

What Personalized Medicine Humans Need and Way to It —also on the Practical Significance and Scientific Limitations of Precision Medicine

Bing Yuan 

HK Modern Chinese Medicine R&D Center, Kowloon, Hong Kong

Correspondence: Bing Yuan, HK Modern Chinese Medicine R&D Center, Room 2, 7/F Kiu Kin Mansion, 566-568 Nathan Road, Kowloon, Hong Kong, Email greenisland@vip.163.com

Abstract: The rise of precision medicine has opened up a broad space for the development of modern medicine and has also given practical significance to the concept of personalised medicine. Precision medicine is establishing a personalized disease classification system that differs from the traditional system. However, the research progress of precision medicine in recent years is far from satisfactory: There are few disease types that can be attributed to the abnormality of a single target; the effects of current 'precision' medications are not ideal, and various side effects remain unavoidable. The methodology of precision medicine is still reductionist, and it would not solve the integration problem of clinical treatment but rather would increase the difficulty of integration. Therefore, the precision medicine approach is not a feasible way to build a personalised medicine system. Based on the analysis and demonstration of the scientific limitations of precision medicine and the consistency of traditional Chinese medicine (TCM) and complexity science methods, this paper draws on the concepts and methods of cybernetics and complexity science, and proposes a fresh set of ideas and methods for the development of personalised medicine. The conclusion is as follows: Along the path of precision medicine, ideal personalised medicine cannot be achieved; what people ultimately need is personalised medicine that can achieve holistic integration. On the basis of TCM with the characteristics of holistic integration and personalisation, and according to scientific norms and the principle of evidence, building a theoretical model and state description system grounded in empirical evidence is the best way to establish a personalised medicine system.

Keywords: personalised medicine, precision medicine, disease classification, state medicine, holistic medicine

Plain Language Summary

This paper examines the current development path of personalised medicine from the larger perspective of natural sciences and life sciences, with the aim to find a more correct direction for the future development of personalised medicine. Through the analysis and demonstration of the research methods and the problems discovered in the research of precision medicine as well as its scientific limitations, this paper points out that although precision medicine belongs to a personalised medicine model, it cannot achieve the ideal personalised medicine along its current development path. So, what kind of personalised medicine do people need, and how can it be achieved?

In recent decades, with the development of cybernetics and complexity science, a complete set of rules and methods have been established on how to regulate-control applied systems to achieve specific functions and goals in fields of natural sciences and social sciences. In essence, the doctor's treatment of diseases is to regulate the state of the human body, repair the damaged functions, and convert the patient from a pathological state to a healthy state. Based on the consistency between the goals and processes of doctor's diagnosis and treatment of diseases and the system regulation-control of modern science, the principles and methods established by modern science in the regulation-control of general applied systems can be adapted to personalised medicine, so as to establish methods and systems suitable for the personalised regulation-control of human diseases.

Today, personalisation and holistic synthesis have become people's aspirations for the future medical model. But what people need is a medicine that embodies both holistic synthesis and personalization, not two separate medicines. Therefore, based on the principles

and methods established by modern cybernetics and complexity science in the regulation-control of general applied systems, establishing the state description and regulation-control systems of the human body from the holistic level, would form a complete set of ideas and methods for the development of personalised medicine.

Introduction

The concept of personalised medicine first appeared in the late 20th century; however, it was not until the rise of precision medicine that the concept gained practical significance. In 2011, the National Research Council (US) Committee released the report “Toward precision medicine: Building a knowledge network for biomedical research and a new taxonomy of disease”.¹ The report proposed the concept of “precision medicine”, the essence of which is “personalised medicine”.² Precision medicine can help to accurately classify and diagnose diseases by correlating patients’ clinical phenotypes with various omics data and provide patients with targeted prevention and treatment measures to ensure that they receive the right treatment at the right dose at the right time.³ In the medical model of precision medicine, medical decisions, treatments, practices, and products are tailored to a subgroup of patients instead of a one-drug-fits-all model.^{1,4} In explaining the distinction from the similar common term “personalised medicine”, the National Research Council explained, ‘Precision medicine tailors medical treatment to the personalised characteristics of each patient and does not mean creating a unique drug or medical device for each patient. Instead, it classifies individuals into subpopulations, which differ in their susceptibility to specific diseases, the course of development and evolution, prognosis, as well as their biological characteristics and responses to specific treatments’.⁵ Furthermore, it is possible to study different subgroups and to administer different treatments to different subgroups.

The near-term goals of precision medicine are focused on tumour prevention and treatment. Through the detection of disease information, including genes, proteins, and metabolites, it can accurately distinguish individual differences between tumours to improve the accuracy of tumour treatment while simultaneously enhancing the prediction and prevention of tumour risks. The long-term goal is to advance our understanding of disease in terms of causes, pathogenesis, prevention, and treatment through more precise detection and analysis, taking a wide range of underlying factors into account and leading to more accurate diagnosis and more effective prevention and treatment. If the long-term goals are achieved, it is expected that health care services will be greatly improved.

Nevertheless, it has been more than 10 years since the concept of precision medicine was first proposed. With the expansion of research, doubts about its development prospects and practical significance are increasing. There is no doubt that the personalisation of medicine will help to get rid of the limitations and dilemmas of disease-based medicine. However, given the current approach to precision medicine, can a system of personalised medicine to deal with diseases more effectively be built? What is the practical significance of precision medicine for the development of modern medicine? Can the long-term goals of precision medicine be achieved with existing approaches? What is the future of precision medicine?

The Practical Significance, Current Problems, and Scientific Limitations of Precision Medicine

The rise of precision medicine has greatly expanded the development space of modern medicine, and the establishment of a new disease classification system will undoubtedly greatly expand the knowledge system of modern medicine. As a result, the identification of disease states will be further refined, which is conducive to the search for more effective drugs and more precise definitions of the selectivity of existing drugs. However, in recent years, the research progress of precision medicine has been far less than what people expected. The actual relationship between biomarkers, targeted drugs and diseases, and a series of problems arising therefrom, which were revealed with the deepening of research, are even more unexpected by scientists.

Chronic myeloid leukaemia (CML) is a very successful example of precision medicine. Chemotherapy drugs used to treat CML are not only ineffective but also have many side effects. Bone marrow transplantation, although effective, requires a suitable bone marrow donor. Half a century ago, chromosomal changes in CML cells were discovered, and 20 years later, the BCR-ABL fusion gene and its relationship to CML were identified. After that, scientists began to seek targeted drugs that could treat BCR-ABL. In 2001, the US Food and Drug Administration (FDA) approved Gleevec for

first-line treatment of CML. Subsequently, similar drugs were released one after another. These targeted drugs worked so well that they completely replaced other chemotherapy drugs and bone marrow transplants for CML.

