

Interdisciplinary Knowledge

Computational Medicine: Past, Present and Future*

LYU Lan-qing, CUI Hong-yan, SHAO Ming-yi, FU Yu, ZHAO Rui-xia, and CHEN Qiu-ping

ABSTRACT Computational medicine is an emerging discipline that uses computer models and complex software to simulate the development and treatment of diseases. Advances in computer hardware and software technology, especially the development of algorithms and graphics processing units (GPUs), have led to the broader application of computers in the medical field. Computer vision based on mathematical biological modelling will revolutionize clinical research and diagnosis, and promote the innovative development of Chinese medicine, some biological models have begun to play a practical role in various types of research. This paper introduces the concepts and characteristics of computational medicine and then reviews the developmental history of the field, including Digital Human in Chinese medicine. Additionally, this study introduces research progress in computational medicine around the world, lists some specific clinical applications of computational medicine, discusses the key problems and limitations of the research and the development and application of computational medicine, and ultimately looks forward to the developmental prospects, especially in the field of computational Chinese medicine.

KEYWORDS computational medicine, model, computational Chinese medicine, artificial intelligence, big data

In recent years, with the rapid development and widespread application of bioinformatics databases (human genome sequences), personalized patient detection technology (such as proteomics, metabonomics, genomics technology, etc.), big data analysis technology,⁽¹⁾ and imaging technology have achieved rapid development and broad applications. People are accumulating increasing amounts of data in medical clinics through various technologies, the data generation represented by the genome is increasing exponentially, data updating is accelerating daily, and a large amount of data has been obtained. The biomedical field has ushered in the era of big data.^(2,3) When each individual reaches hundreds of G and the cumulative data exceeds the Pb level (1 P=106 G), addressing multiple, high-dimensional, massive and heterogeneous information in clinical practice has become a key in the biomedical field for disease prediction, clinical diagnosis and health maintenance. In the era of information and data, the traditional biomedical research model is not suitable. However, the development of new computational medicine based on big data and supercomputing technology is ascendant. This paper introduces the concepts and characteristics of computational medicine and then reviews the developmental history of the field. Relevant search strategies and selection criteria of this overview are shown in Appendix 1.

Introduction

Concept and Related Fields

In a broad sense, computational medicine is a

science that depends on modelling, quantitative analysis and computer simulations of problems in the medical field, with major clinical problems being the primary research object, computer and application software being the tools, and clinical applications as the driving force. This is a new interdisciplinary field involving medicine, biology, computer science, engineering, physics, mathematics and many other disciplines.

In a narrow sense, computational medicine calculates and models the activity processes of organisms at the levels of molecules, genes, cells, organs and tissues according to different time and space scales.⁽⁴⁾ This approach can be used to understand the mechanisms of life and disease in a more realistic way and provide a scientific and efficient way to improve disease prediction, clinical diagnosis and treatment and health maintenance. The goal is to achieve disease prediction, improve diagnosis and treatment plan design, generate curative effect evaluations, engage in new drug development and evaluation, and provide

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"individualized" diagnosis and treatment.

In contrast to evidence-based medicine and precision medicine, computational medicine is a new concept (Appendix 2).⁽⁵⁻⁷⁾ Computer data modelling technology as represented by supercomputing is the key to promoting the development of computational medicine by using the value of data. This field relies highly on a high-performance data analysis platform and is a new discipline that gradually formed with the development of computer technology and medical imaging technology. It involves many fields, such as medical visualization, material metabolism, medical finite element analysis and radiation dose assessment. This approach uses quantitative methods to understand the mechanisms of human diseases intelligently by applying mathematics, engineering and computational science and provides new insights into medical services based on industrialized data, algorithms, computing power and biomedical technology systems. For example, in a clinical study on the reconstruction of ribs and sternums with defects, anatomical images of the rib and right half of the sternum were obtained from chest CT scanning. Then, implants were processed in Formlabs Form 2 (Massachusetts, United States) using metal powder fusion technology and a three-dimensional (3D) experimental model of a sternum in resin, and because the characteristics of the ribs and half-breast implants are consistent with the defects in the 3D model, they were ultimately used in Swansea Morris Hospital (Morrison sternotomy and model implantation were performed in the 3D maxillofacial laboratory of the hospital).⁽⁸⁾

Feature and Advantages

Computational medicine is systematic and data intensive. Compared with the original medical research methods, computational medicine has unique advantages in methodological and clinical research (Figure 1 and Table 1).

