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Toward holistic medicine and holistic biology: life sciences after precision medicine and systems biology

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Toward holistic medicine and holistic biology: life sciences after precision medicine and systems biology

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ABSTRACT

In the field of life sciences, systems biology has encountered insurmountable obstacles caused by the complexity and adaptability of organisms. In the near future, precision medicine is expected to establish a personalized state-description system and a corresponding targeted-treatment system, but the comprehensive treatment of disease will remain a significant and difficult problem that needs to be resolved. As the holistic modeling method in complexity science matures and its concordance with traditional Chinese medicine (TCM) methods is increasingly revealed, the introduction of this method into the life sciences will become a necessity for scientific development. The incorporation of this method in the fields of biology and medicine will lead to the emergence of 'holistic biology' and 'holistic medicine'. Holistic medicine is a personalized medicine system that incorporates TCM's holistic concept and treatment approaches based on syndrome differentiation. Holistic medicine fundamentally solves the problem of complex life system integration and transforms adaptability from an obstacle for understanding organisms into an indispensable tool for more effective regulation and control of organisms. As a result, systems biology and precision medicine will be followed by an era of holistic medicine and holistic biology.

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Traditional Chinese medicine (TCM) textbooks describe two fundamental characteristics of this ancient approach to medicine: the concept of holism and syndrome differentiation-based treatment. The former refers to the human body, human beings and the natural world as a single, mutually connected, mutually influential and indivisible whole. The latter incorporates a description of the basic features of clinical diagnosis and treatment in TCM, in which a patient's pathological state is identified according to observable symptoms and signs, enabling the creation of a personalized treatment plan for each patient.

Biology and medicine, which were separated from ancient empirical medicine 300 years ago, have established their enormous knowledge system by breaking down and analyzing the human body. Today, through studies of organs, tissues, cells and ultimately molecules, the understanding of complex life has reached the most basic compositional level. Unfortunately, many internal laws of the human body remain poorly understood. Faced with many serious diseases that endanger health and life, humans remain helpless. The vibrant life phenomena that cannot be understood at the macrolevel lose even more of their holistic appearance when viewed at the microlevel, and thus, the essence of these phenomena becomes more difficult to understand. In this context, scientists are gradually becoming aware of the fact that life cannot be simply reduced to interactions between cells, molecules or atoms. The reductionist approach, which breaks down life into its constituent units, should not be regarded as the sole viable research approach for revealing the essential mysteries of life.

Systems biology, a field that has been steadily growing since the 1970s, began with a simple idea, i.e. 'the organism as a whole.' In recent years, precision medicine, which emerged due to advancements in genetics, has begun an era of personalized medicine in which patients receive different treatment plans based on their individual characteristics. The beliefs that 'the organism is a whole' and 'treatment plans should be tailored to the individual characteristics of patients' match perfectly the intrinsic meanings of the 'concept of holism' and 'syndrome differentiation-based

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treatment' in TCM. Obviously, modern biology and modern medicine appear to have begun the process of returning to TCM methodology.

However, in recent years, systems biology appears to have encountered insurmountable obstacles due to the complexity and adaptability of organisms. In the near future, the development of precision medicine is expected to establish a personalized state-description system as well as a corresponding targeted-treatment system, but the comprehensive treatment of diseases will still face the difficulties of integration. How will research in biology and medicine begin the process of integration? What type of insight will TCM, which has created countless amazing medical miracles throughout its development for thousands of years, provide for the development of life sciences today?

Precision medicine: the beginning of an era of personalized medicine

Personalized medicine refers to a medical application in which treatment plans are tailored according to the individual characteristics of patients and therefore, cannot be implemented without a system through which the individual features of patients can be described (i.e. a state-description system). TCM can be classified as a personalized medicine system because its treatment system is based on syndrome differentiation and because it is a state-description and control system that is capable of depicting the individual pathological features of patients.

The precision medicine project was first proposed by U.S. academics, leading the world in science and modern medicine. In the U.S. precision medicine program, precision medicine refers to the customization of treatment plans to the individual characteristics of each patient (Timmerman 2013). As a result, personalized medicine, which was previously only a conceptual medical model, has gained practical significance in modern medicine.

In natural science, the common approach to the establishment of a state-description system is to introduce, select and optimize a complete set of independent state variables through empirical or statistical analysis and determine any correlations among these variables. Through this approach, a wide variety of individual states can be described completely and accurately. Currently, the following two advances in precision medicine deserve attention:

(1) The discovery of clinically significant biomarkers and corresponding targeted drugs.
These studies not only provide new methods for the detection and treatment of related diseases but also contribute to the accumulation of indicators that can be used to describe individualized health states.
In recent years, the U.S. Food and Drug Administration (FDA) classified innovative clinical experimentation on precision cancer medicines into two categories. The first category is called the 'basket trial,' in which cancers of different origins with the same target gene are studied in the same basket. This classification facilitates research on drugs for different tumors with the same target genes. The second category is known as the 'umbrella trial,' in which the same disease with different target genes (e.g. lung cancer) is studied under the same umbrella. The objective of this type of study is to detect different target genes in the same process and then assign different targeted drugs according to the target gene (West 2017). For those with some basic knowledge of TCM, it is obvious that basket and umbrella trials are in fact variations of the concepts in TCM of treating different diseases with the same drug or treating the same disease with different drugs. The similarities and differences in treatment methods are precisely based on the similarities and differences in the state of the body under the new state-description system. Obviously, with the addition of the biological target system, which differs from the disease-classification system, an entirely novel health state-description system and a corresponding disease-treatment system are being gradually constructed in precision medicine.
In May 2017, the U.S. FDA issued a decisive message licensing the use of KEYTRUDA (pembrolizumab) from MSD for the treatment of solid tumors in patients diagnosed with microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) cancers. MSI-H and dMMR are two common genetic anomalies. In tumors containing these two variations, the cells' DNA restoration mechanism is too damaged to operate normally. Tumors with these anomalies can occur in many parts of the body, such as the colon, rectum, endometrium, breasts, prostate, bladder, and thyroid. Therefore, differentiating among these

cancers according to genetic mutation features rather than the disease site has proven to be more significant for guiding treatment in clinical trials. Previously, the FDA had insisted on granting licenses for cancer therapies based on the source of cancer in the body (e.g. lung or breast cancer). KEYTRUDA is the first FDA-approved anticancer therapy distinguished by a biological marker rather than the tumor source and thus constitutes a major landmark in the history of medicine (FDA News Release 2017).

In the long term, the importance of this landmark event will not be limited to the classification and treatment of cancer; more importantly, a new evaluation method has been established. The evaluation of efficacy based on this method might lead to the emergence of a new state-description system in modern medicine that will rank alongside the disease-classification system. The new system uses biomarkers to describe disease states. Its relationship with the disease-classification system of modern medicine is similar to the relationship between the disease and syndrome systems in TCM. In other words, a human body state-recognition and treatment system similar to the TCM treatment system based on syndrome differentiation will soon emerge under the framework of modern medicine. As a result, modern medicine will enter an era of personalized medicine combined with disease medicine.

(2) The 'All of Us Research Program' advanced vigorously by the U.S. government constitutes the first systematic study aimed at developing a personalized state-description system.

In the 'All of Us Research Program,' biological marker data (e.g. the number of cells, proteins, metabolites, RNA, DNA, and the complete gene sequence), behavioral data and electronic health records are collected from participants (Collins and Varmus 2015). Through statistical analyses of datasets with large numbers of samples, a set of meaningful and measurable indicators of human health states can be selected as state variables by assessing the correlations between various measurable indicators and diseases. The state variable system can then be continuously optimized through statistical analyses of the correlations among various measurable indicators, and the relationships among state variables can be determined.

As an attempt to explore personalized medicine, 'the All of Us Research Program seeks to extend precision medicine to all diseases by building a national research cohort of one million or more U.S. participants' (National Institutes of Health 2016). However, to ensure that the collected cases cover all identifiable states of the human body and that the cases for each identifiable state reach a basic number required by statistics, one million volunteers is far from a sufficient quantity. Consequently, ensuring the completeness of the established biomarker system for describing human health statuses is difficult. Second, the statistical analysis methods needed to analyze such a massive amount of health data are still in the exploratory stages and have not been designed in accordance with the requirements for constructing a complete and independent state-description system. However, with the completion of the plan, the explored method in the plan is expected to be able to be expanded to a wider collection of clinical records. With the accumulation of medical records based on the standardized health information-collection method and continuous improvements in the statistical analysis methods used in the research process, an evidence-based personalized state-description system can be expected to be established.

The advent of precision medicine has brought practical significance to personalized medicine under the modern medical architecture. With the rapid expansion of clinically significant biomarker systems and with more in-depth research on the correlations between biomarkers and human diseases, a new medical system under the framework of modern medicine in which the characteristics of human diseases will be described with biomarkers will emerge and gradually mature in the near future. In contrast to the previous medicine system based on disease classification, the identification and control of human health states in the new system will be based on states described by biomarkers and will therefore be called a state medicine system under the framework of modern medicine.

State medicine is a scientific term for personalized medicine. Here, according to the general method for establishing the state description of a research subject in the field of natural sciences and considering the role that the state-description system can play, we introduce the following definition of state medicine: state medicine establishes a human health state-description system by introducing a set of state variables that are sufficiently complete and relatively independent to realize the accurate identification and regulation of human disease states. With this system, the laws of evolution of the state of the human body during the progression of a disease can be studied more effectively to predict disease occurrence, development, and prognosis and to optimize the control plan and regulation route (Yuan 2017).

With the establishment of a personalized description system for precision medicine, modern medicine will enter an era in which state medicine is mainstream and disease medicine is supplemental. This transition constitutes the first wave of modern medicine's return to TCM, marked by the current rise in precision medicine. The next wave of the return of modern medicine to TCM will focus on the holistic concept of TCM and will occur when the holistic method is introduced into the modern medical system. The shock wave will affect not only modern medicine but also areas on the frontier of modern biology. It will fundamentally eliminate the dilemma caused by the complexity and adaptability of life systems in systems biology research and radically change the mainstream methodologies with which life is studied in modern science.

