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Perspective

Systems biology of resilience and optimal health: integrating Chinese and Western medicine perspectives

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ABSTRACT

Western science has been strong in measuring details of biological systems such as gene expression levels and metabolite concentrations, and has generally followed a bottom up approach with regard to explaining biological phenomena. Chinese medicine in contrast has evolved as a top down approach in which body and mind is seen as a whole, a phenomenological approach based on the organization and dynamics of symptom patterns. Western and Chinese perspectives are developing towards a 'middle out' approach. Chinese medicine diagnosis, we will argue, allows bridging the gap between biologists and psychologists and offers new opportunities for the development of health monitoring tools and health promotion strategies.

In this paper, health, resilience and stress concepts are explored from an integrated systems biology perspective. This is followed by a discussion about measuring aspects of health and resilience. Then the issue of how to integrate different types of data is discussed. Semi-quantitative modeling appears to be very suitable and looks promising for building integrated health models. The challenge for the future lies in applying those models in developing personalized health monitoring and advice systems that will tempt people to lead more healthy lives.

Key words: Health, Wellness, Resilience, Systems biology, Chinese diagnosis
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Introduction

Modern medicine has been successful in developing numerous methods to solve acute health issues such as heart valve replacements, hip and knee replacements, infections, pain, etc. The underlying paradigm in medicine has been the "war against" principle, for instance antibiotics to destroy microbial invaders in our system. This is reflected in the names of our current drugs which contain elements as anti-/-blocker/-inhibitor (anti-TNF drugs, ACE-inhibitors, beta-blockers, etc.). Despite the successes of modern medicine, the health economics perspectives are worrying as the cost of current health care systems is rising beyond the point that it can be afforded. Even more concerning might be reports that the American medical system has become the leading cause of death and injury in the US with over 750.000 deaths each year[1]. For instance, over 100, 000 people die from adverse drug reactions[2], mainly caused by antibiotics (17%), cardiovascular drugs (17%), chemotherapy (15%) and analgesics and anti-inflammatory agents (15%)[3] while an even larger proportion of people suffer from side effects. The current disease management strategy appears to be hardly effective in chronic conditions and even less so in prevention. For instance, a temporary decrease of haemoglobinA1C (HbA1c) and fasting glucose levels is observed in diabetes type 2 patients taking metformin, though after a few years this effect is lost[4]. Applying a disease fighting model for prevention leads to over-diagnosing and medicalization of the society as the current use of statins to prevent coronary heart disease shows. There is only a 1 in 120 chance that your death is prevented after 7 years of dutiful daily use of statins while risking side effects[5].

Apart from the disease fighting mode a health promotion mode is rapidly gaining interest in many countries. In this mode, nutrition, psychotherapy, medication and life style interventions are developed in concert which stimulate the self-healing capacity of the body, both on a physical as well as a psychological level. Also combinations of disease fighting and health promotion strategies are possible, for instance aerobic exercising and breathing exercising (health promotion) before cardiac surgery (disease management) decrease the length of hospital stay and reduce postoperative pulmonary complications in these patients[6]. Evidence is piling up on the positive effects of daily exercise, not smoking and balanced nutrition on overall mortality and risk for developing chronic conditions and quality of life[7,8]. Despite the accumulation of scientific publications about life style interventions, it appears to be very difficult to define which intervention is effective for which particular individual[9,10].

In the area of health promotion, even more so than in the area of disease management, the one-size-fits-all approach doesn't seem to work. Some people with an apparently very unhealthy diet, smoking, and hardly any exercise still die at

an old age after a long career of hard working. Other people with a seemingly healthy diet and lots of exercise die young. For instance, equally healthy groups of high fat and low fat consumers have been identified[11]. A mixture of genetic components, constitution, acquired flexibility and susceptibility to certain environmental variables seem to determine someone's health[12,13]. Obviously a personalized approach is needed in the area of health promotion that fits with the individual's predispositions. But the key question remains: what actually constitutes health?

Recent insights have shifted the definition of health from a state of complete physical and mental wellbeing to an ability to adapt to the environment[14,15], a more dynamic interpretation of health. This illustrates that various concepts that are somewhat related to health are used in similar contexts, for instance resilience, wellness and well-being. The question then arises: to which situations we need to be able to adapt? In which situations do we need to be flexible? The evaluation of your mental but also your physical state is a personal undertaking and actually determines your feeling of wellbeing. Some people like to move in many uncertain and new situations which present specific challenges and consequently require resilience on many levels while other people like a quiet life full of routine or controlled situations, requiring a different set of resilience capacities (both qualitative as well as quantitative).

In this paper, resilience, health and wellness concepts that arose in Western and Chinese culture are explored. The second part of the paper focusses on how to measure resilience. In the last part a perspective will be sketched on the future of health care and the role resilience measures might play here.

1 Concepts of health, wellness and resilience

When a situation of incomplete adaptation arises, some sort of physical and/or mental resistance will be experienced. However, there are situations in which we feel completely carefree and unified with the environment, an experience of oneness with the universe. It seems that our physiological rhythms are in harmony with the rhythms of nature[16]. In such situations, which are different for everyone, we generally live entirely in the moment without worries about the future and the past. We do not feel resistance, frustrations, or the need for resilience. In such situations we experience a sense of wellbeing or wellness, and tend to completely forget or accept the presence of a chronic disease or any other discomfort. The experience of resilience seems to arise from the partial separation of the *self* from the *other* and the environment[17].