Nevertheless, Gleevec's success has not been extended to targeted drug studies on other kinds of tumours because it is difficult to find tumours linked to only a single genetic variant, and most tumours have several genetic variants. As a result, medical scientists have imagined that targeted drugs could be developed separately according to different genetic variations. Then, genetic diagnosis of patients could be performed, and different targeted drugs could be used according to patients' actual genetic variations. Formulating treatment plans that vary according to the different personalised characteristics of patients is precisely the research and application that precision medicine is committed to promoting.

However, what precision medicine has revealed about the actual relationship between genetic variations and human diseases is beyond the anticipations of medical scientists. In a study published in *Molecular Cancer Therapeutics* in 2015, Schwaederle et al analysed the data of genetic testing on 439 patients with different tumours; of these patients, 96% had at least one genetic alteration in their tumours, and 372 (85%) had two or more abnormalities, with an average of three alterations per patient. Most patients have different types of genetic alterations.⁶ In a 2018 study by Caterina Fumagalli et al published in the *Journal of Clinical Pathology*, a similar conclusion was reached in the detection of 441 patients with non-squamous non-small-cell lung cancer.⁷

To date, there is growing evidence that personalised subtypes of tumours (or other diseases) that can be differentiated based on a single abnormality in a single biomarker are not universal, and that personalised subtypes of most diseases are associated with more than one gene (or include other biomarkers). Each patient often has more than one genetic variant, and the combination of genetic variants frequently varies across patients. For tens of thousands of coding genes (approximately 20,000–50,000),⁸ the combination of clinically significant gene variants in one disease would be a sizeable number. However, the state of diverse human functional activities and diseases is not completely determined by genes. Proteins, microorganisms, lipids, and metabolites also play an important (perhaps more important) role in the occurrence and development of disease. If biomarkers other than genes were considered, the combination of clinically meaningful biomarkers of one disease would imply a much larger number.

To address these problems, the current approach used in precision medicine involves large-scale population cohort studies, which can be used to carry out various systematic epidemiological and omics investigations, to explore the aetiology and risk factors for diseases, to understand the pathogenesis of disease, to identify new disease markers and therapeutic targets, to improve disease classification, and to clarify the timing of prevention and treatment of disease. Precision medicine can facilitate clinical transformation and the development of targeted drugs through pharmacogenomics and other means, and finally achieve personalised, precise treatment for specific patients. The biological sample bank established by large-scale population cohorts is an important foundational platform for precision medicine research, as it can provide a large number of sample resources for the accurate prevention, classification, diagnosis, and treatment of disease.⁹

The precision medicine research project—in which the US government invested \$216 million in 2016 to launch and which is currently called the “All of US Research Program”—encompasses cohort studies based on this approach. The All of US Research Program is a national research initiative run by the National Institutes of Health (NIH). There is a plan to enroll more than 1 million volunteers and to collect their information, including medical records, genetic profiles, metabolites (chemical makeup), microbes on the body's surface, environmental and lifestyle data, patient-derived information, and personal device and sensor data. All US volunteers are adults 18 years of age or older living in the US and include patients with diverse diseases as well as healthy individuals.¹⁰ Obviously, cohort studies are far larger in scope and scale than traditional randomised controlled trials. If a disease (or tumour) involves a combination of dozens (or even hundreds) of abnormal biomarkers, the cohort study would have to amass thousands of cases of the disease to draw convincing conclusions, and the difficulty and cost of organising the research would increase significantly. After 400 years of development, modern medicine has formed a disease classification system amounting to over 50,000 diseases (including injuries and causes of death). However, for a new disease classification system that is much bigger than the current one, how long would it take to form a sizeable scale? How much manpower and material costs would be needed, and how much practical significance would this new system have?

According to the existing approach to precision medicine, a disease (such as a tumour) has several genetic mutations, and targeted drugs need to be studied separately. Thus, clinically, based on the results of the patient's genetic testing, the

corresponding targeted drugs could be selected for treatment. However, the effects of such targeted drugs on the human body are not limited to a single site in most cases. The so-called precision is relative to the target it is aimed at. Compared with the “indiscriminate bombing” performed by conventional chemotherapy and radiotherapy, which do not distinguish cancer cells from normal cells, the precision drugs developed for specific targets are indeed more accurate. However, the actions of precision drugs for areas other than the target cannot be called precise, and in many cases, they may be side effects. The theory of complexity science and the practice of combined medication in modern medicine for many years have indicated that the effects of multiple drugs taken together often cannot be attributed to the simple addition of their effects when taken alone. Hence, for a patient with several biomarker abnormalities (gene variants) who is simultaneously taking targeted drugs with their own side effects that have been developed separately for different single targets, the comprehensive effect will inevitably lead to a certain (or even large) gap in terms of clinicians’ expectations. If so, what outcome will be produced by the combination of the drugs’ respective side effects? In reality, many patients also suffer from other diseases that require treatment, and these diseases also need to be individually differentiated. Thus, based on precise diagnosis, can the combined application of multiple “precision” drugs produce accurate therapeutic effects?

The progress of precision medicine has been achieved in the process of further personalised differentiation of diseases (mainly tumours) on the basis of traditional disease classification. However, with advances in precision medicine research, scientists have discovered that biomarkers introduced to distinguish personalised types of tumours are often associated with tumours in other areas, or even more than one area. The drugs developed for these targets are also effective for corresponding tumours in other parts of the body.

In May 2017, marking a milestone, the FDA for the first time approved the indications of antitumor therapies that are not rooted in the tumour’s source but are instead grounded in biomarkers. KEYTRUDA (pembrolizumab), developed by Merck & Co. (MSD), was approved to treat patients with solid tumours that are high microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR). Previously, the FDA had approved cancer therapies based on where the cancer originated, such as lung or breast cancer. This time, medication was approved for more types of solid tumours, and its indications were founded on two “biomarkers”. In other words, as long as the patient’s tumour carries one of these two biomarkers, the medication can be used for treatment, no matter which part of the body is suffering from a solid tumour. In tumors with MSI-H or dMMR, the DNA repair mechanism in the cell is often affected and cannot function normally. Such tumors are widely distributed and can appear in multiple locations, such as the colorectum, endometrium, gastrointestinal tract, breast, prostate, bladder, and thyroid. Therefore, distinguishing these cancers by the characteristics of genetic variation, rather than the location of the disease, has better guiding significance for the treatment.¹¹ This was confirmed during clinical trials.

