs may have their own specific resilience. It is not yet known whether systemic resilience can be validly assessed.

Historically, resilience in humans was first defined as the system's ability to cope with stress and preserve functioning.[17] Since then, systemic resilience has been predominantly studied in the stress recovery system of the hypothalamic–pituitary–adrenal axis. Later, resilience was studied in-depth in medicine in the domains of psychology and psychiatry, where it was defined as the capacity to recover following psychosocial stressors.[18] A growing series of empirical studies in living systems returned to the original stress-concept of resilience and showed that this may be quantified by several mathematical measures of slowing recovery of complex systems from stressors, both artificial (e.g., heat, chemicals) and natural (e.g., climate change).[9] This was confirmed by controlled laboratory experiments, initially with cyanobacteria and algae.[10,11]

5.2.1. Resilience Indicators in Clinical Psychology

Although the study of complex systems in psychology is young, research on resilience and resilience indicators has made remarkable progress in recent years, especially in the context of emotional regulation research and research on psychopathology networks. Psychopathology network researchers conceptualize psychological disorders as a disordered state of a network of symptoms that directly affect each other and themselves over time.[12–14] Emotion regulation research focuses on the dynamics of emotions and particularly the (mal)adaptive responses of people's emotion processes to internal and external stimuli.[15]

Both fields are related in the sense that complex psychological dynamic systems are the central focus, and this system may become disordered at some point in time. The resilience of the systems determines (in part) the likelihood of unwanted outcomes occurring. For example, a lack of resilience in emotion processes is considered to play a key role in psychological maladjustment, including the development of psychological disorders.[15] In psychopathology networks, people who have symptom networks that are characterized by low resilience are prone to develop psychological disorders.[12,13]

In both emotion regulation and psychopathology network research, a lack of resilience is present when individuals are relatively strongly affected by, and show relatively weak recovery from, the effects of momentary perturbations on the psychological variables (emotions or symptoms) under study.[16] These perturbations can be either negative (e.g., stressors ranging from missing a train, to breaking up with one's partner) or positive (e.g., viewing beautiful art or getting a promotion at work). People with low resilience will have longer-lasting effects of perturbations on their emotions or symptoms, and because there is little recovery, the effects of multiple (even small) perturbations can more easily build up to problematic levels. Key indicators of a lack of resilience of the dynamic system that have been used in psychology are similar dynamical indicators of resilience as used in medical research: strong autocorrelations in the time series for the variables of interest (e.g., emotions or symptoms), strong cross-correlations (interrelations over time) between these variables, and high variability of these variables over time.

For example, a person with a strongly connected network of depression symptoms (see Figure 5.1) will, for example, after experiencing chronic stress (e.g., exacerbated by a strong autoregression for stress or worrying), more easily develop a depressed mood, then worry more, which may lead to sleep problems, subsequently fatigue, and then concentration problems, issues at work and self-reproach, and even more feelings of worthlessness (see Figure 5.1C).[12] On the other hand, someone for whom the effects of stress on mood, of worrying and fatigue on sleep problems and concentration, or of failure on their sense of self-worth are weak will be more resilient against developing a major depressive disorder (see Figure 5.1D).

Autocorrelation has arguably had the most attention within the context of emotion regulation, where it is used as a measure of "emotional inertia" or resistance to change in emotions,[16,17] although it is also an important part of dynamic (psychopathology) networks.[13] The autocorrelation (or autoregression coefficients) for a particular psychological variable (e.g., mood or a symptom) is obtained through time series modeling, and may be negative or positive (ranging from −1 to 1). Positive autocorrelations indicate that a relatively low score now (e.g., for mood) will partly carry over to the scores at later times. Positive autocorrelations are expected to occur for a plethora of psychological variables, especially those pertaining to mood, given that these are considered to typically show some stability over time. Negative autocorrelations indicate that a low score at this moment is followed by a high score at later times, and vice versa. This is something that is rarely seen for psychological variables but may occur for disordered psychological processes of intake (e.g., eating disorders). The stronger the autocorrelations, the stronger the carryover, and the easier it will be to predict future states of the variable from a past state. Importantly, this also means that the variables will recover relatively slowly from perturbations, because their effects are carried over for some period of time (see Figure 5.1A). Multiple perturbations will also more easily add up over time as a result of this. Hence, strong autocorrelation is used as an indication of low resilience. In contrast, when autocorrelations are weak, this indicates that each moment is a "new moment," with little or no