Resilience is inevitably a personal experience depending on life-style, worldview, and preferred coping styles in relation to the experienced environment. Even though a general training of physical and mental resilience is beneficial in many situations, specific training is required targeted to especially demanding environments or activities[18]. Resilience in relation to the environment, from a systems perspective, is directly related to the dynamic response of a given system. Depending on the selected scale of a system: human body, family, physical environment, culture, etc. different parameters need to be taken into account. Moreover, since the quality of the connections between parameters is more important than the characteristics of the parameters individually, resilience can only be measured as the dynamic response to a chosen. For example, chronic, though subtle, disturbances in especially the parasympathetic branch of the autonomic nervous system may over time contribute to measurable alternations within the Hypothalamus – Pituitary gland – Adrenal gland (HPA) axis[19].

The concept of health tends to be more related to the individual, the functioning of body and mind. We catch a cold and experience a headache or sore muscles and think that our health is compromised. In chronic conditions, a set of unpleasant symptoms characterizes the disease process. Wellness tends to be experienced more as a feeling in relation to the environment, which can include family members, colleagues, tasks to do, and other social relationships. Experiencing wellness is much closer to the feeling of oneness, the good life as Becker[20] calls it or eudaimonia, the realization of your true potential as Aristotle first described it[21]. As such, a person with arthritic pain in the hand joints can judge his health compromised but at the same time judge his wellbeing or state of wellness very high. In a state of optimal wellness, someone is connected with the environment and natural rhythms[22].

Figure 1 is an attempt to partly illustrate the concepts and ideas described above. A person is a highly dynamic system which is perceived as healthy and long as it is fluctuating between certain boundaries, shown by the fluctuating line starting on the left side of the figure. This state, which is related to the homeostasis concept, is a dynamic stable state of relative comfort for the person (comfort zone), as challenges (of any nature) can efficiently be overcome with the individuals' available resources. At certain moments in life a challenge occurs that pushes the system towards a state of allostasis[23]: the system needs to adapt to a new situation (challenged zone) as the available resources are (not yet) sufficient to deal effectively with the newly presented challenge. For instance, adapting from European low lands to living in the Himalaya, one needs to adapt to a different time zone and lower oxygen levels due to the higher altitude. Maybe this adaptation goes well the first time, given at least some adjustment time, but making the same trip a few times in a year might demand too much flexibility of the system, pushing it into a vulnerable or impaired state. As the normally sufficient resources to respond adequately to a physical or mental stressor are now insufficient, this adapted state of the system might make the individual (temporarily) more vulnerable for the negative consequences of additional challenges, e.g. may make the individual prone to certain infections and diseases. Lloyd et al. coined the term homeodynamics, the continuous transformation of one dynamical system into another through instabilities at bifurcation points, to describe such processes[24]. This systems dynamics concept

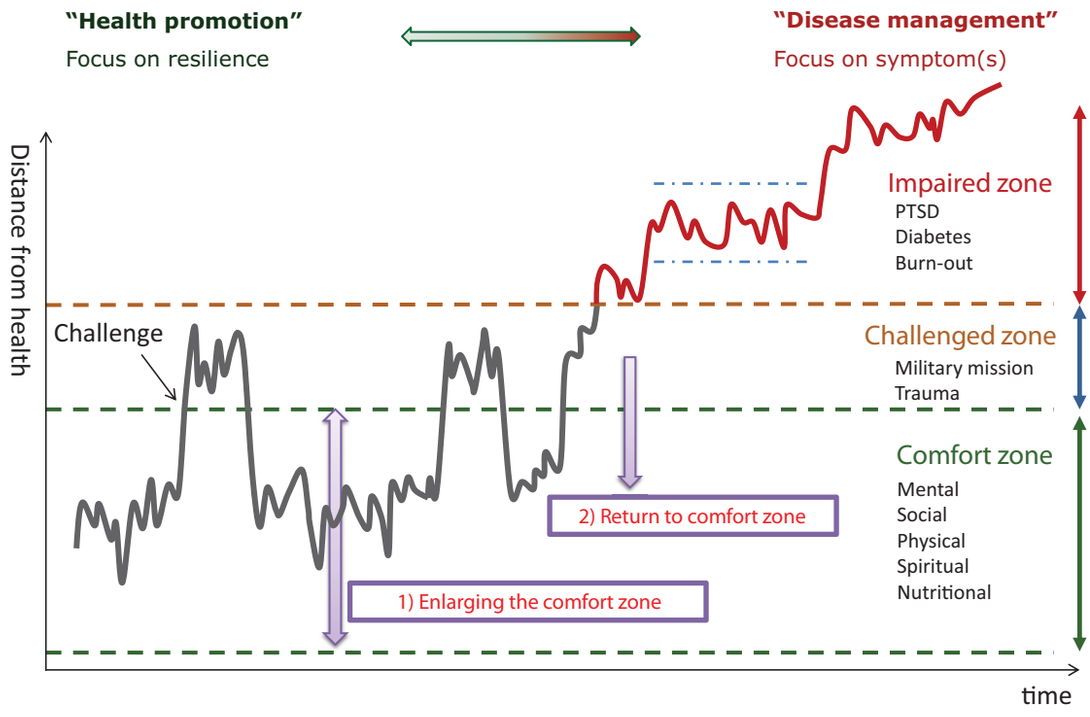

Figure 1. Conceptual positioning of the relationships between health, resilience and impaired health. Health is challenged by acute stressors and by chronic stressors that could build up allostatic load over time and eventually lead towards a dynamic of impaired health.

allows for a methodology to study such switches between stable states.