Targets introduced to distinguish the personalised characteristics of a given disease can also differentiate between the personalised features of other illnesses, and the drugs developed for these targets are also effective for other ailments with this personalised characteristic. Clearly, the personalised classification of diseases and the traditional classification system are not in a hierarchical relationship but rather in a many-to-many network relationship. That is, the targets developed by precision medicine for distinguishing patients’ personalised characteristics will gradually form a new disease classification system that is independent of the traditional one.

Bringing together biomarkers that reflect the personalised characteristics of diseases and establishing a new disease classification system independent of the traditional one will undoubtedly greatly reduce the number of personalised diseases and the scale of the classification system. For a system that currently has approximately 55,000 diseases (including injuries and causes of death), even if dozens of personalised types were added for each disease, the scale would be much larger than it is today. In these personalised types of different diseases, there are many repetitions. Separating new disease classifications that reflect patients’ personalised classification would greatly simplify the classification system by removing these duplications. However, establishing an independent system will raise some new questions: What is the overall structure of the new classification system? What are the relationships among the disease types? If different biomarkers correspond to the same treatment, how can we deal with the relationships between them?

In reality, a disease is often accompanied by abnormalities in more than one biomarker, and patients often suffer from more than one disease. The multiple biomarker abnormalities present in the disease are separated, and the targeted drugs for each biomarker abnormality are studied individually. Obviously, this approach to precision medicine is still based on

reductionism. When personalised medicine needs to consider comprehensive treatment of multiple diseases in patients, the precision of a specific disease and personalised type loses its meaning. If a variety of precision drugs that are effective only for particular targets and have their own side effects are used together, can the precision treatment outcome of improving the abnormality of each biomarker be achieved? Do the biomarker abnormalities found comprehensively reflect the patient's various diseases? Do the effects of targeted drugs cover the fundamental link of the disease? Do improvements in these biomarker abnormalities imply a fundamental improvement in the patient's illness? Precision medicine will still have to face the problems of medical integration and comprehensive treatment, which cannot be solved by modern medicine. Moreover, due to the establishment of the new classification system, the complexity of disease description is increased, which will exacerbate the difficulty of integration.

To date, the personalised therapy developed by precision medicine has not shown very good specificity, and the precision of a personalised type for specific diseases has also lost its meaning when the holistic integration of treatment is needed. Spending vast human and material resources to build such a system that is larger than the modern medical one will undoubtedly further widen the gap between the total amount of medical knowledge and the amount of knowledge that a person can master in a lifetime. The practical significance of doing so is also hard to avoid being questioned.

Precision medicine has started the process of medicine towards personalisation and put the concept of personalised medicine into practice. Due to the significant personalised characteristics of precision medicine, many people directly call precision medicine "personalised medicine" and draw an equal sign between the two. If precision medicine cannot lead modern medicine towards the ideal personalised medicine, then one day, with the fading of precision medicine, will personalised medicine also come to an end? Today, when the development of precision medicine has profoundly exposed problems it faces and its scientific limitations, we have to ask whether precision medicine is the only way to realise the personalisation of medicine. To promote the transformation of medicine towards personalisation, to establish the theory and application system of personalised medicine, and to realise effective personalised regulation-control of diseases, is there a simpler and more effective method?

The Methodological Revelation of Cybernetics Theory and Practice

Since Norbert Wiener published his famous book *Cybernetics: The Science of Control and Communication in Animals and Machines* in 1948,¹² cybernetic thought and methods have penetrated into almost all fields of natural science and social science. Wiener regarded cybernetics as a science that studies the general laws of control and communication in machines, life, and society. Cybernetics ignores the physical, chemical and biological characteristics of various systems and studies them purely in terms of aspects such as basic elements and the basic structure of the systems and control mechanisms. The method of creating a system model and describing, regulating, and controlling systems by means of models has also become the content of scientific research. The establishment of cybernetics is one of the great scientific achievements of the 20th century. Many new concepts and technologies in modern society are closely related to cybernetics. The application scope of cybernetics covers engineering, biology, economics, society and other fields, and it has become a science that studies the common regulation-control laws in various systems.¹³

Control system theory is an important part of cybernetics. Figure 1 shows the general structure of a control system, which entails certain goals and functions composed of a control subject and a controlled system through a control loop. Based on its own performance, the controlled system can change its own state under the action of external environmental input, transmit information about its own state to the environment through the output, and exert some influence on the

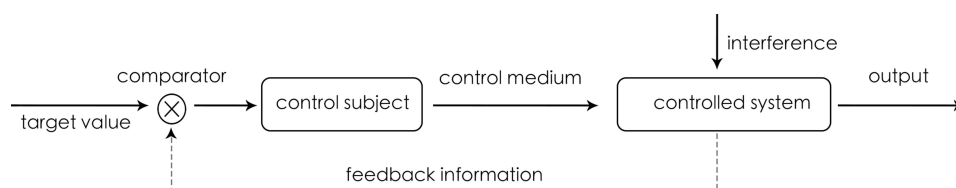


Figure 1 The basic structure of a control system and the general control process. The solid line with arrows in the figure represents the general information transmission route for the control system to realize control, and the dashed line with arrows represents the return route of feedback information from the controlled system.

environment. The input can be a disturbance from the environment or an intervention imposed by the control system. The control of the controlled system via the control subject is based on a certain goal, which can be to make the system reach a certain state or achieve a particular function. The control subject receives the information about the state of the controlled system sent from the controlled system, compares it with the present target, adjusts the control behaviour according to the target difference, and applies the intervention to the controlled system to make it further tend to the target value. By continuously applying the control intervention to the controlled system and comparing the feedback information of the controlled system with the target difference, the intervention input is continuously adjusted; finally, the state of the controlled system can reach the predetermined goal or achieve a specific function. In recent decades, control systems have been widely used in numerous fields, including engineering, biology, medicine, ecology, economics, and sociology. Diverse physical quantities in metallurgy, the chemicals industry, machinery manufacturing, and other industrial production processes (including temperature, flow, pressure, thickness, tension, speed, position, frequency, and phase) have corresponding control systems. Agricultural applications include control systems for water levels, greenhouse environments, and soil composition. In office automation, library management, traffic management, and even daily housework, control systems have a broad range of practical applications.