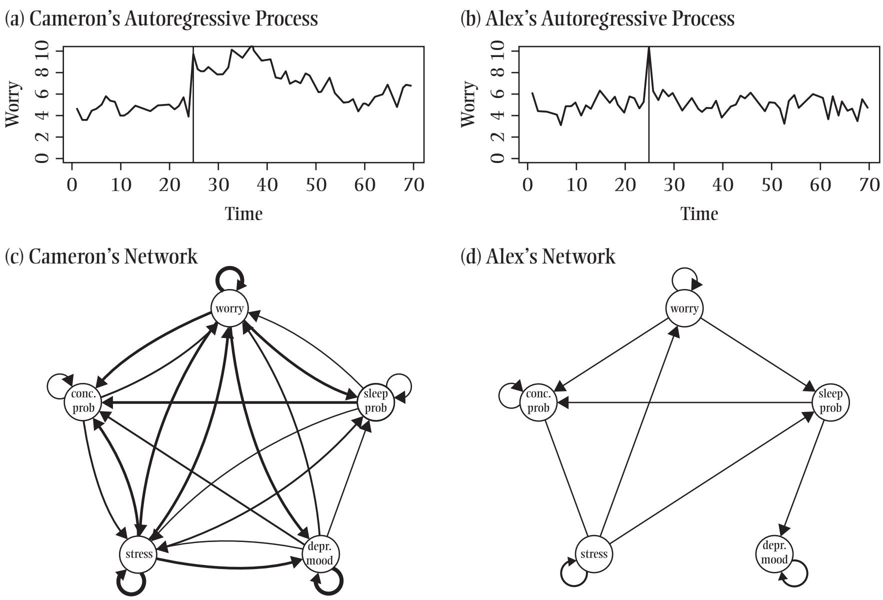

Figure 5.1 Panels A and B: Simulated autoregressive process for worrying for (hypothetical) individuals "Cameron," with an autocorrelation of 0.7 (A), and individual "Alex," with an autocorrelation of 0.1 (B). Both individuals experience a strong stressor at time point 25, but Cameron recovers much more slowly than Alex, because Cameron's process has more moment-to-moment carry-over. Panels C and D: Psychopathology networks for individuals Cameron (C) and Alex (D). Cameron's network is more densely connected than Alex's network, which has less, and weaker, autoregressive and cross-lagged associations.

carryover from previous moments, and as such the relatively resilient system can "recover" very rapidly from perturbations (see Figure 5.1B).

Multiple studies in psychology show evidence that emotional inertia is a risk factor for psychological maladjustment. For example, the level of people's emotional inertia has been found to be correlated to neuroticism, low self-esteem, lower overall positive affect, and higher negative affect; having a major depressive disorder; and even the onset of major depressive disorder two years later.[15,17]

Strong cross-correlations (or cross-lagged effects), which are correlations between variables over time, are also considered indicative of a lower resilience of psychological systems. If variables are strongly interconnected, the effects of perturbations on one variable in the system easily spread to other variables and, hence, can alter the system on a larger scale than may be expected based on just the original perturbation. As such, and especially when strong cross-correlations are combined with strong autocorrelations, consequences of small perturbations can be severe. This idea is central to psychopathology networks, which consist of networks of interrelated symptoms of psychological disorders.[12–14]

High variability in variables over time is also considered an indication of a lack of resilience to perturbations, such as when someone is overly reactive to what could be considered small stressors.[15] However, researchers report some concern in the robustness of using variability as an indicator for resilience, because high variability may also result due to actual strong perturbations instead of overreactions, low variability may also be maladaptive (e.g., when someone is so impervious to perturbations that emotions lose their adaptive function),[15] and a lower variance may also result due to either very low or very high mean levels of symptoms or emotions (ceiling or floor effects).[16,18]