Evolution

Development of Computational Medicine as a Whole

The Institute of Computational Medicine (ICM) at Johns Hopkins University was jointly established by the School of Engineering and the School of Medicine of Johns Hopkins University in 2005. The goal of the ICM is to analyse and mathematically model the mechanisms of diseases through powerful computers, to predict the possible occurrence of a given disease and determine how to cure the disease effectively. An article entitled "Computational medicine: from model to clinical" published in *Science Translational Medicine* on October 31, 2012 indicates that computational medicine has moved from theory to practice, and doctors can use it to treat heart disease, cancer and other diseases.⁽¹¹⁾ With the development of computational medicine, researchers can use digital tools to build models based on experimental and clinical data to help to uncover complex medical mysteries.

Development of Big Data

In the era of information technology, how can massive data be used efficiently? Computational medicine is an emerging discipline based on the developmental needs of the biomedical big data era,

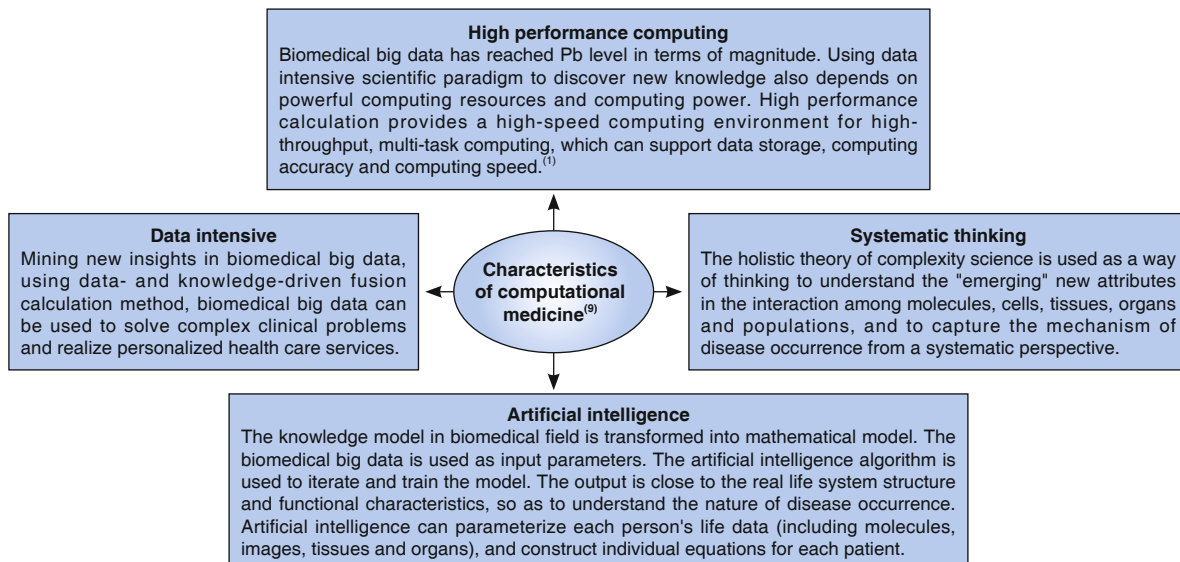


Figure 1. Characteristics of Computational Medicine

Table 1. Advantages of Computational Medicine

| Item | Previous studies | Computational medicine |
|-------------------------|---|---|
| Methodology | The deficiency of reductionism is increasingly prominent: the first problem is that the refinement of different discipline branches is creating obstacles to the flow of information; the other is oversimplification. ⁽¹⁰⁾ In the medical field, research methods based on reductionism in the past at least partially lost information on interactions between different components in the life system and the non-linear characteristics of the structure and function of the life system along the time axis. | This medical field addresses the different activities of complex multi-level networks and the complete complex biological systems that organize these networks together. Computational medicine employs the holism of systems science as the mode of thinking to capture the mechanism of disease occurrence and development from a systemic perspective. |
| Clinical application | Clinical information is fragmented and complicated, and clinical diagnosis depends on the thinking and judgement of doctors. Therefore, it is difficult to prevent inaccuracy in clinical diagnosis and treatment when caused by a lack of information extraction and the doctor level when analysing diseases with traditional biological methods. | Computational medicine can use supercomputing to process clinical big data, which provides medical researchers with a more objective, macro-level and clear perspective on the pathogenesis and therapy of diseases. |
| Scientific research | The biology of health and disease is very complex. It involves the feed-forward flow of information from genes to proteins, networks, cells, tissues, organs and organ systems (feed-forward flow of information). | Computational models can help medical researchers understand the nature of these extremely complex and non-intuitive diseases, and help diagnose and test the effect of different therapies. The test results can be used to optimize the model to achieve higher predictability. ⁽¹¹⁾ |
| Evidence-based medicine | The biggest feature of evidence-based medicine is that it reflects the group nature, but it cannot fundamentally solve the problems of inaccurate diagnosis, vague evaluation and staging, and it is impossible to know the actual curative effect of the therapeutic schedule on a specific individual. ⁽¹²⁾ | Under the methodology of computational medicine, we will look at life systematically, build physiological and pathological models through computer-aided technology, use supercomputing means to mine big biological data to find new key points, and continuously optimize dynamic model construction by combining with artificial intelligence to explore the correlation in the whole body system. The diagnosis and treatment plan based on computational medicine no longer relies on a single gene as the key to judge the efficacy of a drug, nor is it limited to the one-to-one causal relationship between the target and the drug. |
| Precision medicine | Precision medicine will provide accurate disease prevention, diagnosis, treatment and even health guidance through knowledge network. However, in the short term, it is difficult to achieve the accurate integration of various highly related biological information, medical information and health information, as well as the establishment of database and corresponding decision support tools. Due to the complexity of environment and disease, it will be a difficult process to improve human health through precision medicine. ⁽¹³⁾ | |