The process of a doctor diagnosing and treating a patient's disease is a standard control process. Here, the doctor is the controlling subject, and the patient is the controlled system. The patient's pathological state is formed under the action of external disturbance inputs (pathogenic factors) and is manifested in the form of the output. The goal of control is to return the patient to a relatively healthy state from the current pathological state. Based on the gap between the patient's state and the healthy state shown by the patient's clinical findings (the output), the doctor applies intervention inputs (such as drugs, acupuncture, and other therapeutic measures) to the patient to move the patient's state towards the healthy state. The regulation-control of a patient's pathological state is often not accomplished with a single control. Usually, doctors first formulate an initial therapeutic intervention plan to regulate-control the patient based on the identification of the patient's pathological state. During the treatment process, doctors need to continuously collect information that reflects the patient's pathological state, identify the direction and degree of deviation between the patient's state and the healthy state by comparing it with the healthy state, and then adjust the interventions to exert more targeted regulation-control over the patient. Through the control with feedback repeatedly, the patient's state is shifted in the direction of the healthy state.

Based on such a control mechanism, the effect of control depends primarily on two aspects. The first is accurately identifying the deviation between the patient's state and the healthy state (the target difference). Therefore, it is necessary to have a state description system (SDS) that can clearly describe the patient's various disease states. The second is having and being able to accurately select interventions that may correct these deviations. How does cybernetics' regulation-control of general systems achieve precise state description and identification?

Figure 2 is a schematic diagram of the 3D space involved in a middle school solid geometry curriculum. The three state variables in the three dimensions are x , y , and z . This system of three variables, ie, the state, is described by coordinates (x, y, z) . If we use this system to describe the state of a gas in an airtight container, we derive the following:

x_i : represents pressure at time i

y_i : represents temperature at time i

z_i : represents humidity at time i

Then, (x_i, y_i, z_i) represents the system's state at time i .

Clearly, the state of a 3D system is determined by the values of a set of three variables. When the number of state variables of the system exceeds three, the system has no physical meaning, but its state can still be described by a set of values.

How can the state of this system be controlled? We have methods to change pressure (blowing and pumping), temperature (heating and cooling), and humidity (humidification and dehumidification). Obviously, using these methods changes the value of the corresponding state variable and alters the state of the system.

Based on such an SDS, the system's personalised state can be described at any time. Grounded in the control of state variables, the control of any individualised state of the system can be realised. By introducing a set of state variables to describe a system's states, the value of the state variables is changed to the shifting states of the system. This is

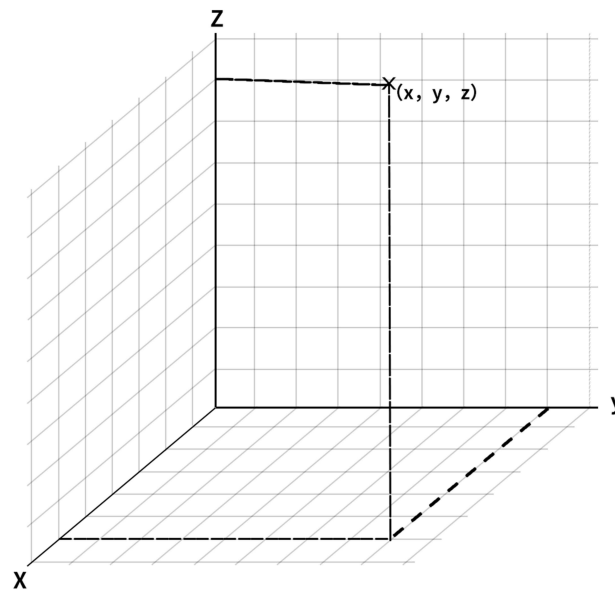


Figure 2 A state space described by a three-dimensional rectangular coordinate system. Each state in the state space is represented by a set of 3 numbers, (X_i, Y_i, Z_i) . The three solid lines in the figure are used to mark the three dimensions (X, Y, Z) of the three-dimensional space, and the three dotted lines are used to mark the state points (X_i, Y_i, Z_i) and the three dimensions (X, Y, Z) association.

a commonly used technique for regulation-control systems in engineering, biology, economics, and society. Currently, this approach has been employed in the regulation-control of temperature, flow, pressure, thickness, tension, speed, position, frequency, and phase in industrial production and the regulation-control of water level, the greenhouse environment, and soil composition in agriculture. The regulation-control of social and economic systems also usually entails this method.

Complex systems usually have multiple aspects of properties and functions. To describe a system's state, it is necessary to introduce multiple state variables and to build a model of the system. If these variables are related to each other, the model should be able to reflect the numerous possibilities of the state change in the system in the interrelated connections. According to the principles of cybernetics, the selection of state variables should meet the following general criteria:¹⁴

The selected state variables must have specific meanings, which can characterise the system's basic features and behaviours and hence have practical significance in guiding the regulation-control of system states. The introduction of meaningless state variables will only increase the system's complexity in vain and exacerbate the difficulty of identification.

The introduced state variable set should be complete, that is, the number of state variables should be sufficiently large, and all factors associated with the control objective should be considered and described with corresponding state variables.

The introduced state variables should be independent, which means that any state variable cannot be expressed as a function of another state variable. In other words, the introduced state variables cannot have redundancy, such as repetition and partial inclusion. Otherwise, the structure of the state variable system will be confusing.

The construction of the SDS should meet the principle of "simplest and applicable"; under the premise of meeting the accuracy level required for system regulation, the number of state variables should be as low as possible, and the interrelationships should be as simple as possible. Thus, it is not necessary to introduce a state variable for a state distinction that is meaningless in choosing a treatment method.

The SDS requires "enough" state variables to ensure the integrity of the SDS, but there is no absolute correlation between the integrity and the number of state variables. That is, the large number of state variables introduced does not mean that

the state variable system must be complete. In contrast, a small number of introduced state variables does not indicate that the state variable system must be incomplete. To describe the state of the human body, completeness means that the functions and behaviours of any aspect of any part of the human body are characterised by corresponding state variables. If the feature or functional state of a certain aspect of the system is not characterised by corresponding state variables, it is impossible to identify the state of this aspect, and it is impossible to regulate-control it. For example, the model and SDS of social and economic systems can comprehensively describe all aspects of social and economic activities and the relationship among them, so as to guide the macro-control of social and economic activities, only when enough state variables are contained in them.

- The state variables to be regulation-controlled by a social system may include the quantity and quality of the population, various compositions of the population, birth rate, death rate, employment number, illiteracy rate, divorce rate, and crime rate, etc.
- The state variables to be regulation-controlled by an economic system may include total social output value, total industrial and agricultural output value, national income, output value of various departments, products, fiscal revenue and expenditure, total profits and taxes, total wages, investments, fixed assets, working capital, foreign exchange receipt expenditure, the price system and its growth index, and the wage growth index, etc.