As discussed previously, changes in resilience may indicate tipping points for sudden transitions in complex systems. Changes in resilience indicators, such as increasing autocorrelations, variances, and cross-correlations, thus may be used as early warning signals for sudden transitions from a normal healthy state to a disordered state.[16,19] Recent work in the context of psychopathology networks provides evidence in line with this, mainly in the context of the development of major depressive disorder (MDD). For example, van de Leemput et al.[16] found that people who showed sudden transitions from normal to depressive states, or vice versa, also had stronger autocorrelations, correlations between emotion scores, and higher variability in these scores before this transition, than people that did not show such transitions. Furthermore, in a case study, a person who had experienced repeated relapse into MDD was taken of their antidepressants during a healthy state (double blind), which eventually resulted in a sudden transition back into depression, and early warning signals were observed before this transition.[19]

Note that not all depression states are the result of a sudden transition, as gradual development is also observed among patients and is consistent with complex systems theory. What kind of change will occur in practice will most likely depend on the circumstances. For example, Cramer et al.[14] showed through simulations of MDD as a complex system people with dense networks may develop depression gradually, while people with strongly connected networks may be prone to sudden transitions to depression. Others presented time series models to study the nature of bipolar disorder and found in their empirical examples that one patient's disorder was better described by gradual transitions between manic and depressive states, while others showed sudden transitions.[20]

5.2.2. Resilience Indicators in Medicine

Personalized healthcare requires a balanced judgment based on the present disease states and the resilience of an individual person to resist or recover from alteration on one or more of these disease severity states. However, whereas a huge knowledge base is available about diseases, we know very little on how people resist, recover from, and adapt to disease. The same is true for how people will respond to or recover from treatment and surgery. This implies that, in medicine, we often have more knowledge on the perturbation (the external factor challenging the equilibrium of the system; i.e., the disease or treatment) than we have on the capacity of the system (the person involved) to deal with this perturbation. In disaster and public health-based theory, resilience is the trajectory a system follows in time while being perturbated. In public health, we want to predict prior to the perturbation the system will respond and how to design systems to maximize their resilience (ability to resist and readily rebound from) perturbations. This is equally true for clinical medicine. It assumes that the response of the system is followed in time (the so-called resilience trajectory) to quantify the resistance and recovery of the system after the perturbation. However, out the same negligence of resilience in clinical medicine, resilience trajectories are not often followed in a systematic way and with objective measures. This leaves clinicians to their clinical intuitions when predicting and following resilience for health challenges or treatments.

This may not be as problematic when enough resilience can be assumed. However, it is problematic and may cause iatrogenic damage when a person has multimorbidity or frailty. A lack of objective resilience indicators makes it difficult to provide personalized healthcare, and timely management of delayed recovery is often not possible. With the increasing availability of (sensor-based) time series on health indicators, the advent of new (dynamic) indicators of resilience now offers a means to quantify, monitor and understand resistance and recovery in medicine.

5.2.3. Indicators of Resilience

Possible measures to serve as indicators of resilience in medicine can be similarly as in the abovementioned field of psychology derived from dynamical systems theory, which first suggests "that the recovery rate after small experimental perturbation can be used as an indicator of how close a system is to bifurcation point."[7p1120] Indeed, in the literature, a number of striking similarities between warning signals for impending acute transitions across a range of chronic episodic disorders have been described, each characterized by longer recovery times following a stressor.[6–8] For example, elongation of the recovery period following an acute heart failure episode acts as risk marker for quick relapse of heart failure (Table 5.1), longer recovery time of repolarization in cardiac muscle cells (longer QTc interval) increases the risk of ventricular fibrillation, and longer neuronal recovery times in epilepsy and migraine predict subsequent seizures and headache attacks. On the other hand, very short periods of state change, also called "flickering," may also signal a later more permanent change (e.g., flickering periods of paroxysmal atrial fibrillation, before chronic atrial fibrillation or only more lasting recovery from substance abuse after several short attempts of quitting but with quick relapse, before it sticks).