and big data are also the basis for the development of computational medicine. The developmental history of big data is shown in Figure 2.

development of computational medicine, and computational medicine is an important method for completing digital human research. The two are complementary. The development of the digital human is shown in Figure 3.

Digital Human

Development of Digital Human

Digital Human is a research platform for the

Importance of Digital Human in Chinese Medicine

Notably, the virtual human project presented

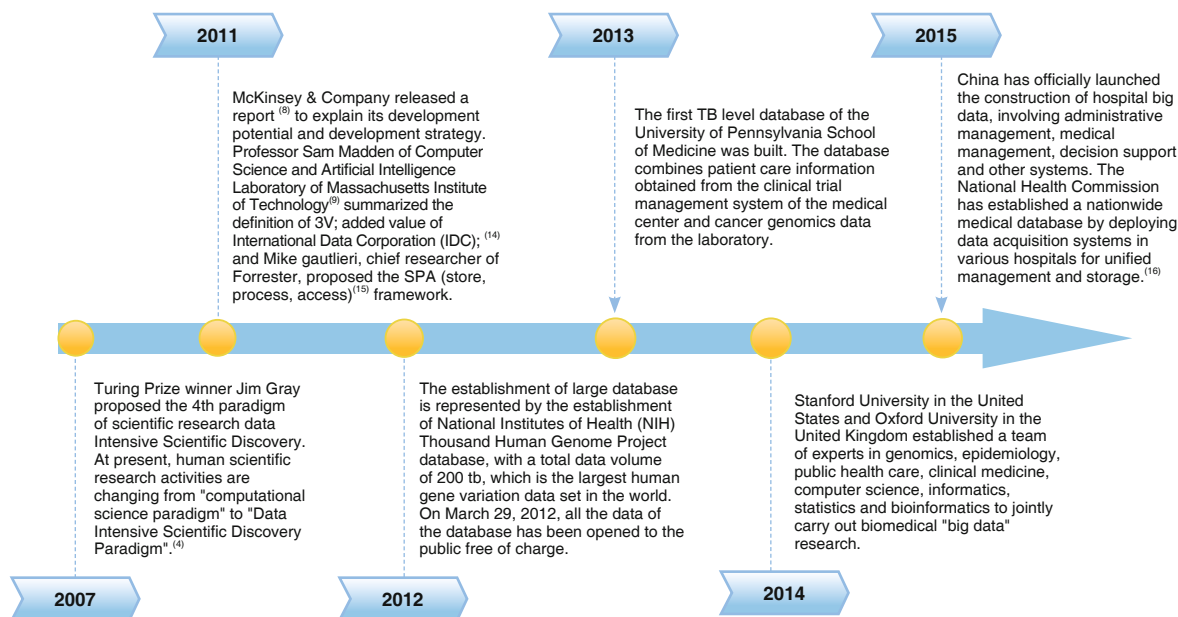


Figure 2. Development of Big Data

by American research teams has fatal defects and it considers the human body as an isolated closed system. In fact, scientists have reached a consensus that the phenomenon of life is a process with an open dissipative system that has a very complex hierarchical and a non-linear non-equilibrium system rather than a material state. The establishment of a virtual human body model should implement this principle and try to express non-linearity and complexity. The research and establishment of digital human cannot remain in organic structures alone, and the research on digital human at the organ function level cannot be ignored.