Real systems are usually hierarchical. The complexity of a model based on a real system is usually closely linked to the starting level of concern for the introduced system description. The lower the starting level, the larger the scale of variables introduced to fully describe the system. For example, a school has 6 grades, each grade has 10 classes, and each class has 50 students. From school to grade to class to individual students, these are the different levels of the school. To build state descriptions from different levels, such as grade, class or student/teacher, the complexity of the system must be different. The SDS established with the class as the starting unit increases the number of elements by 10 times compared to that with the grade as the starting unit, while with the individual student as the starting unit, the number of elements increases by another 50 times. For a class of 50 people, if the number of students included in the description system is less than 50, then the system is incomplete. Raising the most basic elements of the system to the class level reduces the size of the SDS by a factor of 50. As long as all 10 classes are included in the description system, the completeness of the description system will not be affected. However, the SDS established with the class as the basic element cannot reflect the individualised attributes and characteristics of the students in the class.

The independence of state variables means that none of the state variables can be combined by other state variables. A system without independence among state variables will inevitably have redundancy, overlap, confusion, and the lack of a strict logical structure. Based on such a system, it is impossible to achieve a unique expression of personalised status.

The interdisciplinary nature of cybernetics establishes the connection between engineering technology and life sciences and social sciences, which not only enables the concepts and methods that have been developed in one scientific field to be directly used in another, thereby avoiding unnecessary duplication of research, but also offers the possibility of generating new design ideas and control methods by using analogy, especially functional analogy approaches. There are analogies between biological cybernetics and engineering cybernetics, economic cybernetics and social cybernetics. Self-adapting, self-learning, self-organising, and other systems can provide a way to solve practical problems through analogies with biological systems.

In the past few centuries, every breakthrough in the methods and technologies of the modern natural sciences has rapidly expanded to the life sciences and promoted the progress of biology and medicine. As such, based on the widely used methods of regulation-control of general systems in modern science, can a state description and regulation system for personalised medicine be created?

Establishing a Model, State Description and Regulation-Control System for Personalised Medicine

Establishing a state description and control system for personalised medicine based on the methods currently used in general systems means introducing state variables that can characterise and describe human health and various disease

states as comprehensively as possible and finding interventions that can modulate each state variable. The human-body system is obviously far more complex than the gas in the airtight container that we mentioned earlier. Therefore, to fully characterise the numerous disease states of the human body, the number of state variables that need to be introduced will be much greater. Generally, the same system can be described by different groups of state variables, so the choice of state variables has a certain degree of freedom. The human body can also be divided into layers, so models and state descriptions can be established based on different layers. Obviously, under the premise of ensuring the model's completeness, building a model at the holistic level will definitely require many fewer state variables than building a model at the cellular or molecular level.

The anatomy and analysis of the human body in modern medicine began from the level of organs and tissues. However, knowledge at this level alone cannot fully reveal the mysteries of human basic physiological and pathological activities and life processes. With the advent of microscopy, the discovery of cells, and the rise of biochemistry, humans' understanding of life gradually deepened. The founding of molecular biology indicates that the human understanding of life has reached the molecular level, which is the most essential unit of life.

Overall, the study of the human body in biology and medicine is rooted in the concept of reductionism, using methods of anatomical decomposition and single-element analysis. In clinical medicine, various diseases are basically categorised and treated independently. Advances in physiology, biochemistry, and molecular biology have uncovered some associations between human organs, tissues, cells, and molecules after forming a system and the operating mechanisms of related life activities, such as blood pressure, blood sugar regulation, and regulation of hormones. However, research on these regulatory mechanisms and the physiological and pathological activities of the human body has also been carried out in different categories and in isolation. Research on the integration of multiple systems and multiple functional activities is still in a nascent stage, and these partial models created at the cellular and molecular levels cannot be integrated into a comprehensive model.

The emergence of systems biology has begun the integrated study of living organisms. It adheres to the concept of "an organism as a whole", adopts a holistic (rather than reductionist) approach, and strives to integrate information from different levels and parts to study and understand how biological systems function. Systems biology expects that by studying the interrelationships and interactions among all components within a biological system at the molecular level (eg, gene and protein networks related to cell signalling, metabolic pathways, organelles, cells, physiological systems, and organisms), an understandable model of the entire system can ultimately be formed. The integration of systems biology includes the integration of all levels and parts of organisms and eventually the organism level.

Nonetheless, after more than 30 years of research on the integration of organisms, systems biology has shown not the wonderful prospect of integration but the helplessness of scientists in facing the complexities of life: There are hundreds of millions of variations in protein-coding genes in the human body. Scientists today also clearly know that the occurrence and development of human diseases are far from being completely determined by genes. Proteins, metabolites, functional activities of organs and tissues, and daily behaviours also play a huge role in the occurrence and development of illnesses. Compared to the millions of genetic mutations that exist, the abnormalities of proteins and metabolites will comprise a larger system that people have to face. Biomarkers at the molecular level alone are already dizzying. From the molecular level to the whole, there are still intricate interrelationships between the diverse levels and parts. The complexity of organisms has been so clearly displayed that systems biologists issued a pessimistic sigh: The complexity of biological systems is far beyond people's imagination. At this stage, it is not appropriate to study the entire biological system, and we can start only from some relatively independent "small systems" with certain functions.¹⁵

As long as the integrated study of life has not reached the overall level, the holistic model of the human body cannot be established, and the state of the human body cannot be described by a complete state variable system that includes all these elements. Based on the current research level of biology and basic medicine, the treatment of diseases in clinical medicine can only be divided into categories. A patient suffering from multiple ailments can be treated only by different specialists for different illnesses, and comprehensive treatment grounded in the holistic concept cannot be implemented.

Rooted in the theory of cybernetics and complexity science, in a complex system, the regulation-control of the overall system cannot be attributed to simply adding the regulation-control of the various levels and parts that make up the whole.¹⁶ Clearly, the current level of science and technology, the present development of biology and medicine, and

existing treatment ideas and methods used in clinical medicine are far from the essential conditions required for the comprehensive and holistic regulation-control of disease. This is the problem that cannot be solved by traditional disease medicine, and has to be also faced by the emerging precision medicine. With the gradual establishment of a new classification system for precision medicine and the continuous discovery of individualised disease types, the content that needs to be identified in clinical medicine will greatly increase, which will exacerbate the difficulty of integration.

The present situation of the development of systems biology and the predicaments it faces make the prospect of medicine's holistic integration confusing, so will establishing a personalised medicine system with integrated characteristics remain only a dream and not a reality?