There seem to be at least two ways to improve resilience. The first is developing the ability to function optimal and comfortable in a more diverse set of circumstances and environments by training and (gradual) exposure. The second is improving the ability to adapt to a new situation, which is the ability to move faster or more efficiently from a challenged zone towards a comfort zone.

1.1 Resilience, health and wellness in Chinese medicine

Up to this point, the resilience, health and wellness concepts that were mentioned are all very much the product of Western culture, Western philosophy and Western science. In this section we broaden our view and see what can be learned from other cultures such as Chinese culture. Below are two citations that illustrate health, wellness and resilience as it was written down in one of the classics of Chinese medicine, the Nei Jing Su Wen[25].

'Qi Bo replied, "In the past, people practiced the Tao, the Way of Life. They understood the principle of balance, of Yin and Yang, as represented by the transformation of the energies of the universe. Thus, they formulated practices such as Dao-in, an exercise combining stretching, massaging, and breathing to promote energy flow, and meditation to help maintain and harmonize themselves with the universe. They ate a balanced diet at regular times, arose and retired at regular hours, avoided overstressing their bodies and minds, and refrained from overindulgence of all kinds. They maintained well-being of body and mind; thus, it is not surprising that they lived over one hundred years."

'Huang Di stated, "People and nature are inseparable. In nature the cyclical movement of the heavenly bodies produces atmospheric influences that exert control over the rhythms of the seasons and is responsible for change to the myriad living and nonliving things. These cycles are repeated endlessly with patterns of predictability, and yet simultaneously with a tendency towards chaos. It is this chaos in the macrocosm that upsets the balance of the delicate ecology within people that produces disease."

These two citations illustrate the Chinese perspective that people and nature are inseparable. People are connected to the rhythms of nature and rhythms of life and therefore we are dynamical systems. The quality of the connection of the person with nature, or the oneness with nature was perceived as the cause of a long life. Interpreting connections is actually at the core of Chinese medical thinking. Patterns of symptoms can indicate certain disorders which can then be treated. To illustrate this, a Western and Chinese perspective on the HPA axis is given below.

About 2000 years ago, the HPA axis connecting brain functions with glucocorticoid release from the adrenal glands was not known at the molecular and pathway level, but was phenomenologically described in Chinese medicine as the relationship between the functions, processes or concepts of Heart and Kidney. In Chinese medicine concepts such as Heart and Kidney are used to specify functions rather than objects, although the concepts are related to the physical organs. The Chinese concepts are written with a capital first

letter throughout the text to distinguish them from the physical organs.

The concept Heart encompasses joy from virtue and being true to yourself. The concept Kidney is related to existential fear and the ability to know what you can do and what you cannot do. The Heart and Kidney are connected by the extraordinary meridian (also a concept) called Chongmai, the only meridian that is filled with Blood. When the Heart is not anchored sufficiently to the Kidney, symptoms such as insomnia, anxiety, dream disturbed sleep, poor memory and palpitations arise (Figure 2)[26].

There are two main symptom patterns that are according to Chinese medical philosophy related to a reduced stress resilience. One pattern, *Liver Qi Stagnation*, is a reaction to acute or chronic stress from outside stimuli characterized mainly by tense muscles, distension of abdomen, distension of chest, feeling a lump in the throat, feeling wound-up, moodiness, depression. This pattern is also associated with higher plasma adrenaline levels and an increased heart rate[27]. The other pattern, called *Heart Blood Deficiency* (see figure 2), is the result of being untrue to yourself, for instance, because of pleasing others too much. This pattern is characterized by palpitations, insomnia, poor memory, anxiety, dizziness and dream disturbed sleep. Both the *Liver Qi Stagnation* as well as the *Heart Blood Deficiency* symptom patterns are stable but dynamic patterns of symptoms.

According to the Chinese perspective, the Liver, whose function is to move Qi, distributes Blood to the Chongmai and the Heart. A stagnation of the Liver function therefore can give rise to a Heart Blood Deficiency, causing the previously mentioned symptoms that are in western medicine generally closely associated with for example the diagnosis of Generalized Anxiety Disorder and/or excessive brooding. This in turn can give rise to a Chongmai Blood Deficiency, which in turn damages the Kidney function. The main function of the Kidney is to store and control Essence, or Jing, which is related to growth and development, memory, determination and will power.

The function of the Spleen is to produce Blood. *Liver Qi Stagnation* damages the Spleen leading to less Blood production. However, a Spleen Deficiency is also characterized by a desire for sweet foods and fast carbohydrates, the Chinese medicine explanation for stress eating and reduced metabolic flexibility. The sweet food and refined carbohydrates create Dampness and Heat which sustains the Liver Qi Stagnation, creating a pattern which is difficult to break.

Despite the mainly poetic terminology used above to describe psycho-physiological processes and relationships between them, the two described symptom patterns can be used to distinguish between different types of stressors and the diversity of resilience resources one needs when encountering these types of stressors. For instance, stress due to military missions in a hostile environment might require strengthening of Liver function, while stress due to lack of family support for the mission might require a good Heart function. In reality every person has a unique stress symptom profile that might change over time. Changes in patterns of symptoms are essential to understand the stress-related