Chinese medicine (CM) is a bioscience that considers organ function. Human life and health firstly depend on the state and strength of body organ function and organ function originates from the mutual coordination of biological tissues. The coordination function of organs maintains the stability of the internal human environment and adapts to the external natural environment. In addition, the orderly structure and movement of an organism depend on the constant exchange of material, energy and information with the environment. Through material circulation and energy flow, the organism and the environment form a unified whole. The most significant characteristic of CM is that humans interact with geographical and social environment over their entire lives, which compensates for the deficiency in virtual human body research. Only by combining the digital human of CM can we simulate digital human with human body functions. The research plan on digital virtual human without CM participation is incomplete, and research on the digital human body using CM is one of the primary research directions of computational medicine. Therefore, it is an urgent task for the CM community to develop computational medicine and establish a digital CM human body consistent with the international virtual human program.

Research Status

Current Situation of Disciplinary Research

Some achievements of computational medicine have been proven clinically and the research status are listed in the right box.

Orthopaedics

Kevin S, et al⁽²⁰⁾ used a computer model to evaluate the number of femoral epiphyseal fractures in patients with open double bundle posterior cruciate ligament reconstruction. Ten patients with skeletal dysplasia (6 girls,

- Advanced mathematical models enable researchers to understand how molecular networks are represented in cancer and then use this knowledge to predict which patients are at risk.
- A discipline called computational physiology uses computer models to study how biological systems change from healthy to unhealthy over time. This approach can be used to help treat cancer, diabetes and heart disease.
- Computational anatomy uses changes in medical images to detect, for example, the shape of various structures in the brain. Researchers have found morphological changes that may be associated with Alzheimer's disease and neuropsychiatric disorders such as schizophrenia.
- The calculation model of ECG activity has been used to guide doctors in the prevention, diagnosis and treatment of sudden cardiac death.
- Director Raymond Winslow recounts an example of rapid acceptance in the medical field regarding a new iPad app that uses computational anatomy to guide doctors in deep brain stimulations of Parkinson's patients.⁽¹¹⁾ An artificial intelligence enterprise building a life data analysis platform is the embodiment of the research results from the Institute of Computing, Chinese Academy of Sciences. It socializes the application of artificial intelligence in biomedical data processing, constructs a life information engine, and empowers the clinic.
- Through Twirls, a subsystem of the life information engine, we analysed more than 14,000 articles related to coronavirus worldwide. Within 4 h, we found the potential mechanism of the "cytokine storm" caused by the new coronavirus and then suggested a new target for treatment. This finding was verified in a paper on the research square platform on 25 March, 2020 by WANG Chao-fu, Professor of Pathology, Shanghai Ruijin Hospital, and BIAN Xiu-wu, academics at the Chinese Academy of Sciences.
- The machine learning model can deeply interpret global variations in the tumour genome and evaluate the activation state of the tumour signalling pathway, which can stage the tumour, evaluate the origin of a primary tumour, predict the progress of tumour, assist doctors and patients in selecting targeted, chemotherapy and immune treatment drugs, and evaluate the efficacy of the drugs.
- This approach can help researchers on failed clinical trials find new indications for drugs.

4 boys) were selected for the study. Each patient's MRI scan was converted into a 3D model using computer-aided design and manufacturing software. The 3D model was used to simulate the anatomic double beam technique using tunnels with diameters of 6, 7, 8 and 9 mm. Through computer modelling and the simulation of immature bone knee joint