Complexity and adaptability: the difficulties that life sciences must face on the Road to holism

Progress in precision medicine will undoubtedly be accompanied by remarkable advances in medical testing and the diagnosis and treatment of disease. Currently, precision medicine's targeted drug system based on biomarkers is expanding rapidly. Human genome studies have revealed that the number of protein-coding genes in the human body is approximately 19,000 (Ezkurdia et al. 2014), and the number of types of genetic mutations in the real population is much larger. Today's scientists also clearly understand that the occurrence and development of human diseases cannot be completely determined by genes; proteins, metabolites, and daily human behaviors also play an important role in this process. Compared to massive genetic mutations, abnormalities of proteins and metabolites will constitute a much larger system that must be confronted. Who today can answer the following question: how many targeted drugs do humans need to effectively address all diseases associated with abnormal biomarkers?

Recent advances in precision medicine have revealed that in many disease processes, personalization is not marked by a single genetic variation. Instead, in many cases, certain types of diseases are associated with more than one gene or with a combination of genetic variations (Schwaederle et al. 2015). Therefore, research on targeted drugs based on genetic mutations should focus not only on mutations of single genes but also on combinations of genetic mutations. In other words, different combinations of genetic mutations sometimes require different targeted drugs. Obviously, with the development of personalized medicine in the modern medical system, we will have to face a targeted drug system that is more extensive than today's drug system based on disease medicine. Will such a large targeted drug system enable us to address various diseases easily and effectively?

Current medical research, whether focused on disease or abnormal biomarkers during the course of disease, is performed within separate categories. The occurrence of human disease is often accompanied by abnormalities in the structure and function of multiple tissues and organs, which manifest as abnormal changes in numerous biomarkers. In response to the need for clinical treatment, doctors often have to consider the comprehensive application of drugs that target multiple diseases (or multiple abnormal biomarkers) simultaneously.

Two papers published in *Nature* and *New England Journal of Medicine* in September 2016 received considerable attention from the medical community. The authors summarized the clinical results of personalized treatments for some tumor cases, which was followed by pessimistic comments (Drew 2016; Tannock and Hickman 2016). Obviously, these drugs targeted against biomarkers were far less effective than expected. Even if highly effective drugs for each single biomarker are found, can we imagine the consequences of administering multiple targeted drugs simultaneously to patients with multiple biomarker abnormalities?

The human body is extremely complex. The course of a disease is characterized by extensive networks of interactions among different parts. When a drug enters the body, its effect is usually not limited to the intended target, and a variety of different targeted drugs entering the body at the same time might result in alterations in the composition and efficacy of the drugs due to chemical reactions among them. Different drug combinations or dosage ratios might also exert different synergistic or antagonistic effects in the human body. Obviously, the personalized medicine system that is gradually being developed under the banner of precision medicine is still unable to address a series of problems caused by the complexity of the human body and disease; thus, its practical contribution to medical progress will be very limited.

Organismal complexity is a puzzle not only for modern medicine but also for modern biology, which underpins modern medicine. As the vanguard of modern biology, systems biology is a new area of research on complex biosystems that emerged with the development of systems science in the past few decades. Systems biology focuses on complex interactions within biological systems and studies them through a holistic approach.

The main methods used in systems biology research are experimental methods and mathematical modeling methods. Experimental methods focus on understanding a system through repeated controllable experiments. Mathematical modeling methods involve establishing dynamic models based on the internal mechanisms of a system, quantitatively describing the interactions among various elements of the system, and then predicting the system's dynamic evolution. Recent studies have exhibited a tendency to combine the two methods such that the mathematical modeling method is dominant, while controlled experiments and statistical observations are used as the basis for verifying and perfecting the model. The most prominent characteristic of systems biology is integration. Systems biology seeks not only to integrate the different elements of a system (e.g. DNA, mRNA, protein, biological small molecules) together during research but also, more importantly, to realize integration at all levels, from genes to cells, organs, tissues, and even the whole body.

However, after over 30 years of research on the integration of living organisms, systems biology has shown helplessness in the face of the complexity of life rather than wonderful prospects for integration. This situation stems from two basic characteristics of biological systems: complexity and adaptability.

Because of their large number and variety, molecular-level biomarkers are already difficult for people to handle, and there are still complex relationships among various parts of the biological system from the molecular level to the organismal level. In the face of reality, system biologists have pessimistically lamented that the complexity of an organism is far beyond the imagination; thus, current science and technology are far from sufficient for studying the entire organism and are capable of studying only some parts or some chains of organisms.

Although systems biology uses a kinetic modeling approach to quantitatively describe the evolution of a system, its basic idea does not extend beyond the limitation of 'refactoring systems based on analysis'; thus, systems biology remains essentially a reductionistic approach. The difference is that traditional biology applies a reduction analysis, while systems biology focuses on analysis-based reconstruction (Yuan 2016). The 'analysis-reconstruction' cognitive method was commonly used in the early stage of systems science in the 1970s. This method is effective for simple systems and even simple giant systems but was found to be quite insufficient after systems science clarified the problems of simple systems and gradually ventured into complicated systems (Dongchuan and Fuyong 2004). While perplexed by organism complexity, systems biologists find it more challenging to address the inherent adaptation of organisms. In experimental science, a new discovery earns recognition if other scientists can repeat it in the same way. Even an unexpected but important discovery will be reduced to an accidental, unmeaningful event if it cannot be validated through repeated experiments.