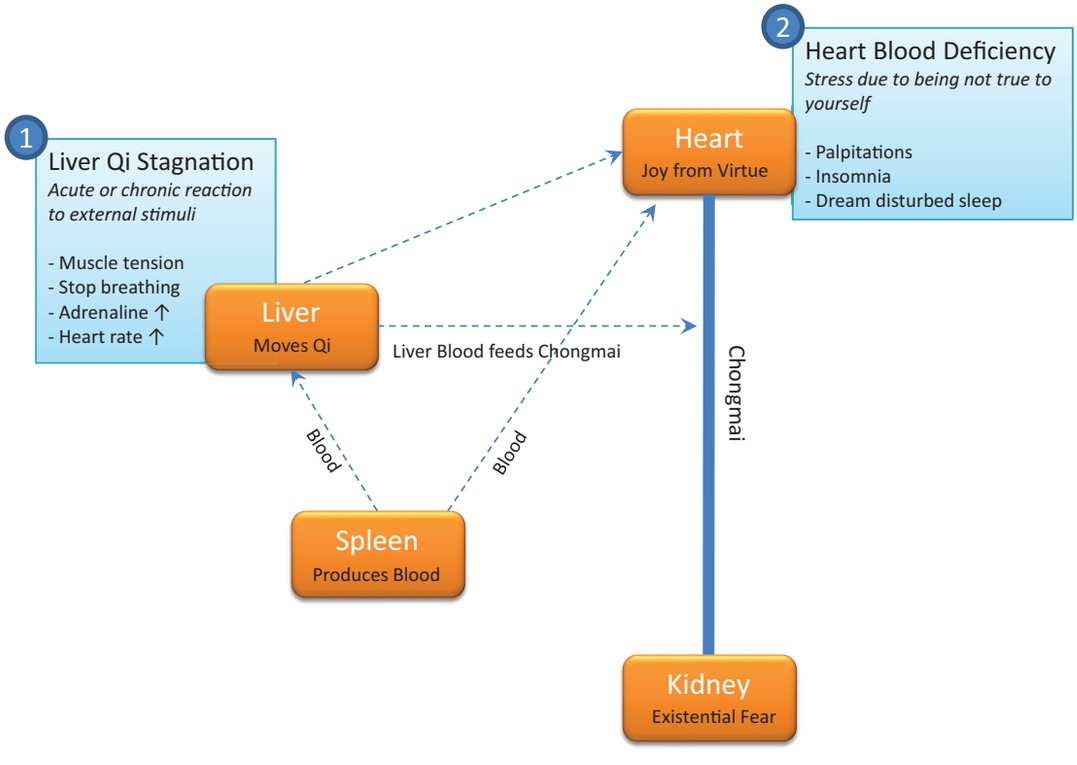

Figure 2. Chinese conceptual perspective on HPA axis-related stress and resilience. Heart, Liver, Kidney, Spleen and Blood are concepts not related to the organs as in the Western world. Two major types of stress are distinguished: 1) an acute or chronic reaction to external stimuli leading to *Liver Qi Stagnation* and 2) stress related to not being true to yourself leading to *Heart Blood Deficiency*.

behavior of individuals and identify individual resilience components. The individual symptoms that constitute such symptom patterns indicate that there is no body-mind split in Chinese medicine, allowing a comprehensive evaluation and integration of physical symptoms as well as mental and spiritual symptoms[28,29]. Symptom patterns can therefore be used as a unique non-invasive phenomenological health, wellness and resiliency monitoring tool in addition to other resilience measurement methods.

2 Measuring resilience

In order to develop methods to improve the resilience of any given individual it is essential to be able to assess or quantify resilience (for different quantification approaches see for example Petros et al.[30] and Yu et al.[31]). As resilience is a dynamic process, longitudinal data in response to a challenge or stressor are required[32]. In the psychological domain this could imply a challenge or stressor to either induce a fast response in mental and/or emotional state[33,34], or more chronic responses such as burden or stress associated with clinical depression, post traumatic syndromes, burn-out, anxiety, or adverse social-economic circumstances. These conditions do not only cause responses on behavioral, cognitive, and emotional levels, but have also been proven to induce significant physiological and endocrine reactions[35,36,37]. Due to exposure frequency and severity these responses may cause permanent changes over time[38,39,40]. Such changes may lead to either a new homeostatic balance, though more commonly to subtle though significant long term health risks[41,42]. The ability to adapt to new or even (initially) adverse circumstances might be a sophisticated interplay between diverse psychophysiological domains, that can either support each other under pressure and as such build up overall resilience, or getting one derailed after the other with neither reaching a satisfactory (adapted) state of homeostasis. This may over time cause a palate of a-typical somatic and psychological symptoms that are (at least from a western perspective) hard to capture within a single (medical) diagnosis.

Therefore, it is recognized that, to predict the response of an individual to certain stressors or adversity a comprehensive assessment of resiliency is needed[43]. This assessment should ideally include measurements of the subjects as well as measurements of his/her environment at multiple levels or organization as well as over the course of a period of time. In Figure 3 the 'Life's complexity pyramid' as introduced by Oltvai et al.[44] is used to illustrate levels of organization of the living system. In the lower part are genes, proteins, molecules which can be measured using modern -omics techniques such as genomics, proteomics and metabolomics. These techniques are also used to study the gut microbiome which is essential for understanding interactions with the environment[45]. It is more difficult to understand the relationships between the measured molecules. Bioinformatics helps to elucidate these relationships and has resulted in an improved understanding of biological pathways and regulatory mechanisms[46]. Going a level up in the organization, systems such as the immune system, the nervous system and the endocrine system can be measured. The large scale organization of the system is the most elusive and is partly captured by techniques such as heart rate variability[47], electroencephalogram measurements, ultra weak photon emission measurements[48], dynamic metabolomics analysis[49] and psychometric measurements such as stress, mood and temper, mental state, or resilience questionnaires. Such techniques that allow measurements in time are essential to capture the behavior of various dynamical systems and the interplay between those in response to certain stressors[50,51,52]. The integration of measurements of several levels of organization can then be used for a comprehensive assessment of resilience in certain particular situations. Several techniques will be explored in more detail in the next sections.