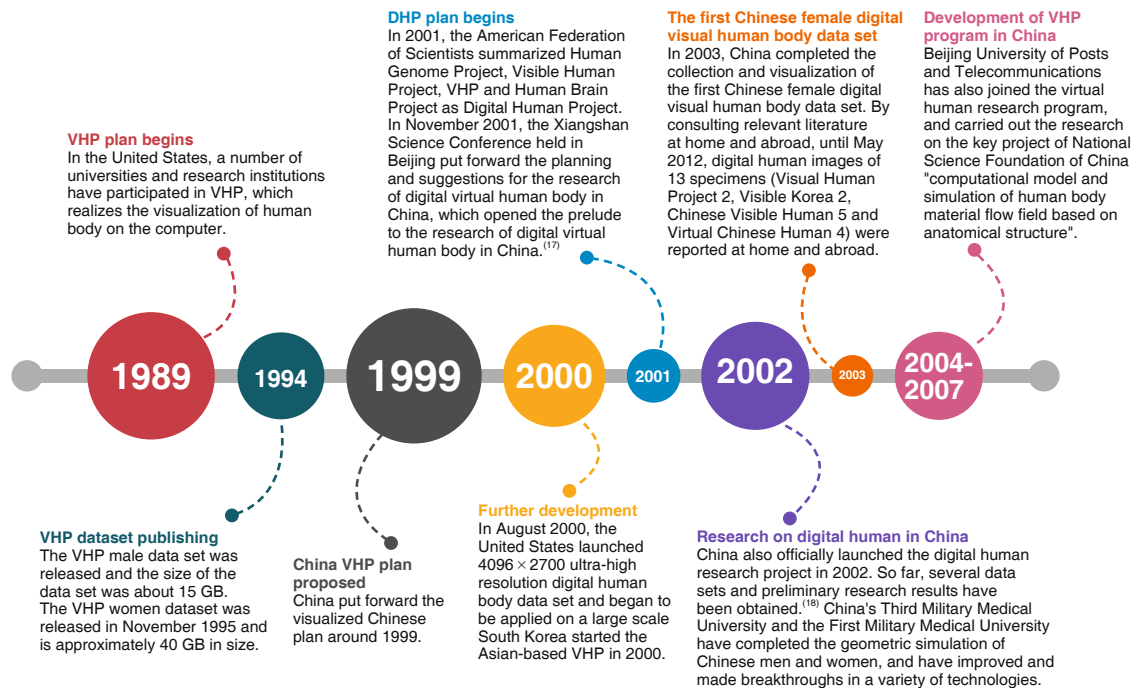


Figure 3. Development of Digital Human Program

Note: VHP: Virtual Human Project

double bundle posterior cruciate ligament reconstruction, it was found that the posteromedial tunnel prevented the fracture of the distal femur bone graft, and the volume of all the epiphysis removed was less than 4%.

Clinical Medical Examination

A patient-specific pulse oximeter and pressure sensor called P3 was used. During the entire manufacturing process, a digital calliper was used to measure the patient's fingers, and then the computer-aided design model of the finger cuff was designed based on the measurement results. Lastly, the finger cuffs were printed in 3D by using FRE technology and polydimethylsiloxane (PDMS). The results showed that the FRE printing of a polydimethylsiloxane elastomer cuff can be used to make wearable devices for patients, which can be comparable to commercial devices for measuring the heart rate and blood oxygen saturation percentage.⁽²¹⁾

Cardiology

To assist in the study of myocardial microdamage caused by intermittent high-intensity ultrasound pulse circulation contrast agent microbubbles, a computer-assisted histological evaluation of the effective treatment volume, an optimization of the ultrasound pulse parameters, an estimation of the exposure time and a contrast agent dose were taken. As many as 40 tissue sections were imaged by light field and fluorescence

microscopy. First, tissue recognition and microdamage detection are performed based on two-dimensional images, and then an image registration is performed on the micro-injury mask. A volume-based model is reconstructed according to the morphology of the heart. Lastly, the total volume of the micro-focus is determined along the axis of the therapeutic beam. The macroscopic lesion in the radial symmetry fraction was characterized by a variable radius step disk, and a radial symmetry lesion model was proposed as a robust treatment for evaluating myocardial cavitation.⁽²²⁾

Human Histology

Indirect 3D printing technology was integrated with imaging technology to create a patient-specific scaffold that accurately matched the external contour of the patient. A custom-made scaffold simulating the human mandibular condyle was created using polycaprolactone and chitosan for potential osteochondral tissue engineering. The ability of this technology to control the internal morphology of the scaffold accurately was tested by creating orthogonal interconnection channels in the scaffold by using the computer-aided design model. The results showed that bone marrow stromal cells showed good survival ability in the scaffold, and the apatite coating further enhanced cell proliferation. This technology may be valuable for complex scaffold manufacturing.⁽²³⁾

Research Trajectories of Computational Medicine at Some Well-Known Institutions

The research directions of computational medicine in some well-known institutions are listed in Table 2.⁽¹⁰⁾ After 20 years of research and exploration, the Institute of Computing Technology at the Chinese Academy of Sciences has vigorously promoted computational medicine with the rapid development of supercomputing. The achievements in supercomputing at this institute are in the first echelon in China. The professors in the program, who are represented by TAN Guang-ming and ZHANG Chun-ming, are researchers with 20 years of experience in supercomputing. This institute has been actively