Repeatability is the basic principle of natural science research. Theoretically, any successful scientific experiment can be repeated by different researchers. This phenomenon refers to the objectivity of science. The focus of science is not an accidental phenomena but rather universal laws independent of time, space and human error. It is precisely for this reason that the laws of science are objective and predictable.

Adaptability refers to a phenomenon in which the response to a stimulus changes due to the continuous or repeated action of the stimulus. Adaptability is a major feature that distinguishes living systems from nonliving systems. However, due to this characteristic of organisms, when we repeat experiments under the long-standing and widely held belief of reproducibility, the strict reproducibility of experimental results becomes an 'extravagant' claim. In experimental methods in systems biology, the most important research means is interference. Advances in systems biology are mostly attributable to constant progress in the means of interfering with biological systems. The adaptability of organisms greatly weakens the repeatability of the responses of experimental subjects to interference. However, quantitative analyses and calculation of interferences and responses are important foundations for systems biology modeling and for the analysis and integration of system behaviors. It is clear that the scientific principles established by centuries of development in simplicity science appear to be challenged by highly adaptive and complicated life systems. Continued adherence to the traditional principle of reproducibility will make it difficult to identify strict scientific laws for adaptive biological systems. Without reproducibility, how can the regularity of scientific discoveries be confirmed?

As an inherent feature of living organisms granted by nature, adaptability is an objective reality. The problem can only be attributed to the way current science is used. In other words, existing systems biology research methods might be essentially unsuitable for studying complex and adaptive life.

It is possible that systems biology can still achieve significant scientific discoveries and applications based on previous integration methods, just as traditional molecular biology, cell biology, and analytical medicine have not yet reached the limits of their development. However, to achieve the original goal of integrating all parts of an organism into a whole and to effectively confirm the regularity of scientific discoveries regarding complex adaptive systems, new methodologies and evaluation principles may be needed.

Both precision medicine, as the vanguard of medicine, and systems biology, as the vanguard of biology, face the same obstacles and crises as they develop. Overcoming these obstacles and escaping these crises will trigger another revolution in the medical field. This revolution will not be confined to medicine but will extend to the wider fields of biology and the life sciences.

Toward integration: two personalized state-description systems with different levels

The study of real systems using systems science methods has already surpassed the point of simple systems and simple giant systems and has begun to face complexity directly. Systems theory, cybernetics, and information theory, as well as more recently developed theories, such as dissipative structure theory, catastrophe theory, and synergetics, have gradually converged to form today's complexity science. In the face of the complexities of living organisms and with revelations of emergent phenomena and laws of complex systems, complexity science has not only abandoned the traditional reductionistic approach but also fundamentally negated the integrative approach of 'reconstruction based on analysis.'

In complexity research, the most important concept introduced by scientists is 'emergence.' The emergence of new properties is the chief characteristic of complex systems. Combining different elements into an organic system will inevitably bring forth new properties not found in a single element. The method of simply accumulating an understanding of each part of the organism is essentially unsuitable for describing holistic emergence. The more complex the system, the less effective this approach is for understanding and grasping the whole. Emergence is inherently unpredictable because a system's macrostructures or properties cannot be inferred from the composition and behaviors of its microlevel systems. Non-inferable and unpredictable novelty is a typical characteristic of complex systems (Xinrong 2007). The human body, as the subject of medical research, can be categorized as this type of complex system. Modern science has shown that many of the mysteries of the universe can be attributed to holistic emergence. Reductionism cannot reveal these mysteries because holistic emergence disappears after the decomposition of a system into its parts. The discovery of the characteristics and laws of the emergence of complex systems proves from another angle that it is impracticable for modern medicine and biology to try to grasp the human body as a whole through 'analysis-based integration'.

Because it is impossible to achieve an overall understanding of a complex system through reductive analysis and analysis-based integration, a complex system can be studied only as a whole and according to its true characteristics. As a result, a holistic approach that establishes functional models of a complex system through metaphors and analogies based on an investigation into the inputs and outputs of the system has emerged. This method is widely used in current research on complex systems in complexity science. Holland's echo model, which was built during the study of complex adaptive systems, succinctly reproduces how complexity emerges and adapts. Through the echo model, the complex mechanisms of how the adaptive system evolves, adapts, aggregates, competes, cooperates, and at the same time creates great diversity and novelty are clearly explained. Bak P. established the famous 'sand pile model' based on the metaphorical concept of self-organized criticality. This model has been widely used in such phenomena as solar flares, volcanic eruptions, economics, biological evolution, turbulence, and the spread of infectious diseases. It is through this simple model that Bak reveals the secrets of the evolution of complex systems. Researchers on artificial life represented by Langton also use this method to explore various models of artificial life generation and evolution when studying the complex phenomena of artificial life, such as autopropagation cellular automata, the bird group model, the ant colony model, the Tierra model, the Avida model, and 'Amoeba World'.