In clinical practice, these principles may serve to develop bedside tests to measure the physical resilience of a patient by the development of tests based on the stimulus–response paradigm. These tests apply a standardized, but safe (in the sense that it doesn't carry the risk to elicit the actual critical transition),

Table 5.1 Recovery Times as an Indicator of Resilience and Prognosis for Recovery after Passing Tipping Points in the Course of a Range of CHRONIC diseases.[6]

Discipline	**Disease**	**Recovery time**	**Disease state predicted by longer recovery time**
Cardiology	Arrhythmia	QTc elongation time	Torsade de Pointe arrhythmia
G-enterology	Colitis	Clearing time clostridium dif.	Clostridium D. overgrowth
Geriatrics	Falls	Centre of mass recovery time	Falls, loss of balance
Hematology	Acute leukemia	Lymphocyte recovery time	Relapse of disease
Immunology	Breast cancer	Lymphocyte recovery time	Relapse of disease
Neurology	Epilepsy	Depolarization recovery time	Epileptic state
Oncology	Neck cancer	Lesion regression time	Relapse state
Psychiatry	Depression	Positive mood recovery time	Depressed state
Public Health	Smoking	Craving decay over time	Relapse of smoking
Pulmonology	Tube-ventilation	Ventilation recovery time	Ventilation weaning failure

Source: Olde Rikkert MG, Dakos V, Buchman TG, et al. Slowing down of recovery as generic risk marker for acute severity transitions in chronic diseases. Crit Care Med. 2016;44:601–606. doi:10.1097/CCM.0000000000001564

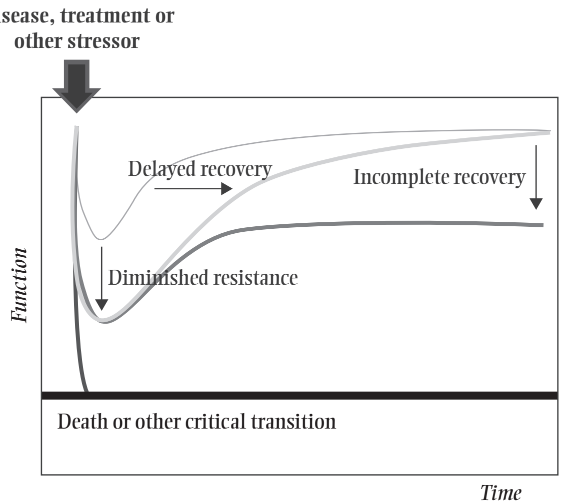

Figure 5.2 Relation between resistance and recovery as part of overall dynamical resilience of a person following a stressor or disease.

perturbation, and the response of the system perturbated is followed both for how much the system is perturbated (resistance) and for the recovery time (Figure 5.2).

Empirical evidence for the feasibility and validity of such stimulus–response paradigm based tests is available as is illustrated by impaired systolic blood pressure recovery after standing up under test conditions, which was predictive of this person's survival in the following period.[21] A second class of measures may be offered by characteristic changes in the patterns of fluctuations of a system in the response of the system to the natural perturbations it is permanently subject to. This response may also change when a system's resilience is changing. The specific changes hypothesized are an increase in variance and temporal autocorrelation within time series as well as an increased cross-correlation in two or more time series describing aspects of the functioning of the system of interest. In this respect, we followed the self-perceived physical, mental and social well-being of 20 persons living in a nursing home for 100 days, and this provided empirical evidence of the validity of these Dynamical Indicators of Resilience (DIORs) in discriminating persons with different levels of frailty.[2] In a group of high-functional older persons (i.e., the opposite of frailty) the DIORs (especially variance) also discriminated persons at different levels of successful aging persistently over one-year follow-up.[8] These DIORs may prove valuable as dynamical resilience indicators in other time series of biological systems as well.