Table 2. Research Trajectories of Well-Known Institutions

| Institution | Research direction |
|--|---|
| University of Bristol | Special emphasis is placed on various-omics techniques for common metabolic diseases, such as diabetes and cardiovascular diseases. |
| Laboratory of Computational Medicine and Visualization, Bengbu Medical College | Since 2004, this group has been devoted to the study of stereotactic localization, three-dimensional reconstruction and visualizing the sulcus and gyrus. Three-dimensional localization data sets and visualization models of the sulcus in vivo based on thin-layer MRI have been constructed. |
| Third Military Medical University and Southern Medical University | Eight high-precision Chinese digital human data sets have been constructed and organ tissue modelling has been performed. |
| Huazhong University of Science and Technology | Physiological-omics research based on the digital human body is being performed. |
| Johns Hopkins University School of Engineering and School of Medicine jointly set up Institute of Computational Medicine | This program is committed to using computational modelling to predict how protein mutations can trigger the development of breast cancer, compare the shapes of brain structures in healthy people and patients to determine the differences that may lead to brain diseases and better diagnosis and treatment methods, and study computational models for the initiation and maintenance of cardiac function during dangerous arrhythmias to determine how to use defibrillators to stop these irregular hearts. They are performing research on visceral rhythms and other subjects. |
| University of Colorado/ University of Washington/ The University of Michigan and University of Hamburg | This work focuses on the application of the virtual human in biomedical research and education. |
| University of Michigan cooperates with U.S military | Developing virtual soldiers. |
| Chinese University of Hong Kong | Research on 3D rendering of digital human organ structure, virtual acupuncture and virtual surgery model and systems. |
| Xiamen University | Construction of a virtual eye model. |
| Shandong University | The objective is to establish a digital model of liver segments and a new standard for liver segment division in Chinese patients. |
| European Union Centre for Computational Medicine | This program is committed to computational neuroanatomy, the image-based brain connectome, imaging genetics, imaging and genetics of brain diseases and cognitive impairment. |

participating in national projects for many years. To promote the development of computational medicine and cooperate with the human genome project, genomics processing technology has been developed, and a gene data computing model and fusion model have been established.

Outstanding Issues in Research

With the development of computer technology, the scope of applications in the medical field is expanding, and achievements in clinical practice are increasing daily. Researchers in the field are full of expectations for the future. However, the development of computational medicine needs to be adjusted to address the challenges of data processing, model building and the implementation of these tools in routine clinical practice. To address these challenges correctly, the first step is to clarify the scope and content of these problems. This section will discuss the key issues and limitations of computational medicine in research, development and application.

Generally, there are three points to consider: how to build a fair data governance framework and use platform; computer technology understanding (including an understanding of its limitations and how to explain its discovery) when building digital models; and how to solve process safety, ethics, supervision and other issues in clinical practice.

Data Concerns

The complexity of the human body makes the sample information highly complex, which may cause deviations in the collection and input of data, affecting its accuracy.⁽⁷⁾ In addition, because medical record data involve patient privacy and have special protections, it is easy to reduce the degree of patient cooperation and affect the amount and diversity of data.^(24,25) Moreover, the suddenness and linearity of clinical medical treatment can lead to the fragmentation and easy loss of hospital records, which will reduce the utilization rate of the existing data; however, due to the influence of factors such as national interests, commercial interests and the ambiguous ownership of medical data, there is a lack of reasonable data sharing and circulation mechanisms, so data sets are not often shared and cannot be circulated and collected, and good utilization methods cannot be promoted, developed and applied in practice.^(7,26) The large amount of biomedical information is of great importance to national security and scientific and technological development prospects, so ensuring the security of model data when using data is also an

important challenge when building a fair data governance framework and usage platform.

Technological Considerations

The establishment of computer algorithms and models requires strong computer technology, which requires the integration of other information processing technologies and related disciplines. To achieve this integration, there are many challenges, such as creating a standard form of knowledge representation and transfer, understanding the effective interaction between subsystems, and developing a new method for the comprehensive representation of numerical models and non-numerical knowledge. It also includes a combination of a quantitative model and a qualitative model to conduct qualitative reasoning at a faster speed. While hardware guarantees computing implementation, software is the core of computing, and the implementation of computer algorithms also requires the promotion of powerful hardware facilities and software systems.⁽²⁷⁾ Another difficulty is that an algorithm of deviation may be produced to strengthen the data processing on the basis of race, gender, or other characteristics of discriminatory practices. Training data transparency and the interpretability of the model will be allowed to check for any potential bias.^(7,24) The theory of computational model construction is different from the real human condition. The current flood and conflict of available medical and biological information, coupled with the absence of functional models that reflect the pathogenesis and pathological evolution of complex diseases, leads to the inability to address the occurrence and development of diseases coherently and to build fully realistic models. It is important that we acquire part of the necessary knowledge and use analytical methods and processes (collectively referred to as "system biology") to generate computer simulation models. However, if there is no analysis method that specifically analyses the data facts (that is, the so-called information cannot be determined whether it is useful or not, and all information should be regarded as prior suspects), then the attempt to model the situation will fail due to a large quantity of uncertain information.⁽⁷⁾ In addition, there is no uniform international standard for the definition and clinical manifestations of certain diseases, which will further increase the difficulty of the modelling process and the uncertainty of the model.