Today, when we look at metaphors and analogies as scientific methods and re-examine Chinese medicine with new scientific concepts brought about by complexity science, we notice that for more than 2,000 years, TCM has been using this approach to study the structure and function of the human body as well as the evolution and regulation of the state of the body during illness. The visceral manifestation theory of TCM is a human body model constructed by Chinese ancestors through metaphors and analogies after research on the body's physiological and pathological activities. The TCM treatment system based on syndrome differentiation is a state-description and regulation system based on this theoretical model (Yuan 2015). Therefore, compared with precision medicine at the forefront of modern medicine and systems biology at the forefront of modern biology, TCM possesses a more profound methodology.

In the earliest classic work of TCM, the Yellow Emperor's Internal Classic, there were descriptions of the internal organization of the human body. In the human body, there are five solid organs called 'Zang': heart, liver, spleen, lung, and kidney, and six hollow organs called 'Fu': stomach, gallbladder, large intestine, small intestine, bladder, and triple Jiao. The function of the five 'Zang' is storage of essence and Qi, and the function of the six 'Fu' is absorption and transfer of nutrients and metabolites. The meridian is the channel that connects these organs to each other and to various parts of the human body. This channel runs Qi and blood and delivers nutrients to the whole body to maintain functional activities in all parts of the body. On the basis of such a human body model, TCM introduces some state variables (called syndromes) both at the holistic level and at the Zang-Fu level to describe the functional state of the holistic body and its various parts. The values of these state variables are defined by the symptoms that the patient can feel and the signs that the doctor can observe. In TCM, the two aspects of the human body that are opposite and interdependent are expressed by Yin and Yang, such as function and matter, cold and heat, Qi and Blood, etc. Through metaphors and analogies, the relationship among Zangs and Fus are expressed by the relationship among the five basic substances: gold, wood, water, fire, and soil. For example, regarding the heart, which is one of the five Zang, TCM believes that it promotes Qi and blood to run throughout the whole body and controls a person's mental awareness and thinking. The maintenance of heart function requires sufficient Qi, blood, Yin and Yang in the heart, the smooth running of Qi and blood within the heart, and no invasive pathogenic factors such as damp heat or fiery heat. Deficiency of heart Qi, blood, Yin, or Yang; blood stasis; or external invasive pathogenic factors such as damp heat and fiery heat can lead to abnormal heart function and corresponding symptoms or signs, as shown in the following table(Yuan 2011):

Syndrome of the Heart	Main Clinical Manifestations
Deficiency of Heart Qi	Heart palpitations, shortness of breath, fatigue, sweating, pale complexion
Deficiency of Heart Blood	Heart palpitations, insomnia, dreams, dizziness, forgetfulness, pale complexion or chlorosis, pale lips
Deficiency of Heart Yin	Heart palpitations, insomnia, dreams, hot flashes, night sweats, upset, feverish sensation in the chest, palms and soles, red cheeks, dry throat, red tongue, less moss on the tongue
Deficiency of Heart Yang	Heart palpitations, shortness of breath, fatigue, cold sweat, chills, cold limbs, pale complexion
Blood stasis in the Heart	Stuffy and oppressed feeling in the heart and chest; chest pain or pain radiating to the shoulders and back, blue-purple lips and nails; brown spots or freckles on the tongue
Exuberant Heart Fire	Upset, impatient, insomnia, dreams, red face, thirst, oral or tongue ulcers, yellow urine, urinary frequency

Through thousands of years of clinical practice, TCM has developed a drug program for these syndromes, which can effectively improve the symptoms and signs of these syndromes and normalize the functional activities of the corresponding Zang-Fu.

However, when Western medicine was introduced to China and medical textbooks were translated into Chinese, various anatomical tissues and organs were hastily associated with the nouns of the human organs in TCM. Later, it was noted that the understanding of the structure and function of the human organs based on anatomy and physiology observations and experiments is quite different from the descriptions in TCM. As a result, many people have begun to doubt the scientific nature of TCM. One explanation of TCM specialists for this problem is that the TCM organs are different from the anatomical organs with the same name. For example, in TCM, the heart is not limited to the anatomical heart; rather, it includes some functions of the central nervous system. Additionally, in TCM, the spleen has little to do with the anatomical spleen; rather, it includes the functions of organ tissues such as the stomach, intestines and digestive glands of modern medicine. In recent years, with the progress of complexity science research, people began to understand the essence of the theoretical system of TCM from the scientific level: the internal organs (Zang and Fu) of TCM are not the anatomical organs of the human body, but functional models that can describe the basic life activities of the human body from the overall level. As modern medicine moves to an era of personalized medicine, people have gradually realized that establishing a state-description system based on a holistic model will lead to a personalized description and regulation of the human body, which will be a safer and more effective method than disease-based medicine.

According to the complexity science method used to establish state-description systems for other natural science fields, precision medicine will be able to describe the state of the human body holistically by establishing a personalized state-description system in the foreseeable future. To achieve this goal, the first step is to perform a correlation analysis of state variables (biomarkers) to ensure their relative independence by removing linearly-related biomarkers and gradually reducing the scale of the state variable system. Second, the completeness of the state-description system (i.e. the ability to completely describe all of the different personalized states) can be improved by expanding the scope of illnesses and by increasing the number of cases from which data are collected. A state-description system established using this method, similar to the TCM syndrome system based on the TCM theoretical model, can be classified as a personalized medicine system. Then, what is the difference between the two state-description systems? What are the respective advantages and limitations associated with the identification and treatment of human disease states?

