Research Commentary
Intelligent Systems and Technology for Integrative and Predictive Medicine: An ACP Approach

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One of the principal goals in medicine is to determine and implement the best treatment for patients through fastidious estimation of the effects and benefits of therapeutic procedures. The inherent complexities of physiological and pathological networks that span across orders of magnitude in time and length scales, however, represent fundamental hurdles in determining effective treatments for patients. Here we argue for a new approach, called the ACP-based approach, that combines *artificial (societies), computational (experiments), and parallel (execution)* methods in intelligent systems and technology for integrative and predictive medicine, or more generally, precision medicine and smart health management. The advent of artificial societies that collect the clinically relevant information in prognostics and therapeutics provides a promising platform for organizing and experimenting complex physiological systems toward integrative medicine. The ability of computational experiments to analyze distinct, interactive systems such as the host mechanisms, pathological pathways, and therapeutic strategies, as well as other factors using the artificial systems, will enable control and management through parallel execution of real and arficial systems concurrently within the integrative medicine context. The development of this framework in integrative medicine, fueled by close collaborations between physicians, engineers, and scientists, will result in preventive and predictive practices of a personal, proactive, and precise nature, including rational combinatorial treatments, adaptive therapeutics, and patient-oriented disease management.

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1. ACP FOR INTEGRATIVE AND PREDICTIVE MEDICINE

The fundamental challenges in medicine arise from the inherent complexities of interacting complex biological networks. Examples of these networks include normal physiology, host defense mechanisms, pathological pathways, pharmacogenetics, and pharmacodynamics. The operations of these networks are generally stochastic in nature and these networks can interact in complex manners [Becskei and Serrano 2000, Ottino 2004]. The complexity is often beyond intuition by considering a subset or even all networks. Therefore, it is increasingly realized that an integrative perspective

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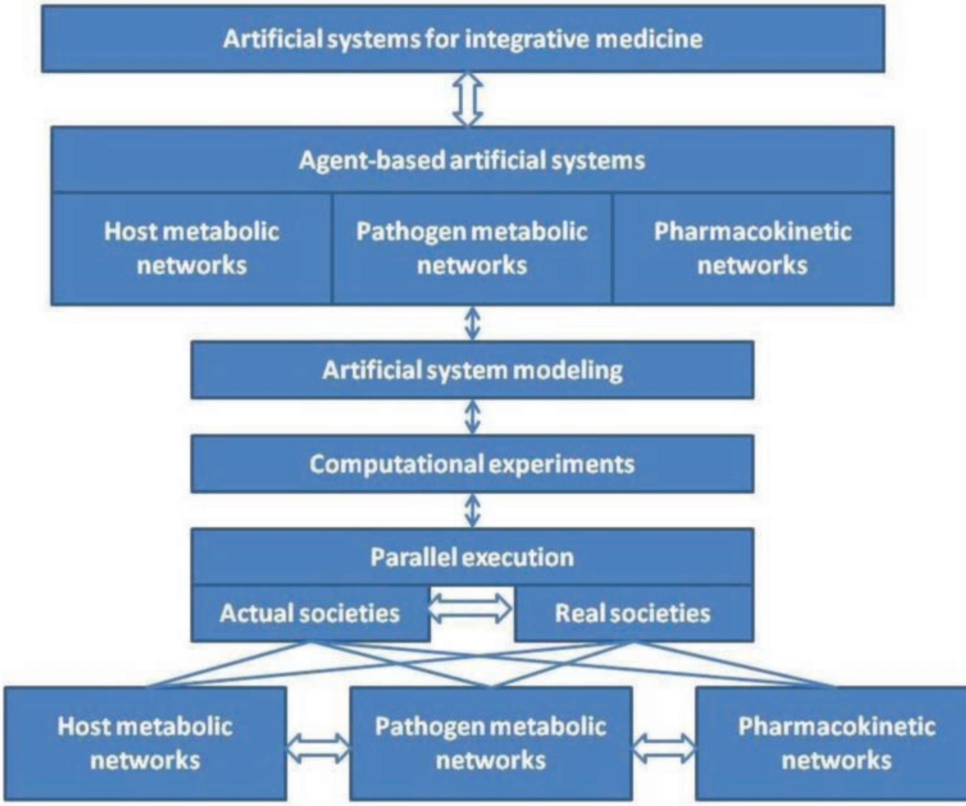

Fig. 1. The ACP-based framework for integrative medicine.

enabled by advanced bioinformatics and biotechnology may serve as the catalyst for the fruition of a new generation of integrative medicine. This integrative perspective in conjunction with modern biomedical sciences will collectively address the major roadblocks in patient treatment. It will also develop a new generation of quantitative, interrogative, and integrative medicine (Figure 1).