During the development of computational CM, it is important to consider that many CMs have unique bidirectional regulatory effects. How can these

functions act on the human body and then play their roles in treating diseases? How can we establish a CM model based on this factor? How can the mechanisms of action of CMs be reflected during the modelling process? In addition, the composition and quantity of CM prescriptions will vary with the patient's constitution, disease condition and environment. How can the specific curative effect be reflected when the model is running? Any of these uncertainties increases the technical difficulty and accuracy of CM modelling.

Clinical Practice Considerations

Some barriers are related to practical problems in the healthcare industry, including reimbursement and liability. For example, how can reimbursement be performed for medical insurance?⁽²⁶⁾ Who is responsible for a medical accident? Is it the machine development organization, model system builder, hospital or doctor? These responsibilities include ethics and laws. How can these responsibilities be divided?⁽⁷⁾ This method of human-computer integration for clinical diagnosis and treatment requires a new medical operation mode.

Some of these challenges are related to the capabilities of developers. Both research and development and the application of computational medicine involve many fields, such as medicine, mathematics, and biology. Interdisciplinary cooperation is essential to ensure that the goal of programmer algorithm development is consistent with that of clinicians to provide patient care. It is necessary to cultivate a team of cross-trained staff so that doctors, data scientists, computer scientists and engineers can communicate and collaborate, which will be crucial.⁽⁷⁾

Other problems are related to the ability and future direction of doctors. The development of computational medicine brings more challenges than help to doctors. For example, doctors may not need to know the detailed mathematical calculation used in the calculation model, but because the model operation and prediction cannot come in contact with patients in the real world, the doctors may make mistakes, so they need to master the operation principles of the model,⁽²⁸⁾ to interact with the computing system, supervise the model operation, optimize the treatment scheme according to the actual situation, and improve the throughput. This is a key problem to solve in the clinical practice of computational medicine to distinguish what can be done by computational medicine and what can only be done by doctors when computational

medicine develops going forward and its clinical application is gradually widespread. For example, the treatment scheme obtained by the calculation model lacks a human touch, and its reliability and authenticity easily create questions in patients and require explanations by doctors. In addition, the patient's medical level is limited, and doctors are needed to help them understand the model scheme and select the best treatment scheme among those proposed by the model.

Computational medicine provides a powerful tool for analysing a large quantity of complex medical data. It uses a model construction designed to predict and select treatment options to improve the quality and efficiency of medical services. However, the clinical application of computational medicine is restricted by these three above mentioned aspects. It is necessary to improve the quality and circulation of data, the algorithm also needs to be improved for better model building technology, and iterative optimization must be performed for actual clinical problems.

Future Prospects

Application Fields

The earliest application of computational medicine in the clinic is computational anatomy based on anatomical knowledge using image processing, digital geometry, mathematical modelling and virtual reality. It focuses on the quantitative analysis of biological morphological variation, human body structure modelling, surgical planning, stereotactic surgery, precise radiotherapy, image navigation surgery, robotic surgery and the morphology and function of nervous system evaluation. For example, there are many applications of computer-aided bioprinting microvessels in disease modelling and drug testing, including cardiac applications, the encapsulation of human umbilical vein endothelial cells in bioprinted microfibres to create a fused epithelial layer and the implantation of myocardial cells in scaffolds to create endothelial myocardial tissue, the fabrication of a vascularized aerial chip model by a 3D vascular network and airway epithelial cells, the 3D reconstruction of the liver lobule model, the use of a bioprinted kidney model to detect renal resorption through the interaction between proximal tubular epithelial cells and glomerular microvascular endothelial cells, bioprinting microvascular system applications for placental modelling to understand preeclampsia and other reproductive diseases, and bioprinted tumour models to detect tumour metastasis.⁽²⁹⁾ It is expected that in the near future, more computer-aided modelling will be applied to clinical and basic research.

Other areas that need to integrate many different types of data, such as computational physiology, computational epidemiology, computational pharmacology and other basic disciplines, or areas with prominent program components, such as computational surgery, may take longer to integrate operations based on computational medicine technology. All the related applied research on computational medicine is advancing rapidly, but although the theory of computational medicine is powerful, its clinical applications are few. Although we know that this situation will soon change and implementing this technology will become inevitable, the question is not whether it will happen but when it will happen. To promote this process, we must think and discuss the future of computational medicine.

Integration with Artificial Intelligence

To develop a new computational medicine application algorithm and improve the existing computational medicine model algorithm, we need additional research.⁽³⁰⁾ The application of artificial intelligence, especially machine learning, is increasing in clinical practice. The combination of computational medicine and artificial intelligence is an important direction for the improvement and development of clinical decision support systems.