In TCM, the body state during the course of a disease is completely captured at the organism level. The state-description system (i.e. the syndrome system) involves only holistic observations of the body's basic physiological and pathological activities, as well as sign- and symptom-based descriptions of the body's state during illness. Currently, the number of syndromes (state variables) used in TCM is approximately 100. Thus, the number of combinations of no more than five syndromes at a time will be on the order of 10 billion, which means that the total number of personalized states that the system can distinguish is more than 10 billion. In the state-description system established by precision medicine, many state variables are introduced at the microlevel. As mentioned earlier, the number of known types of genetic mutations is already very large. As the introduced biomarkers expand to proteins, metabolites, etc., the total number of state variables involved might be astronomical.

Based on analyses of the correlations of biomarkers (e.g. genetic mutations and protein anomalies) with human diseases, scientists will undoubtedly select only biomarkers with clinical significance as state variables and will quantify their clinical significance using statistical analysis methods. The state-description system can then be gradually optimized in two ways: (1) replacing some biomarkers that are difficult to detect and have less clinical significance with biomarkers that are easy to detect and have greater clinical significance (good correlation) and (2) eliminating the redundancy among biological markers arising from linear correlation. As a result, the state-description system will gradually shrink.

Currently, we cannot predict the order of magnitude of the state variables required for a complete state-description system. Even if it is reduced to the order of millions, its scale is 10,000 times larger than that of the TCM syndrome system. Obviously, the state-description system that precision medicine is expected to establish is far more sophisticated than the syndrome system of TCM.

In the clinical practice of TCM, if multiple syndromes coexist, such as qi deficiency, blood deficiency, yin deficiency, qi stagnation, and blood stasis, multiple drugs for different syndromes are usually used in combination. The side effects of herbal medicines are usually minimal and can be further weakened and controlled by the synergistic and antagonistic effects of the drugs. Therefore, for thousands of years, when Chinese doctors treated patients with herbal formulas, it was usually not necessary to conduct a trial of the combined use of these drugs in advance. Typically, the selectivity of various actions of a formula and the dose ratio of a drug were determined according to the priority of the different syndromes, and the side effects of the individual drugs in a formula were effectively restricted to optimize the overall effect of the formula.

Targeted drugs for biomarkers developed in precision medicine will also undoubtedly face the problem of combined drug use when multiple biomarkers are abnormal. Targeted drugs developed for biomarkers of clinical significance are projected to constitute an enormous system in the near future. Current research on targeted drugs has shown that each drug not only exerts effects on the targeted biomarkers but also usually has other effects, some of which might be side effects that injure the structure and function of the human body to varying degrees. Therefore, when multiple targeted drugs are used in combination according to the condition of the patient, their overall effects often become less certain. If the combined use of different drugs needs to be tested in advance to avoid unexpected interactions of such drug combinations, the required workload will be too great for science and mankind to bear.

Obviously, the state-description system based on biomarkers constructed by precision medicine is a personalized state-description system that is much more refined than that established by TCM. If patients are comprehensively tested based on this state-description system and a method similar to that of the 'All of Us Research Program,' multiple biomarker anomalies might be found in many patients. If dozens or hundreds of these biomarker abnormalities have to be treated using multiple targeted drugs with different side effects, can the possible consequences for patients be imagined?

Modern analytical studies conducted in China on TCM syndromes in recent decades have failed to clarify the essence of the syndromes, but some of the phenomena uncovered have provided beneficial inspiration for today's medical developments.

In studies of qi deficiency using modern analytical methods, scientists have noticed that qi deficiency is accompanied by a series of abnormal changes in various aspects of the human body, such as glucose and lipid metabolism, protein, DNA, and RNA synthesis, blood levels of albumin and γ-globulin, peripheral leukocyte count, phagocytic function of the reticuloendothelial system, and cellular and humoral immunity. Modern pharmacological analysis of qi-invigorating herbs has shown the following effects at the microlevel: regulation of glucose and lipid metabolism, promotion of protein, DNA, and RNA synthesis, increased albumin and γ-globulin levels, increased peripheral white blood cell levels, enhanced phagocytic function of the reticuloendothelial system, and improved cellular and humoral immunity. If multiple drugs with the abovementioned functions are administered together, can they yield an effect of qi invigoration similar to that obtained with Chinese herbs? The answer to this question, whether based on analytical research by pharmacologists or clinical practice, is no.

The state-description system that precision medicine is establishing might describe the human body to a finer degree than TCM. Undoubtedly, there will also be some disease conditions for which effective treatments can be found only after the microlevel problems have been clarified. In this case, the precise positioning and treatment of a disease target might lead to a major medical breakthrough. However, the regulatory effect of a complex system does not always improve with increases in the granularity of the state-description system. The use of state descriptions that are too fine not only increases the workload of state recognition and the complexity of regulation but also adds uncertainty to the results of regulation, weakening the ability of medicine to control the holistic health state of the human body. In fact, holistic modeling of a complex system does not blindly strive for fine granularity but rather follows the simplest applicable rule; that is, under the premise of ensuring the degree of precision required for control, the simpler the model the better (Yuan 2010). Therefore, both treatment methods based on modern medicine and personalized targeted drugs based on precision medicine are unable to achieve holistic disease regulation through integration via 'analysis reconstruction.' The movement of modern medicine and even modern biology toward holistic integration will face another wave of more profound revolutions related to methodology.