The complexity and challenge of integrative medicine can be exemplarily illustrated by considering the treatment of infectious diseases caused by bacterial pathogens. The emergence of MultiDrug-Resistant (MDR) pathogens has been referred to as a "world-wide calamity" [Kunin 1993]. Pathogens responsible for many of the common human infectious diseases such as urinary tract infection, gastroenteritis, pneumonia, and wound infections have proven highly adept in acquiring mechanisms of antimicrobial resistance [Levy and Marshall 2004]. To understand the antimicrobial susceptibility of pathogens, knowledge of the bacterial metabolism and their interactions with different drugs is required. The metabolic networks of the host should also be considered in terms of the efficiencies, toxicities, and other side-effects of drugs. The pharmacokinetics and pharmacodynamics that determine the fate of a substance in the patient's body could also influence the treatment procedures and results. Furthermore, the management of infectious diseases is actually beyond a pharmacological problem and requires a global perspective in current clinical practice. Currently, standard culture-based diagnosis of bacterial infections, including pathogen identification and antimicrobial susceptibility testing, requires 2–3 days for clinical sample acquisition to result reporting [Kunin 1997]. The absence of definitive microbiological diagnosis at the point of care has largely driven the over- and misuse of antibiotics that accelerate the development of MRD pathogens. As a result, the need for new antibiotics has far outpaced the development of new classes of antibiotics by the pharmaceutical industry (2 in the last 20 years), in large part due to prohibitive cost and overall poor investment returns. These highlight the complexity of many healthcare problems and call for new approaches in integrative medicine.

One of the key concepts in integrative medicine is managing diseases from a system perspective. Combination therapy, in contrast to monotherapy, is an excellent example demonstrating the requirement of integrative medicine. Multimodal therapy and combinatorial treatment, in many cases, are more effective than using a single treatment. For instance, Traditional Chinese Medicine (TCM) often considers dynamic funcational activities of the body from a system perspective. Treatments including chinese herbology, acupuncture, and massage are often applied in combination. However, it is a highly challenging task to optimize multiple therapeutic options by trial-and-error. Recently, system theory and information technologies have proven to enable new opportunities in this regard. Using stochastic search and statistical metamodeling techniques in experimental settings (enabled by advanced biotechnology), synergistic antimicrobial and antiviral combinations that have high efficiency, and at the same time lower toxicity to the host, can be rapidly identified [Chen et al. 2010; Wong et al. 2008]. This provides an example of the applicability of interdisciplinary approaches in healthcare and medicine.

Advancements in complex systems analyses, computer sciences, artificial intelligence, operations research, bioinformatics, biotechnology, and systems biology have enabled novel possibilities in integrative medicine. Based on the fruitful development of artificial societies and social networks over the past decade [Wang 2007; Wang and Tang 2004], interdisciplinary perspectives and novel concepts based on artificial systems are introduced into this fundamentally important area of integrative medicine. The conceptual framework and technological tools developed represent the integration of knowledge across multiple disciplines. A framework for predictive and integrative medicine can be categorized into three major steps, including modeling and representation with artificial systems, analysis and evaluation by computational experiments, and control and management through parallel execution, the so-called ACP-based approach. Our long-term goal is to develop this approach for sustainable development of integrative medicine.

2. ARTIFICIAL SYSTEMS FOR MEDICAL AND HEALTH MODELING AND REPRESENTATION

A fundamental challenge in modeling biological systems toward medicinal purposes is the complexity of biological networks. A system is considered complex if it possesses emergent properties that are not obvious from the properties of the individual components. While traditional modeling techniques can describe some aspects of a biological system, these methodologies are not tailored to manage complex systems in general and have limited capability in analyzing the emergent properties. On the other hand, artificial societies and agent-based modeling techniques provide highly effective platforms for this purpose. The implementation of artificial system modeling typically involves cellular automata and related modeling agents, descriptive rules for modeling agents' behaviors, multiresolution analyses of the local agents and global behaviors of the networks, Petri nets, and machine intelligence for decision making by individual components. These techniques have been applied for describing a wide spectrum of complex systems, such as transportation, political science, and finance, and are capable of considering the combined effects of multiple networks in an effective manner.