Artificial intelligence involves the development of computer algorithms to perform tasks usually associated with human intelligence. It is widely used in technical vocabulary and popular vocabulary, covering a range of learning, including but not limited to machine learning, presentation learning, deep learning and natural language processing (Appendix 2). Regardless of the specific technologies, the overall goal of using these technologies in medicine is to use computer algorithms to discover relevant information from data and assist in clinical decision-making because it can perform a wide range of functions, such as assisting in diagnosis generation and treatment selection, risk prediction and disease stratification, reducing medical errors, and increasing productivity. Both artificial intelligence and computational medicine assist in clinical decision-making by means of computers. Artificial intelligence focuses on data information to rule summary, and computational medicine focuses on data models for operational prediction. Those based on computer technology have their own advantages and complement one another. When computational medicine, artificial intelligence and clinicians work together, there will be a synergistic effect that is better than one or

all of them combined, which will definitely revolutionize the clinical decision-making system.

Importance of Computational CM

Computational CM is an essential part of the development of computational medicine. Although CM has not established its own theoretical system by reductionism and defining axiomatic systems, the fuzzy detection, judgement and decision-making methods in the theory of CM can be used to innovate a set of new scientific thinking and reasoning methods as long as the methods are sorted out, perfected, and improved by using the theories of mathematics and system science, completely avoiding the problem in which modern science is subject to a fatal Gödel's incompleteness theories.⁽¹⁹⁾ On one hand, to inherit and develop the scientific theory of CM, we must strive to modernize it; that is, we must establish a set of concepts and methods of computational CM science. On the other hand, computational medicine provides another methodology and mode of thinking for computational medicine, which is an essential part of the development of computational medicine. Although people are increasingly interested in computational medicine, including digital CM, the substantial transformation of these technologies in clinical application has not yet appeared. In the next few years, solving the problems involved in developing computational medicine will have a profound impact on the future of the field.

Medical Clinical Practice and Scientific Research

In the era of computational medicine, the clinical diagnosis and treatment process will be optimized. In addition to guiding the implementation of treatment plans accurately, clinical medical workers can focus on global clinical management, including personalized drug side effect management, postoperative management, rehabilitation program management, emergency management, prognosis management, follow-up, accurate definitions of individualized rehabilitation indicators, etc. The model building system of computational medicine provides an effective experimental simulation method for future scientific research. This system can customize specific disease evolution models. For example, in the 8th edition of the Genotype-Tissue Expression (GTEx) project, a probability model for personal genome interpretation was developed to evaluate tens of thousands of rare gene mutations, some of which were related to gene expression patterns, and disease risk had an important impact. The model integrates the methods for identifying

expression, allele-specific expression and alternative splicing outliers and describes the RV landscape under each abnormal signal. The results show that the use of this signal can enhance personal genome interpretation and RV discovery, integrate more abundant functional RVs into the genetic load model, improve the level of disease gene identification, and achieve accuracy in genomics research.⁽³¹⁾ Based on the needs of clinical medicine and scientific research, computational medicine should adhere to two research directions. One is to apply information science to life science and medical research and adopt a data-driven learning method to understand the mechanisms of diseases and explore new drug targets and treatment schemes; the other is to review the knowledge of professional fields comprehensively by establishing a man-machine interface and summarize and establish a knowledge model. Combined with functional genomic data, this approach can help medical researchers infer the unknown from the known and engage in further development.⁽⁹⁾

Conclusion

Modern society has entered the information age, and biomedical data in the medical field have entered the Pb level era. To break through the existing "bottleneck", the biomedical field must accelerate the layout of the new digital infrastructure underlying computational medicine, give play to the driving role of computational power, artificial intelligence methods and big data, and fully engage the value of biomedical big data.

We have reasons to believe that, with the deepening of the related disciplines around the development of science and technology major requirements, this emerging discipline of medicine will continue to develop. It provides a new and unique awareness, detection and treatment of diseases using quantitative methods to serve the correct understanding of life, for the service of the "individualized" diagnosis and treatment of diseases, and along with further development, it will create a refined, quantified, and new era of individualized medicine.

Conflict of Interest

The authors declare no competing interests.

Author Contributions

Lyu LQ and Cui HY contributed equally to this work. They contributed to the central idea, analyzed most of the data and wrote the initial draft of the paper. Shao MY made

key modifications to the important knowledge contents. The remaining authors contributed to refining the ideas, carrying out additional analyses and finalizing this paper. All authors agree to be responsible for all aspects of the work to ensure that the accuracy and integrity of any part of the work are properly investigated and solved.

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