Western science is very good at measuring molecules and has followed a bottom up approach with regard to this pyramid of life. Elucidating higher levels of system self-organization has proven to be difficult by studying genes, proteins and metabolites. Knowledge of health and maintaining health is very limited compared to the knowledge that is gained about the molecular basis of diseases. Health promotion is only recently gaining attention as a research topic[53,54]. Chinese medicine on the contrary has evolved as a top down approach, a phenomenological approach based on the organization and dynamics of symptom patterns[29]. Interesting question that yet remains unanswered is if, and in what way, the (combination of) symptoms associated with long term allostatic disturbances mimic the diagnostic criteria within Chinese medicine. We envision that bridging both approaches, a middle-out approach, will result in an enormous boost in understanding resilience, wellness, health and the means to promote health and resilience[29,55,56]. Novel modeling approaches will play a key role in combining Chinese and Western concepts and integrating different types of data.

2.1 Measuring metabolic flexibility

Metabolic flexibility is defined as the capacity for the organism to adapt fuel oxidation to fuel availability[57]. Physical and mental activity patterns change over the day and this requires various amounts of fuel for particular organ systems at particular periods of time. Food intake also varies over the day requiring storage of fuel after meals and mobilization of fuel during fasting. Reduced capacity of the organism to deal with food intake can over time lead to chronic conditions such as obesity, metabolic syndrome and eventually to more severe conditions such as diabetes type 2.

Metabolic flexibility is commonly assessed by evaluating the response to metabolic challenges such as a glucose or fat load. An oral glucose tolerance test (OGTT) is usually performed by taking 75 grams of D-glucose after overnight fasting[58]. The dynamics of the response of plasma metabolites and insulin on the OGTT is then measured at various time points to reveal the flexibility of an individual to switch

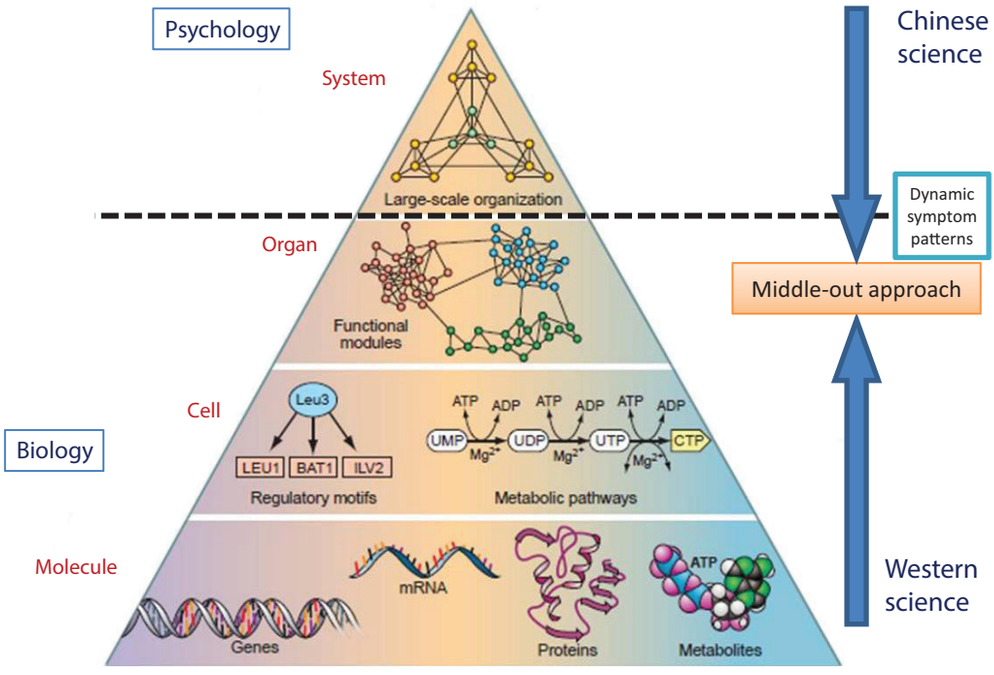

Figure 3. A representation of levels of system organization, techniques to measure these levels of organization and the convergence of Chinese and Western science. Western medicine usually takes a bottom up approach, building knowledge from molecules to pathways. Chinese medicine in contrast takes a top down approach by describing processes and changes in patterns of relationships. A middle-out approach towards health is envisioned where Chinese science and Western science meet. Adapted from Oltvai et al, Science 298 (2002), p 763.

from a catabolic to an anabolic state. To evaluate fatty acid oxidation, a high dose fat challenge is mainly used[59]. Staying closer to daily life situations the response to less standardized challenges such as a mixed meal challenge are used as well[60].

A number of processes have been identified in the literature that are stimulated or inhibited by such metabolic challenges. In summary, the identified processes are related to 1) brain, including gut-brain signaling and endocrine responses, 2) gut, 3) adipose tissue, 4) kidney function, 5) vascular health, 6) muscle function, 7) liver, and 8) pancreas. The various metabolic challenges affect different sets of these processes, depending also on the health situation of the subject. Many changes in the response to challenges have been reported in impaired health situations such as overweight and diabetes type 2[61,62,63]. Additionally, changes in response have also been reported during nutritional interventions[64,65]. Monitoring changes in response to nutritional challenges therefore allows the detection of early deviations from the healthy situation. What is usually not measured in such studies is the effects of metabolic challenges on psychological parameters.