There is a massive amount of information available in biology and medicine. A critical task is to collect and gather the information toward useful description for integrative medicine. Numerous databases have been developed in collecting this information. For example, the identification of samples and the preparation of medicinal compounds are contained in pharmacopeia and genetic information can be found in the genome database. These provide useful starting points for building an artificial system for predictive and integrative medicine. Clearly, there is also information that is not available for describing the networks and, more importantly, the interactions between these networks are, at most, partially known. It is one of the major tasks for the artificial intelligence community to create a framework to address these problems. A related problem in integrative medicine modeling is the multilevel complexity of our bodies. Multilevel complexity is a signature in biomedical systems. This presents a challenging research problem in system modeling. With a biomedical or biological point of view, efforts have been attempted to describe all elements in a biological system down to molecular level. While exact descriptions of a physical system and artificial systems are not mutually exclusive, description of the functional characteristics or "equivalent" behaviors is a more effective approach when considering systems that possess multiple levels of complexity. This is nicely summarized by the famous quote from Albert Einstein.

"*It can scarcely be denied that the supreme goal of all theory is to make the irreducible basic elements as simple and as few as possible without having to surrender the adequate representation of a single datum of experience*" [Einstein 1934].

3. COMPUTATIONAL EXPERIMENTS FOR MEDICAL DESIGN, TEST, AND EVALUATION

Most information that we have in medicine is based on passive observation and statistical methods, as it is difficult to conduct active clinical tests and trails. Often there are a large number of uncontrollable parameters in clinical experiments which render the result inconclusive and unusable. This is particularly challenging as most complex systems cannot be understood through simple analytical reasoning. This is not to say experimental observation is not important. On the contrary, the development of an artificial society or system can lead to a "computational lab" or a bio-informatic framework for organizing and testing the known knowledge and can guide additional studies to obtain critical information in those networks that are not available. Analyzing complex systems using such computational experiments will allow medicinal investigation from a system perspective. This is particularly required to estimate the best treatment option to determine the risks and benefits of a therapeutic procedure.

An important example that illustrates the importance of computational experiments is the treatment of the Human Immunodeficiency Virus (HIV), which causes Acquired ImmunoDeficiency Syndrome (AIDS) [Perelson et al. 1997]. The current standard treatment for patients with AIDS is to apply Highly Active Antiretroviral Therapy (HAART) to suppress viral replication. This allows the body to rebuild its immune system. Patients are required to take at least two classes of antiretroviral drugs every day. However, these drugs can often cause unwanted side-effects such as vomiting and nausea. Among these patients, a significant portion ($\sim$25%) stops therapy within the first year due to these side-effects. Therefore, the optimal treatment of AIDS is actually a delicate balance between the antiviral effect and drug toxicity. Clearly, optimal dosage and combination of antiretroviral therapy cannot be determined by trial-and-error and requires quantitative knowledge of the viral load and host responses in a time-dependent manner. Computational experiments that analyze complex responses in a systematic manner will provide a potent strategy to evaluate the various effects of different therapeutic options. Incorporating optimization strategies in operation research and artificial intelligence will allow physicians to predict the best HAART with minimal side-effects to patients.

4. PARALLEL EXECUTION FOR CLINICAL AND HEALTH IMPLEMENTATION AND MANAGEMENT

Another fruitful development for managing a complex system is parallel execution. Parallel execution refers to the implementation of a real system and one or more corresponding artificial systems in parallel. Therefore, the parallelism here is argumentation, different from the idea of divide-and-conquer as in conventional parallel computing. This approach is originally proposed and applied for engineering complex transportation systems, electrical power grids, ecosystems, and social economic systems and can be considered as a generalization of conventional control methods, especially adaptive control in automation.

Three major modes of parallel execution are available: learning and training, experimenting and evaluating, and controlling and managing. In learning and training mode, real and artificial systems are loosely connected and actual coupling between the two is not required. Artificial systems in learning and training mode can serve as physician training systems or backup to support the actual operation when patient information is not available. In experiment and evaluation mode, artificial systems are used in conducting computational experiments to analyze and predict behaviors of the patient. This is one of the most important modes for integrative medicine and can also be applied in determining combination therapy and patient-oriented disease management. In control and management mode, artificial and real systems are connected in real time. The real-time interactions between the real and artificial systems are required for adaptive therapeutics. However, it is also the most challenging mode to implement among the three different modes of parallel execution, as indicated by engineering problems [Huang et al. 2012; Lun 2012].

5. CONCLUSION

In summary, ACP-based methods provide a low-cost, reliable, and flexible platform for intelligent, effective control and management of medical systems from a system perspective. Efforts are being devoted to a comprehensive operational framework that will connect networked biomedical components [Tang and Yang 2012; Lampos and Cristianini 2012]. The research will enable networks to seamlessly communicate and result in preventive and predictive practices with the three Ps: Personal, Proactive, and Precise, for example, rational combinatorial treatments, adaptive therapeutics, and patient-oriented disease management.

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