5.3. FUTURE CLINICAL APPLICATIONS

Applying complexity science methods, if clinically verified, may lead to major scientific breakthroughs in psychology and medicine, as this could lead to new individualized forecasting tools to be used in a wide range of diseases and clusters of symptoms. The toolbox of time series analyses techniques and DIORs could go “viral” in a range of medical disciplines, as many medical researchers, psychologists and physicians regularly encounter TP dynamics.

However, first we must tackle the major challenge of moving complexity science applications beyond group level validity and realize improved predictions based on individual time series that may positively guide individual older patients toward improved outcomes. This may seem far away; however, studies on continuous glucose, wearable sensors, and electro-encephalographic monitoring already suggest that this complexity science approach enables improved forecasting and have successfully prevented hypoglycemic episodes, as well as epileptic seizures by a more reliable warning system for upcoming seizures.[21–24] In psychology, individual time series of mood and experienced emotion already can help explain major changes in mood in patients with bipolar disorders.[16,25]

Whether and how these tools will be implemented in clinical practice on a global scale is hard to predict, but complexity science tools may show up as emergent support tools in our more and more complex patient populations, and likewise in our complex medical system. Further, some of these tools are already in use in clinical practice, such as in intensive care units as wearable devices to alarm periods during which patients have higher risks on epileptic insults.[22] This can lead to changes in medication or lifestyle to guide patients toward a more resilient state, which may be considered as concrete successes of complexity science in medicine.

5.4. CONCLUSIONS

After a period of reductionism in medical and psychological sciences and clinical forecasting, focusing on in-depth and detailed characterization of individual diseases, molecular, cellular, and organ functions at a single time point, we can now make a move toward linking these subparts in human physiology and psychology. This integrative change is greatly supported by the availability of complexity science tools for time series and network analyses, and the clinical availability of technical devices (“wearables”) to follow bodily and psychological signals reliably over time. This creates new data sets, not just consisting of large amounts of data (as in “big data”), but foremost of “complex data” with numerous interdependencies in the data structure. These data are interrelated as large series of data are acquired per person, which therefore have multiple cross- and auto-correlations. The current growth of complexity science with methodology to intelligently and reproducibly analyze such data is timely and pushes the frontier of insight in the complex problems of both the outside skin and the inside skin world greatly forward.

This results in many complex clinical and research questions and hypotheses to be answered and tested, complex data to be analyzed, and innovations to be developed using dynamic network knowledge and dynamic forecasting signals from clinical practice. Iterative cycles of knowledge acquisition and implementation according to complexity science may finally integrate specialized subparts of human knowledge again and therefore may also bridge the gaps between the many super-specialists and their disciplines involved in this process. Therefore, the application of complexity science in medicine, psychology and the humanities has the potential to open new horizons of interdisciplinary (team) research on the complex big clinical problems, such as how to manage the quickly increasing chronic and multimorbid disease burden and how to improve resilience for the stressors of modern life that we now globally face.