Based on the control methods of complex systems developed by cybernetics and complexity science, when examining TCM, which has a history more than 2000 years, we were surprised to find that the TCM syndrome system is exactly in line with the features of the SDS used by modern science for the regulation-control of complex systems, and the TCM treatment system on syndromes is an individualised regulation-control system rooted in state descriptions. Creating a functional model that reflects the physiological and pathological activities of the human body through metaphors and analogies, establishing a SDS on the basis of the model by introducing state variables, and regulation-controlling human pathological states through the regulation-control of state variables, which is exactly the method that has been used for the regulation-control of human diseases in TCM for nearly 2000 years.^{17,18}

Today, in any textbook on TCM, you will find the expressions “holistic concept” and “treatment based on syndrome differentiation” as the core characteristics of TCM.^{19–21} The holistic concept embodies the integrated characteristics of medicine, while the treatment system based on syndrome is a regulation-control system grounded in an individualised state description. The human-body model of TCM is established based on the holistic level, and the description of the physiological and pathological activities of the human body has a considerable degree of completeness. Given such an SDS, the patient's individualised state as a whole and each part can be identified, and an individualised plan can be created to comprehensively regulate-control the diseases of the whole and each part of the human body. Obviously, TCM is a personalised medicine system with integrated characteristics.

In TCM, based on the human-body model, the human body is divided into two levels: the overall level and the subsystem level. At the subsystem level, the human body is composed of five zang and six fu organs, the structure from the outside to the inside (wei qi ying xue) and basic life substances such as essence, qi, blood, and bodily fluids. The variables that describe the body's state are called syndromes in TCM. Syndromes describing functional status at the holistic level have been used in recent years as an essential classification of the human body's constitution.^{22,23} There are approximately 10 types of syndromes at the holistic level: qi deficiency, blood deficiency, yin deficiency, yang deficiency, qi stagnation, blood stasis, cold dampness, damp heat, phlegm drinking, and fiery. There are approximately 60 state variables that describe the functional state of the subsystem, including the state variables describing the functional state of the heart subsystem—heart qi deficiency, heart blood deficiency, heart yin deficiency, heart yang deficiency, heart fire inflammation, and heart blood stasis—as well as state variables describing the functional state of the stomach subsystem—stomach cold, stomach heat, and food stagnation in the stomach.

If we regard TCM syndromes, such as qi deficiency, blood deficiency, yin deficiency, yang deficiency, qi stagnation, blood stasis, and damp heat as state variables, then the state of the human body at a certain moment can be represented by this set of state variables.

Deficiency of qi (2), deficiency of blood (0), deficiency of yin (0), deficiency of yang (0), stagnation of qi (2), blood stasis (1).

[The number in brackets after the syndrome represents the degree of the syndrome.]

If we introduce 100 state variables (syndromes) to completely describe the health state of the human body, the state of the human body can be represented by 1 point in the 100-dimensional state space:

$S = x_1, x_2, x_3, \dots, x_n$ Among them, $n = 1, 2, 3, \dots, 100$

This state description method, on the surface, is different from the diagnosis process of TCM practitioners. When TCM physicians actually diagnose and treat patients, they usually pay attention only to the abnormal state variables and do not need to cover all the state variables that describe the state of the human body. In fact, the clinical diagnosis of

TCM practitioners adopts a simplified state identification method: Only the abnormal state variables are listed, and other state variables are regarded as normal.

In TCM, the regulation-control of the patient's pathological state is achieved by regulation-controlling the patient's abnormal state variables (syndromes). In the 2000 years of clinical practice of TCM, corresponding medications intervention method has been developed for each state variable (syndrome), and the description of the properties and functions of Chinese herbal medicines (CHMs) is also based on a medicine's effect on the state variable (syndrome). Examples are ginseng, astragalus to nourish qi; angelica, wolfberry to nourish blood; and skullcap to clear lung fire and remove damp heat.²⁴ The understanding of the effects of these herbal medicines in TCM has been verified by the clinical practice of countless people for thousands of years.

In TCM, the abnormality of each state variable is attributed to the clinical manifestations (including symptoms, signs, and detection indicators) as the output of the human body. For example, the corresponding clinical manifestations of heart qi deficiency are palpitations, insomnia, and dreaminess, and the corresponding clinical manifestations of liver qi stagnation are mental depression, chest tightness, abdominal distension, a susceptible sigh, and loss of appetite.²⁵ Thus, based on the symptoms, signs and detection indicators, TCM practitioners can identify the state of each state variable of the human body, and can thus fully and accurately grasp the body's holistic state. Based on the accurate identification of abnormal state variables and the understanding of the actions and indications of CHMs/prescriptions, TCM physicians can choose appropriate medications and prescriptions to effectively regulate-control the patient's disease state. Clearly, the description and regulation-control of the state of the human body by TCM treatment based on syndromes are consistent with the methods used by modern science for the description and regulation of applied systems.

In the era when the concept of reductionism is the mainstream scientific notion, the scientific nature and superiority of TCM methods are not widely recognised. The “Ban medicine and keep medications” policy implemented during Japan's Meiji Restoration era banned traditional medicine from China,²⁶ and Japanese Kampo medicine became a “water without a source” and a “tree without roots” with only medications and no theory to support them. In China, where traditional medicine has a 2000-year history, after experiencing the impact of the “abolish TCM” movement in the Republic of China²⁷ and the “integration of traditional Chinese and Western medicine” since the founding of the People's Republic of China (PRC), TCM has gradually degenerated into a subsidiary of modern disease medicine. The holistic concept and state regulation-control methods, as its core features, are limited to an increasingly smaller range, and TCM is becoming ever more marginalised.

In recent decades, with the emergence of cross-cutting disciplines such as systems theory and cybernetics and the development of complexity science, the idea of building models and model-based regulation-control has become deeply rooted, and mainstream science is moving from methodology grounded in reduction analysis to an era where complexity can be faced head-on. Today's science has developed to the point where it can unveil the “mystery” of TCM and restore its original scientific appearance.

Differences in the Regulation-Control Effects of SDSs at Different Levels

The TCM treatment system based on syndromes formed naturally during the course of TCM's development over more than 2000 years. From ancient times to the present, with the development of this SDS that is similar to that of modern science, the level of individualised regulation-control of diseases by TCM continuously improved. On the basis of the new disease classification system established by precision medicine, it is possible to develop an SDS by continuously removing redundancy and structuring the state variables in accordance with the principles of completeness, independence, and the simplest applicable. What is the structural relationship between the two systems? What are the characteristics of the two in regulation-control of disease? Which will be more representative of the future direction of personalised medicine?