Toward holistic medicine and holistic biology

In the past few centuries, medical advances have been achieved almost in parallel with natural science. Every step forward in natural science and technology has propelled research in medicine and related fields forward. In contrast to the introduction of methods and technical means, the introduction of new scientific concepts is often accompanied by the reconstruction of a discipline's inherent knowledge system. When a new scientific concept is embraced and used to reconstruct the existing knowledge system, it is gradually established as the new pattern of thinking associated with the discipline. Methods and technical means can be introduced anytime and anywhere. However, scientific concepts often involve the structure of a theoretical system, and relative stability is required. Scientists in an applied field cannot reconstruct the knowledge system according to one concept today and another concept tomorrow.

The existing knowledge system of modern medicine was essentially constructed under the guidance of the theory of reductionism, which dominated natural science before the 1970s. As the frontier of modern biology, systems biology reconstructed traditional biology by introducing the concept of systems science in the 1980s. After more than 30 years of development, systems biology has significantly deepened our understanding of the dynamic properties of organisms. However, the complexity of the holistic study of organisms and the fatal impact of an organism's inherent adaptability on the reproducibility of experiments has caused considerable confusion. Thus, it might be time for modern biology to rebuild itself again with the introduction of new scientific ideas.

In dealing with complex systems, today's complexity science has abandoned the early 'analysis-reconstruction' approach and has begun to directly face complexity. The holistic approach has matured to allow a system's functional model to be directly constructed at the organism level based on the investigation of the inputs and outputs of the system. From a methodological perspective, this represents a return to the science of ancient holism. However, today's metaphors and analogies are no longer confined to human thinking but rather can be implemented through big data analyses, machine learning and computer simulations. Instead of being based on intuitive experience, model-based state-description is now reliant on strict statistical and empirical analyses. In the process of studying complex systems, such as ecosystems, geological systems, and social systems, complexity science usually adopts such methods to establish simulation models.

Regarding the adaptability exhibited in living organisms, some of them belong to the microlevel characteristics of the organism, and some belong to the short-term or transient characteristics of the organism. In the human body, which is an enormous, complex system with a variety of components and a multilevel structure, the model built from the holistic level can only be a fairly abstract and simplified model. The description of state variables usually focuses on macroscopic, stable states. Microscopic, short-term or instantaneous behaviors are ignored in many cases because they have no practical meaning. This means that the organism's responses to interfering stimuli are usually macroscopic and relatively stable average responses that include adaptation; and the patient's responses to treatment interventions are also usually comprehensive effects that include adaptation.

Studies in complexity science have shown that living organisms are inherently self-organizing, self-adaptive, and self-regulating. The interaction of various parts of the organism always pushes the state of the system toward a certain steady-state balance. This property of organisms to always seek a steady-state balance is precisely the cause of adaptability. It is because of this self-regulation and self-adaptation of the human body that therapeutic interventions often only need to have the effect of pushing the state of the system toward a steady-state balance. Even if the effect is less precise in terms of direction and strength, the state of the system also often tends toward a certain steady-state balance under the action of this 'automatic seek' mechanism. When the system is in a certain steady-state balance, even if we consciously move its state away from the steady point, when the intervention disappears, the system will still return towards the steady-state balance through its own adjustment and adaptation. The two-way regulation of blood pressure and blood sugar with herbal medicine, which is often talked about, is the embodiment of this mechanism.

Obviously, the functional model is built on the holistic level, which focuses on describing and regulating the macroscopic and long-term effects of the organism. As a basis for constructing models, observations of system behavior often involve adaptive responses, thus greatly reducing their impact on observational and experimental reproducibility. Understanding of the role of interventions (such as drugs) is usually based on comprehensive effects that involve adaptability. Therefore, the regulation by TCM of the pathological state of the human body using a drug includes the direct effects of the drug on the pathological state, as well as the 'seeking target' effects driven by the human body's self-adaptive and self-regulating properties under the actions of the drug. It is precisely because of the self-regulation and adaptive properties of the human body that the effect of regulation is enhanced and the complexity is reduced. Obviously, in TCM, complex adaptability is not an obstacle to people's understanding of the regularity in the organism, but an indispensable aide for more effective regulation of the organism.

Science is leading mankind's understanding of the world back to holism, and TCM is precisely based on the ideas and methods of ancient holism. Currently, biology and medicine are attempting to establish body models and state-description systems using complexity science methods, which undoubtedly represent a return to the tradition of TCM. The difference from TCM is that by introducing computer simulation technology and the idea of empirical science, the human body models and state-description systems will be based on rigorous empirical data. In addition, clinically meaningful individualized indicators and corresponding targeted drugs discovered by precision medicine will provide convincing and practical evidence for refining human body models at the organism level. In accordance with the 'simplest applicable' principle, the integration of the syndrome differentiation-based treatment system of TCM and the targeted therapeutic system developed by precision medicine will allow the formation of a unified human body model and state-description system embodying holistic integration and reflecting individual differences at the microlevel. As a result, this system can be used to achieve precision descriptions and optimal regulation of individualized states of the human body.