2.2 Measuring psychological and mental resilience

An evolutionary perspective on individual differences in stress reactivity, anxiety related personality phenotypes and associated psychophysiological phenomena is essential for understanding differences in mental resilience, and the relevance of this inter-individual variation for the survival of the human species[66,67]. This variation becomes very overt in for instance soldiers on a mission, whose positive and negative consequences of individual differences in 'proneness' for stress (coolness and accurateness under pressure, i.e. under fire, versus sensitivity to develop post traumatic symptoms) are observed. Low stress reactive people are able to thrive in many circumstances[67], similar to the ability of dandelions to grow in many types of soil, levels of moisture and amounts of sunlight. High stress reactive people are more like orchids which show exceptional beauty only when highly specific growth conditions are met. Although the high reactive phenotype shows more health problems and diseases in adverse circumstances, in nurturing and safe environments this phenotype shows less health problems than the low reactive phenotype. The two phenotypes have been suggested to coexist and develop as a reaction to either a high stress environment in early childhood or a moderate stress environment. Knowing the stress reactivity phenotype of people might therefore be predictive of poor health outcomes after military operations in a hostile environment.

According to Del Guidice et al.[67] the phenotypical variety in the human stress response system might be reflected in four prototypical response patterns that are each highly sensitive for developmental influences, i.e. are in a constant state of adaption and re-calibration through sequential developmental stages. This leads to the Adaptive Calibration Model (ACM), an evolutionary–developmental theory of individual differences in the functioning of the stress response system. It basically underlines the complex dynamics underlying

physiological needs and urges, emotion regulation and behavior that includes among other competitive risk behaviors, learning, attachment and specific coping styles. It stresses once again that humanoid 'resilience' may be reflected in subtle signals in a wide variety of parameters associated with cardiovascular control mechanisms (e.g specific Heart Rate Variability components), metabolic needs (diet), endocrine functions (disturbed HPA-axis functioning), emotional states (mood disturbances and exaggerated feelings), cognitive performance (e.g. concentration, motoric functioning and working memory); motivation (lack of inspiration and drive) and coping styles, to overt behaviors and statements.

Practically speaking assessments could incorporate among others, either one or more of the following: physiological responses to stress (e.g. heart rate and specific derivatives, skin conductance responses); hormonal disturbance and response to a direct psycho-social stressor (e.g. cortisol measurements in saliva); cognitive tasks (e.g. Stroop task, Vig Track, N-beck); self-reports (e.g. by means of validated questionnaires) on experienced emotional states (e.g. Anxiety, aggression, others), coping styles (e.g. proactive, reactive), motivation, mind-set; and behavioral observations. Investigating any of these requires specific expertise, skills, and methodology, which means that to capture the integrative nature of 'resilience' it fundamentally requires the combination of multiple assessment strategies and methodologies.

2.3 Measuring self-organization

Self-organization in the living system might be measured on different levels. One level is the synchronization or coherence between physiological systems or processes such as heart rhythm, respiration, electroencephalography (EEG) and blood pressure. Another level is the coherence of ultra-weak photon emission (UPE) across body parts and changes in patterns of UPE parameters in response to perturbations of the system. This type of measurements might reveal information related to particular domains of resilience.

Spontaneous UPE levels of the hands and other parts of the body have been found to show a diurnal pattern which is low during the day and rises during the evening[68]. UPE levels were also found to be higher on average in the summer than in the other seasons with a stronger effect on the dorsal side of the hand than the palmar side[69]. UPE might therefore be an interesting non-invasive method to detect changes in rhythmicity. Additionally, changes in the symmetry of UPE intensity between the right and left hand have been reported in hemiparesis patients[70], and subjects suffering from a common cold[71]. Changes in symmetry between left and right hand UPE measurements have been found to decrease due to acupuncture treatment[70].

A number of properties can be derived from the UPE signal that reveal additional information, such as skewness, kurtosis, and fractal properties such as squeezed state parameters[72] and the Fano Factor (variance divided by the mean)[73]. Differences in Fano Factor properties between individuals have been reported that are not correlated with intensity[74]. Individual differences in squeezed state parameters were found as well as differences between meditators and non-meditators[75]. These findings indicate that the various UPE signal properties might reveal different aspects of system organization and allow measurement of changes of this organization[76]. UPE together with other physiological measurements may be a unique set of measures of self-organization.

3 Modeling resiliency

A systems view on resilience must take into account many interactions and feedback loops. Obviously, this leads to a network of interacting mechanisms which cannot be understood by human intuition alone. Therefore, computer simulation based on mathematical modeling is an indispensable tool to deal with this complexity. However, it is not easy to design models including biological, psychological, and social factors related to resilience because the relationships between the domains are less well understood. Semi-quantitative causal loop diagrams have been found to be very promising for interdisciplinary model building[77]. This approach allows for a categorical estimation of the strengths and speeds of relationships between variables, which corresponds very nicely with expert experience. Morris et al. used the causal loop diagram approach to generate a better understanding of stress and especially the relationships between the 'fussy' human behavioral factors involved[78]. The resulting model was used to simulate human behavior, leading to new hypotheses for further testing. Another example concerns the modelling of social forces related to diabetes using a similar approach[79]. One of the benefits of this model is the elucidation of feedback and reinforcing mechanisms, which are important mechanisms for stabilizing or destabilizing a system. Causal loop diagrams can be constructed together with stakeholders and used to discuss health care issues and possible changes. Homer et al. applied such a systems dynamics approach to organize care for chronically ill people within a community[80].