Generally, from the perspective of identification and control, the higher the level of state variables, the more macroscopic, the better the abstraction; thus, the simpler the SDS will be, and the easier it will be to understand and control. From the standpoint of control means research, the regulation-control methods researched with relatively macroscopic state variables as the controlled quantity have fairly macroscopic actions and wide coverage. This macro effect usually covers multiple state variables at the microlevel; that is, its utility is usually the sum of the direct or

indirect effects on multiple state variables at the microlevel. The use of macroscopic state variables to describe and identify the state of the system requires lower precision, while the use of interventions for macroscopic state variables for the regulation-control of disease will also reduce the accuracy requirements for understanding the actions of intervention control methods accordingly. As an analogy, from a high-altitude airplane, if you want to observe the beards of soldiers on the ground, you need a high-powered telescope, whereas if you want to observe mountains or rivers, the focus does not need to be so precise. Similarly, if the target of a missile is a vehicle, the strike volume harnesses the energy of ordinary artillery shells, the trajectory needs to be accurately positioned and controlled. However, if the missile is a nuclear bomb and the target is a city, the accuracy requirements for positioning and control will be greatly reduced.

Clearly, precision in a treatment approach for individual variables at the microlevel does not imply precision in the overall state of the patient. With the same accuracy, the higher the level of the state variables, the greater the accuracy of describing the overall state of the human body. The precision required by the treatment method to regulate-control the human body is also closely related to the level of the state variables that we want to regulate-control. The higher the level of the state variables, the lower the accuracy needed and the smaller the side effects of medications researched based on it. This is also our intuitive feeling in the process of studying CHMs and Western medicine. The Chinese Materia Medica has a vague description of the properties of CHMs, but it is basically sufficient for the clinical practice of TCM; the pharmacy of modern medicine describes the properties of medicines in a fairly detailed manner, but from a macro perspective, there are more uncertainties and side effects.

The biological specimen data that precision medicine plans currently need to collect, such as genes, proteins, metabolites, RNA and DNA, and whole-genome sequencing, are mostly microlevel indicators. Obviously, achieving a complete description of the various states of the human body on the basis of the SDS established at this level implies better accuracy and a larger amount of data. Hence, there is a long way to go, whether to achieve “precision” detection and diagnosis, “precision” medication research, or “precision” control of the human body.

The human-body SDS of TCM (ie, the treatment system based on syndromes) uses no more than 100 basic syndromes (state variables) and their combinations to cover all the essential pathological processes of the human body. As mentioned earlier, if the number of all pathological states in which no more than 5 state variables are abnormal is counted, these 100 state variables can be combined out of more than 1 billion different pathological states. If the scope of calculation is not limited to 5 state variable abnormalities, this number will be larger. Even so, this system is much smaller than the SDS composed of hundreds of millions of genetic variants. However, with the ability to describe more than 10 billion different states of personalisation, the scale of this system is considerable.

Current human genome research has revealed that there are approximately 20,000 to 25,000 protein-coding genes in the human body.⁸ Estimating the number of genetic mutations based on this number may entail calculating in millions. Current research in precision medicine has encountered the problem where a specific personalised state needs to be defined by more than one biomarker. Thus, the number of combinations of state variables grounded solely in genetic variation has been astronomical. The millions of genetic variants and the astronomical number of their combinations are a far more complex system than TCM syndrome differentiation. And, to ensure the completeness of the system, the introduction of proteome, metabolome, and other omics information and behavioural data related to human diseases will make us face a larger, more complex SDS. Obviously, the SDS of TCM is at the highest level of the human body and has the top level of abstraction; therefore, the demand for “precision” diagnosis and “precision” medication research will be lower. As such, it is not difficult to understand that CHM based on TCM theory has better macroscopic and long-term efficacy.

Just imagine, if we use an SDS with 100 variables (such as syndromes in TCM) as a frame of reference to understand the state of the patient, when we have accurately identified 80 of these variables, we can say that the accuracy of understanding the patient’s status has reached 80%; and if we use an SDS with 10,000 variables (such as the detection indicators of modern medicine) as a frame of reference to understand the patient’s state, even if we have “accurately” identified 500 of these variables, we can only say that the accuracy of understanding the patient’s status has reached 5%. This is why TCM, although it is far less accurate in identifying symptoms and signs than modern medicine, has a grasp of the holistic state of the patient that is far beyond the reach of modern medicine. Obviously, the accurate comprehension

of the human body's state not only is related to the technical problems of the measurement method and the precision of the measuring instrument, but also has a more important connection with the level of the SDS and the total number of state variables as the frame of reference. The lower the level of an SDS, the greater the total number of variables introduced and the more difficult it is to achieve accurate identification using it.

Precision medicine establishes a description of the state of the human body at the molecular level, and the targets of its drug and treatment research are mostly abnormal state variables at the molecular level. The human body has a huge number of variables related to health at the molecular level. When a disease occurs, even if only 1 in 10,000 variables are abnormal, the number can be in the hundreds or thousands. Even precision medications developed in the future cannot be expected to have the same precision as missiles on action sites and nature, and side effects are unavoidable. The accuracy of a medication for a particular state variable does not mean that it is also accurate for other abnormal state variables or has no adverse effects. Just imagine, when we administer multiple precision medicines, each with its own side effects, to a patient at the same time, can we ensure that their overall effect will only bring the abnormality of the target to a normal level without causing multiple side effects? If this kind of combination drug has difficulty producing good effects and will cause a large number of drug-induced diseases, how much practical value does it have, even if such a classification system, which consumes a lot of manpower and wealth can be realised?²⁸

Today, modern medicine is still in an age of inaccurate comprehension of the actions of medications. As the number of "precision" medicines continues to grow, medicine must face the situation of dozens (or even hundreds) of precision medications needing to be applied at the same time. If multiple drugs that target a single abnormal state variable, but have more or fewer side effects, are used comprehensively in a complex disease situation, the short- and long-term actions are uncertain in many cases, and this uncertainty will also show the trend of "individualisation". To clarify these problems, we will face the research workload of combinatorial explosion based on hundreds of millions of abnormal state variables, which may require the unremitting efforts of many generations. Even if these problems are clarified, it does not mean that there is a feasible solution for personalised medicine.