With holism-based body models and state descriptions as the core, this medical system will maximize the integration of the knowledge, experience and technology of TCM and modern medicine. The system will surpass the narrow geographical and cultural concepts of Eastern and Western medicine and lead to an unprecedented revolution in terms of the concepts and ways of thinking in the medical field. Today, as the concept of complexity science gradually becomes a mainstream concept of science, we refer to this all-new medical system as holistic medicine.

The term holistic medicine has long existed in the West, but the holistic medicine that we propose has new meaning under the scientific setting of the twenty-first century. It is a brand new state medicine system based on the concepts and methods of complexity science, in which the holistic concept of TCM and the empirical methods of modern science are organically combined.

Holistic medicine will apply the methods of both TCM and complexity science by using metaphors and analogies to establish functional models reflecting human physiological and pathological activities. The structural analysis methods of modern science will be used to create models with strict logical structures. More importantly, big data analysis and machine learning techniques can be utilized to implement the model through evidence-based computer simulation. Holistic medicine will continue to embrace the syndrome differentiation-based treatment approaches of TCM, but its state-description system will be improved in terms of the completeness and independence of state variables by introducing general methods for establishing state descriptions in natural science. Such holistic medicine can be used to capture and regulate body states in an integrated manner. The biomarkers developed in precision medicine and the innovative detection methods of modern medicine can be applied to describe body states in finer detail. Therefore, the corresponding treatment methods of modern medicine will be integrated into the holistic medicine treatment system, and the integration of Chinese and Western medicine at the application level will be achieved.

With the rise of complexity science, the transition of modern medicine from disease medicine to personalized medicine, and the comprehensive renaissance of TCM, medicine is on the eve of unprecedented changes. Between state descriptions at the organism level in TCM and the revelation of life activities at the microscopic level in systems biology and precision medicine lies a huge unknown network of causal relationships. Refining the functional model of holistic medicine to the extent that it can fully describe the pathological differences at the microscopic level is a long-term and difficult process; based on the 'the simplest applicable' principle, the degree of refinement is also limited by necessity. Holistic medicine provides an effective solution to individualized pathological states and treatment methods that cannot be described by disease medicine. Disease medicine's understanding of pathogenic factors, the disease process and universal treatment methods cannot always be described by the state-description system of holistic medicine, in which case holistic medicine is not effective. Therefore, in the foreseeable future, modern medicine will enter an era in which holistic medicine is dominant and is complemented by disease medicine.

In the field of biology, to surmount the current dilemma of systems biology, biologists will have to face the limitations of the 'analysis-reconstruction' integration method, introduce the holistic modeling method of complexity science, and begin truly holistic studies of organisms. In other words, biologists will have to directly establish a functional model at the organism level based on the investigation of inputs and outputs. The inputs mentioned here do not refer to our understanding of inputs in a traditional sense but rather include a variety of environmental factors that might affect the state of the organism, such as the resources necessary for the growth and survival of the organism and the various interfering stimuli that might be encountered during life, as well as the interference methods specifically designed for experimental biology. Furthermore, the outputs mentioned here are not limited to various phenomena observed in living organisms but also include various indicators detected by physical, chemical or biological detection means in studies of experimental biology. Holistic biology focuses on the holistic attributes and behaviors of an organism; thus, the state variables introduced by the model need to reflect the holistic attributes of a certain aspect of the organism, and the inputs and outputs of interest must also show good correlation with the holistic attributes of the organism. Obviously, the differences between holistic biology and systems biology are mainly reflected in methodological aspects, such as the level of the state description and the methods used to achieve integration. In other words, the dilemma currently encountered in systems biology cannot be simply attributed to the limits of the technological development level, which can be gradually solved as technology advances. To overcome this dilemma, biological research will have to face a new round of more profound revolutions involving methodology.

Conclusions

There is an old saying in China, 'People who don't account for the long term cannot plan for a while, and people who do not consider the whole cannot plan for a part.' Today, systems biology and precision medicine are at the forefront of life sciences. Placing these fields in the context of the evolution of natural science concepts and methods will help to clarify the underlying causes of their current predicaments. While the concepts and methods of the natural sciences are returning to the holistic sciences of the ancient East, exploration along the historical trajectory of the evolution of human culture and scientific methods will help clarify the future direction of the life sciences.

The establishment of holistic medicine means that modern medicine, which is undergoing a transformation from reduction analysis to holistic synthesis, and TCM, the theory of which is becoming more scientific and standardized, will ultimately merge together along different pathways of development. In other words, 'the integration of modern medicine,' 'the scientification of TCM' and 'the establishment of a unified theoretical system that integrates Chinese and Western medicine,' three dreams that have been pursued in the past century, will be perfectly fulfilled under the unified framework of holistic medicine.

Disclosure statement

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