REFERENCES

1. Prigogine I. Sengers I. Order out of chaos. 2017, Verso New York. (Original publication 1978)
2. Gijzel SMW, van de Leemput IA, Scheffer M, et al. Dynamical resilience indicators in time series of self-rated health correspond to frailty levels in older adults. J Gerontol A Biol Sci Med Sci. 2017;72:991–996. doi:10.1093/gerona/glx065.
3. MacMahon S. Multimorbidity a priority for global health research. 2018, London.
4. Editor Lancet. Making more of multimorbidity: an emerging priority. Lancet. 2018;28;391:1637. doi:10.1016/S0140-6736(18)30941-3
5. Richters A, Nieuwboer MS, Olde Rikkert MGM, et al. Longitudinal multiple case study on effectiveness of network-based dementia care towards more integration, quality of care, and collaboration in primary care. PLoS One. 2018;13:e0198811. doi:10.1371/journal.pone.0198811.
6. Olde Rikkert MG, Dakos V, Buchman TG, et al. Slowing down of recovery as generic risk marker for acute severity transitions in chronic diseases. Crit Care Med. 2016;44:601–606. doi:10.1097/CCM.0000000000001564
7. Gijzel SMW, van de Leemput IA, Scheffer M, et al. Dynamical indicators of resilience in postural balance time series are related to successful aging in high-functioning older adults. J Gerontol A Biol Sci Med Sci. 2018;74:1119–1126. doi:10.1093/gerona/gly170
8. Canli T, Yu L, Yu X, Zhao H, et al. Loneliness 5 years ante-mortem is associated with disease-related differential gene expression in postmortem dorsolateral prefrontal cortex. Transl Psychiatry. 2018;10:2. doi:10.1038/s41398-017-0086-2.
9. van Nes EH, Arani BMS, Staal A, van der Bolt B, Flores BM, Bathiany S, Scheffer M. What do you mean, "tipping point"? Trends Ecol Evol. 2016;31:902–904. doi:10.1016/j.tree.2016.09.011
10. Scheffer, M. Carpenter SR, Lenton TM, et al. Anticipating critical transitions. Science. 2012;338:344–348. doi:10.1126/science.1225244
11. Veraart AJ, Faassen EJ, Dakos V, van Nes EH, Lürling M, Scheffer M. Recovery rates reflect distance to a tipping point in a living system. Nature. 2011;481:357–359. doi:10.1038/nature10723
12. Borsboom D, Cramer A. Network analysis: an integrative approach to the structure of psychopathology. Annu Rev Clin Psychol. 2013;9:91–121.
13. Bringmann, L, et al. A network approach to psychopathology: new insights into clinical longitudinal data. PloS One. 2013;8:e60188.
14. Cramer A. et al. Major depression as a complex dynamic system. PLoS One. 2016;11:e0167490.

15. Kuppens, Peter, Nicholas B. et al. Emotional inertia and psychological maladjustment. Psychol Sci. 2010;21:984–991.
16. van de Leemput, IA, Wichers, M. Cramer AOJ, et al. Critical slowing down as early warning for the onset and termination of depression. Proc Natl Acad Sci U S A. 2014:111:E879.
17. Suls J, Green P, Hillis S. Emotional reactivity to everyday problems, affective inertia, and neuroticism. Person Soc Psychol Bull. 1998;24:127–136.
18. Bos E, De Jonge P. Critical slowing down in depression is a great idea that still needs empirical proof. Proc Natl Acad Sci U S A. 2014;111:E878–E878.
19. Wichers M., et al. Critical slowing down as a personalized early warning signal for depression. Psychother Psychosom. 2016;85:114–116.
20. Hamaker E, Grasman R, Kamphuis JH. Modeling BAS dysregulation in bipolar disorder: Illustrating the potential of time series analysis. Assessment. 2016;23:436–446.
21. Lagro J, Schoon Y, Heerts I, et al. Impaired systolic blood pressure recovery directly after standing predicts mortality in older falls clinic patients. J Gerontol A Biol Sci Med Sci. 2014;69:471–478. doi:10.1093/gerona/glt111.
22. Cook MJ, O'Brien TJ, Berkovic SF, et al. Prediction of seizure likelihood with a long-term, implanted seizure advisory system in patients with drug-resistant epilepsy: a first-in-man study. Lancet Neurol. 2013;12:563–571. doi:10.1016/S1474-4422(13)70075.
23. Abraham MB, Davey R, O'Grady MJ, et al. Effectiveness of a predictive algorithm in the prevention of exercise-induced hypoglycemia in type 1 diabetes. Diabetes Technol Ther. 2016;8(9):543–550.
24. van Beers CA, DeVries JH. Continuous glucose monitoring: impact on hypoglycemia. J Diabetes Sci Technol. 2016;10(6):1251–1258.
25. David SJ, Marshall AJ, Evanovich EK, et al. Intraindividual dynamic network analysis—implications for clinical assessment. J Psychopathol Behav Assess. 2018;40:235–248. doi:10.1007/s10862–017–9632–8.