Medications developed with macroscopic state variables as the frame of reference usually have the effect of regulation-controlling the macroscopic properties and functions of the body and therefore have a broader scope of action. Decades of analysis and research on the viscera and syndromes of TCM in China, as well as clinical studies of the integration of traditional Chinese and Western medicine, have shown that one viscera of TCM often involves the functional activities of multiple anatomical tissues and organs, and a syndrome (state variable) of TCM will involve the abnormality of multiple elements and variables at the microlevel. Therefore, the researched medications that can correct abnormal syndromes will undoubtedly exert a therapeutic action on the corresponding abnormal elements and variables at the microlevel. If achieving a macrolevel control effect through controlling multiple lower-level micro variables, it means to separately study medications that target multiple lower-level micro variables. Due to the nonunique actions and side effects of precision medications on the human body, even if we had found all the microlevel variables related to this macro variable, separately developed precision medications for each of them and given them to a patient at the same time, this does not mean that they would be able to bring the abnormal macroscopic variables (syndromes) towards a normal state. There are two reasons for this: On the one hand, abnormal state variables at the microlevel might not be the cause of the abnormal state variables at the macrolevel but might only be the appearance or result of the abnormal macrolevel variables. Without correcting the cause of the abnormality of the macroscopic variables, it is impossible to eliminate the abnormality of the macroscopic variables, and ultimately, it will be difficult to completely correct the abnormality of the microscopic variables. Once the action of the medication disappears, there will be a relapse, driving the microscopic variables to return to their original abnormal state. On the other hand, the non-uniqueness of the actions of precision medication and its side effects makes it difficult to control the combined forces of all its direct and indirect actions; the patient's personalised health status will also have a personalised impact on the effect of the combined application of precision medications. All these factors will make the final outcome of the combination of precision medications uncertain.

This point is also proven by modern research on CHM. For example, in TCM, the main function of ginseng and astragalus is to invigorate qi. Modern pharmacological studies on qi-invigorating CHMs have shown that qi is usually reflected in the following actions at the microlevel: regulating sugar metabolism and lipid metabolism; promoting the

synthesis of proteins, DNA, and RNA; increasing albumin and γ -globulin content; increasing the number of peripheral white blood cells; enhancing the phagocytic function of the reticuloendothelial system; and improving cellular immunity and humoral immunity. If we take a variety of medications at the same time that can regulate sugar metabolism and lipid metabolism, promote protein, DNA, and RNA biosynthesis, increase the phagocytic function of the reticuloendothelial system, and enhance cellular and humoral immunity, will their combined actions show the effect of TCM for invigorating qi? The answer to this question, whether it is based on the analysis of pharmacologists or the practice of clinicians, is very clearly “No”. Lowering the level of controlled amounts of medication research will greatly increase the complexity of the research and the uncertainty of medication actions from a macro perspective. In terms of finding precision medications, compared with the bottom-up path of modern medicine, the top-down path of TCM is simpler and more effective. The correspondence between the developed medication and the overall state of the human body will have greater precision.

On the other hand, the human body, as a living organism, is a complex system with self-organising and self-adapting capabilities. In such a self-organising system, the upper level generally has the ability to control and constrain the behaviour of the lower level. As in a well-organised army, the general’s command of the soldiers is achieved through the hierarchy of organisation. In fact, the regulation-control of self-organising and self-adapting systems does not need to go directly to the microlevel in most cases. Hence, there is no need to create such a complex state description at the microlevel.²⁸ The regulation-control method of precision medicine ignores the self-organising characteristics of complex systems and the constraints of the upper level on the lower level as determined by the nature of the body itself. This is similar to a general commanding the army, skipping the organisational level of the army, and directing every action of each soldier under his command. The simplest and most effective way to regulate-control organisms is to harness the ubiquitous control and restraint of the self-organising system’s upper level for the lower level and to proceed from a holistic level. Only for diseases that can be attributed to specific sites or specific causative factors and for which specific treatments have been found should the combination of a specific precision therapy be considered.

Therefore, the disease medicine of modern medicine studies the general laws of the occurrence, development, and evolution of diseases and general treatments for diseases. Although precision medicine has certain personalised features, its development should be limited to identifying specific sites and factors that have a decisive role in the disease as well as developing targeted therapy methods with high specificity. Personalised medicine should have the characteristic of holistic integration at the same time. Its theoretical model, individualised state description, and regulation-control system should be established at the holistic level based on the theory and practice of TCM.

Conclusion

Both personalisation and holistic integration are expectations of humans for the future medical model. However, what humans need is a medicine that has both individualised and holistic integrative characteristics, not two separate medicines. The above analysis shows the enormous advantage of establishing state descriptions at the macrolevel for the regulation-control of diseases. The development of precision medicine will undoubtedly develop some targeted drugs with unique effects for specific personalised states, but in terms of the comprehensive treatment and overall regulation of diseases, it is far from being comparable to TCM. The reductionist features of precision medicine imply that it will still face the predicament of being unable to achieve holistic integration, and it will be more severe. The TCM model embodies these two characteristics simultaneously. Therefore, a return to TCM in terms of the holistic concept is the best way for modern medicine to move towards personalisation.

With TCM, which has a long history and has been verified through practice, personalised medicine does not need to build a state description and regulation-control system from scratch. In the recent developments of modern medicine, based on the experiences of using *Artemisia annua* to treat malaria in TCM, modern medicine discovered artemisinin, which enriched treatment methods for malaria; based on acupuncture therapy grounded in TCM, modern medicine developed trigger-point dry needling therapy, which enriched its clinical treatment system. Similarly, according to the general method of state description and state regulation-control established by modern cybernetics, rooted in the theoretical model and the treatment system based on syndromes of TCM, modern medicine can also develop a set of personalised medical systems that conform to scientific norms. This system can describe the health state of the human

body more accurately, reasonably and simply, and will also make the regulation-control of the health state of the human body more precise, comprehensive, and efficient.

Abbreviations

SDS, state description system; TCM, traditional Chinese medicine; CRM, Chinese herbal medicine.

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Author Contributions

The author graduated from the Beijing University of Chinese Medicine in 1983 and subsequently studied undergraduate courses in computer software design. He has background knowledge and research experience in modern medicine, traditional Chinese medicine, philosophy of science, complexity science, artificial intelligence, etc. and has more than 40 years of clinical experience in integrating Chinese and Western medicine. The author has long been engaged in the research of history and methodology of Eastern and Western medicine. In recent years, he has been paying attention to the research progress in the frontiers of life sciences such as precision medicine, systems biology, integrated medicine, personalized medicine and constitution medicine. He is dedicated to exploring trends and methodologies in modern medicine and biology and has published a series of influential academic papers and treatises. His recent representative work “Towards Holistic Medicine: An evidence-based medicine that embodies holistic concepts and personalized principles” will be published by the CRC Press soon.

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