These examples are promising for using the same methodology to integrate Western and Eastern thinking about health and resilience. A model could be designed describing relationships between physiological variables, which are also used for diagnosis in Chinese Medicine. Such a model can be extended with a set of variables that describe certain health aspects from a Chinese perspective, once metrics for these variables have been defined e.g. based on a set of equations or rules. Simulations for a number of well-chosen conditions can then be used to display side-by-side the effects of these conditions on Western and Chinese indicators of health. This could provide mutual understanding and a common ground for discussions and exchange of knowledge between Western and Chinese oriented experts.

One issue that needs to be addressed is the design of datasets containing both clinical data as well as TCM diagnostic data. Several studies have been conducted in which TCM symptom patterns have been compared with gene expression and metabolomics datasets using integrated multivariate data

analysis methods. For instance, the group of Li studied the relationships between Cold syndrome and gene expression profiles, and found a clear relationship with energy metabolism[81]. Cold and Heat pattern information was also collected in several rheumatoid arthritis patient cohorts, and correlated with metabolomics and clinical chemistry profiles[82,83]. Very interesting correlations between traditional tongue diagnosis and tongue coating microbiome profiles were found, including sets of enriched microbiota in Cold and Heat syndrome patients[84]. Urine metabolomics profiles of metabolic syndrome patients have been correlated to specific TCM syndrome patterns[85]. These studies are all based on multivariate statistical approaches, not dynamic causal loop based models, and based on relatively small numbers of subjects. Therefore, there is a great need to collect more substantial datasets.

A full combined Eastern Western dynamic causal loop model has not been constructed yet. Figure 4 shows a first step in the direction of such a combined resilience model. This prototype systems health model describes various aspects of health, including glucose metabolism, mental stress and inflammation. The inputs of the model are factors related to lifestyle, such as food intake, exercise and sleep. This model was built in Marvelous, a modeling tool that combines a relatively simple representation of the system of interest[86] with an easy-to-use

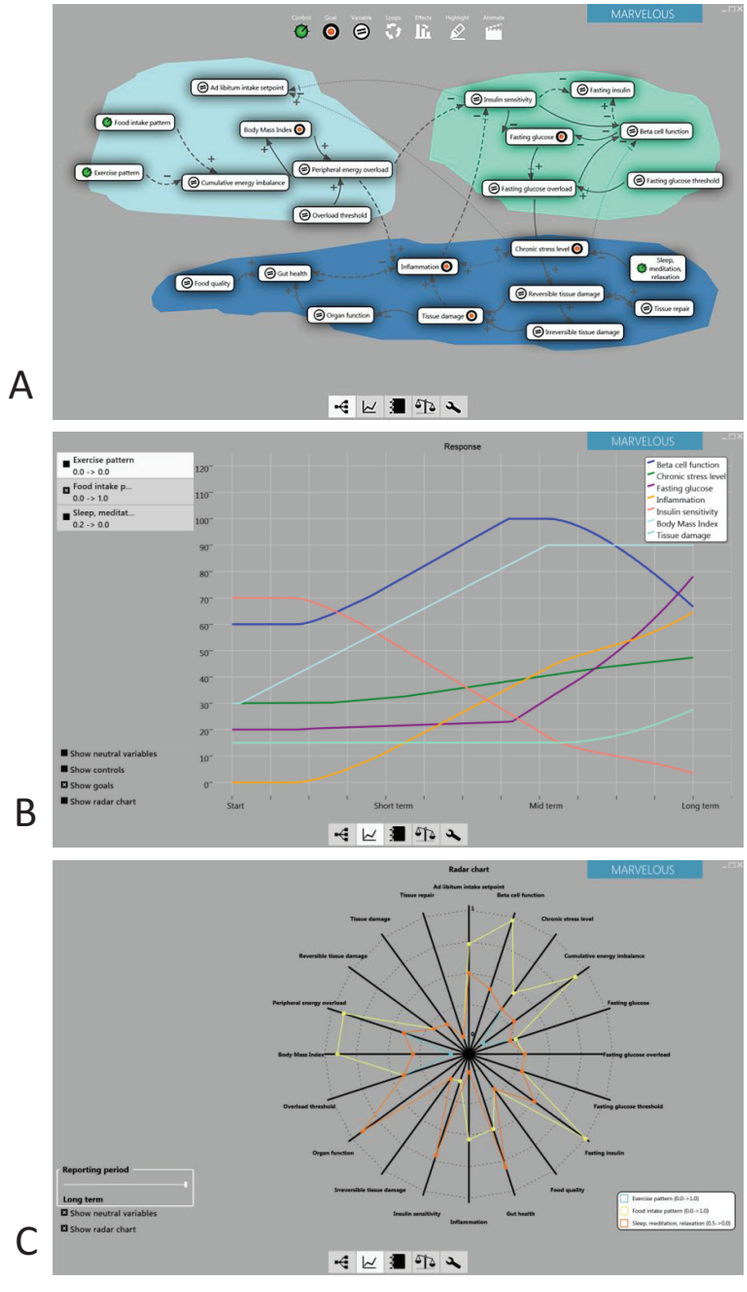

Figure 4. Prototype systems health model built in Marvelous. Panel A shows the variables and their interactions (shapes of arrows indicate strengths and speeds or interactions). Panel B shows a simulation of the dynamics in which cumulative overfeeding leads to the onset of Type 2 Diabetes. The radar chart in Panel C provides an alternative visualization of cause-effect relationships derived from simulation results.

user interface. The variables, relationships between the variables, the strengths and speeds of those relationships were determined by extensive literature search and expert judgment[87]. The model covers a time span of 6 years. The interface allows the use of a touch table in interactive discussion sessions with domain experts and stakeholders. Although a simple representation has some drawbacks, it also has a number of clear advantages: it can intuitively be understood by people who are not familiar with modeling and it allows fast simulation of the effects of changes in input variables, allowing for vivid interaction with the experts. Panel A of Figure 4 shows the variables and their interactions (shapes of arrows indicate strengths and speeds or interactions). The simulation view in Panel B shows the dynamics of a simulation in which cumulative overfeeding leads to the onset of Type 2 Diabetes. The radar chart in Panel C provides an alternative visualization of cause-effect relationships derived from simulation results. Such alternative visualizations may be preferred by certain experts or stakeholders. This type of semi-quantitative modeling and simulation can provide a common ground for discussions amongst experts from different disciplines and can be used for the generation of new hypotheses[86].

4 Discussion

A number of challenges for modeling resilience of dynamic systems need to be addressed. First of all resilience seems to be very personal, making it hard to compare resilience objectively between subjects. Resilience depends to a large extent on the environment. The environment or situations that someone wants to operate in will determine what types of resilience are needed. Furthermore, while generic resilience training programs will be successful to a certain extent, there is no one-size-fits-all approach possible to reach an optimal resilience for each individual. Also the modeling of resilience will need a personalized modeling approach.

Another important aspect is chronobiology, the dependence of the system and it's organization on a variety of rhythms[86]. These rhythms include environmental natural rhythms such as seasons and day-night cycles, but also rhythms inside of the body for instance of hormone levels[88]. Measuring resilience should therefore include longitudinal data sampling. Chinese medicine and ultra-weak photon emission can provide new insights in the internal rhythms of the body and the connection with natural rhythms.

Chinese symptom patterns may overcome the body-mind split in Western medicine which is absent in Chinese medicine (a middle-out approach). Bringing body and mind together again is highly necessary to move the current health care system towards prevention and health promotion. Chinese body-mind movement arts such as Tai Chi have shown health benefits in many areas, ranging from fibromyalgia[89] and Parkinson[90] to cognitive function in elderly[89]. Another benefit of a middle-out approach is the combination of health promotion strategies from Chinese medicine with Western disease fighting strategies. For instance in many hospitals Chinese herbal medicine is used to reduce fatigue and nausea during chemotherapy treatment, which greatly improves the quality of life of the patient[91].

Finally, it will be a challenge to combine various types of data from different scientific disciplines to develop a comprehensive understanding of aspects of resilience. New modeling approaches will be required to connect data captured at different time scales, from different processes (e.g molecular, societal) and at different levels of detail (e.g amount of molecules versus amounts of happiness). A workflow for generating resiliency monitoring and feedback tools is envisioned in figure 5. Applications resulting from

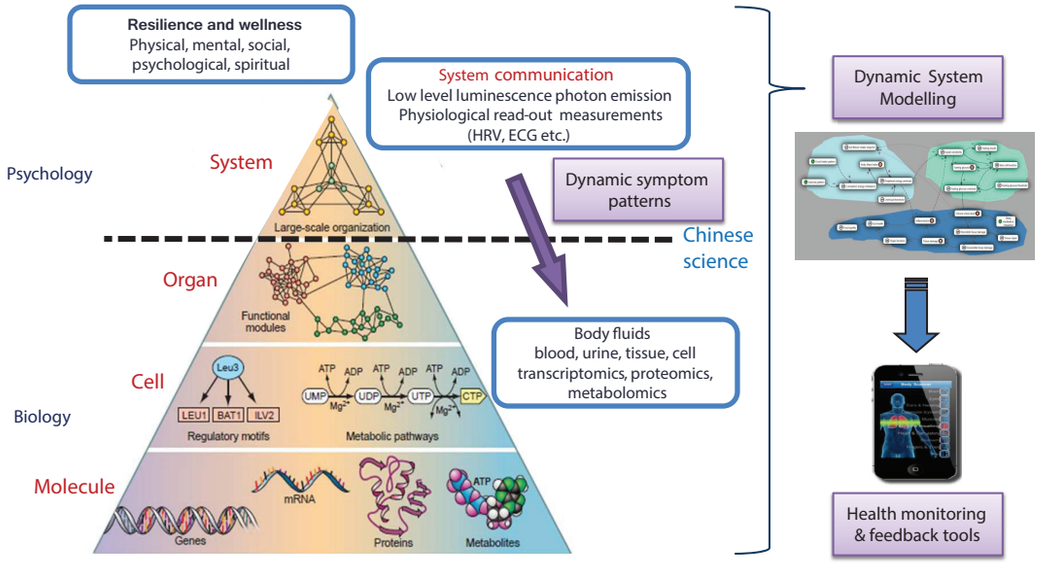

Figure 5. Workflow for the development of resilience monitoring and feedback tools. Ideally measurements from various levels of system organization are conducted, including physical, mental, social, psychological and spiritual measurements. Dynamic symptom patterns based on Chinese medicine offer options for bringing psychology and biology together again. Models built from the relationships between the measurements can be used to predict the efficacy of interventions and offer personalized health advice. (partly adapted from Oltvai et al, Science 298 (2002), p 763)

measuring and modeling the interactions between the various system readouts allow the possibility to develop personalized resiliency and wellness coaching and support programs.

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Conflict of interest

The authors declare that there are no conflicts of interest.

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