Micro-holistic body model: reconciliation of Traditional Chinese Medicine with modern biomedicine?

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Abstract

Development of molecular biology reveals that multicellular organism could be considered as a cell community. By scrutinizing constitution and activities of a single cell under context of the whole community, I got a micro-holistic body model constituted of two aspects and seven compartments. The two inseparable aspects are the extracellular signalling molecules and the cells that communicate with each other using extracellular signalling molecules. The seven compartments include three universal sub-cellular compartments running within every cell in the body and four specific systems comprised of specific cell groups and molecules providing particular services needed generally by cells in the body. The constitution and internal relationship of the model match the fundamentals of traditional Chinese medicine (TCM) perfectly, thus can philosophically bridge the understanding between traditional Chinese medicine and western medicine, provide research hypotheses, and connect molecular level research with clinical diagnosis and treatment of complex diseases more directly, and may cause profound revolution in human healthcare technology.

Keywords
Micro-holistic body model, Molecular medicine, Traditional Chinese Medicine, Macro-holistic body model, Gene network

Introduction

With decades of the progress of molecular biology in various aspects, tremendous collection of molecular and cellular level knowledge and facts about multicellular organism are accumulated. To make better use of the knowledge in biomedicine and to make further investigation at different levels, there is always the need to piece up the molecular phenomena into systemic properties of human body. People usually resort to mathematical and computational tools for such efforts. However, it is always helpful to carry a clear theoretical picture about human body in mind in order to construct better and experimentally instructive models. Basically there are three theoretical recognitions of human body. First, human body is a highly sophisticated machine and possesses all mechanical properties; second, human body is a huge chemical factory whose main activities are focused on energy and material metabolism; third, human body is a society of various types of cells and is a complex self-adjustable
system. None of the recognitions is wrong; each describes a single dimension of human body. The first two dimensions are extensively addressed in previous researches of biological and medical field, and may be the most influential in the mind of researchers who are now engaged in model building for systems biology. However, the third one remains a background statement in molecular and cellular biological field, which I feel may be the key point for some breakthroughs in systems biology and mechanism studies of some complex diseases. This paper is the first one that directly addresses the internal molecular sociality of a multicellular organism using sociological strategy upon molecular and cellular constitution of human body. Moreover, the match between the micro-holistic body model and Traditional Chinese Medicine (TCM) body model implies scientific, philosophic and cultural significance in the future researches and practices of medicine.

The foundation of any kind of medicine starts from knowledge about human body, both physically and functionally, thus it can define the health and sickness, tell the abnormal from the normal, and evaluate the outcomes for various treatments.

Basically, conventional western medicine reaches this goal by first structurally dissecting the human body, then integrating the function of the isolated body components as dynamically as possible. Even though the recognitions of life have undergone tremendous changes in the 20th and 21st century due to the progress of biology and related natural sciences, the structurally dissecting then functionally integrating methodology remains intact in conventional medicine field, and is subsequently dominating the evolving genome and proteome medicine researches too (see figure1).

Undoubtedly, this methodology has been a great success in the establishment and development of modern medicine and is deeply rooted in our modern life and culture. Our mainstream healthcare systems throughout the world are based on such philosophy; and we are now enjoying better life quality and longer life span than our ancestors. But both the philosophy and current medicine are far from perfect, so do the medical treatments we are receiving now. The core of this dissecting/ integrating methodology is assuming our body as a highly sophisticated machine, so the nature of the body’s function is mechanical and predictable by interactions and relations among sub-components. On certain level, it is true; but when the dissecting adventure has come to cellular and molecular level it is becoming harder and harder for the machine hypothesis in our mind to match the observational facts. From a current molecular biologist point of view, the genome of an organism is more like a detailed outline for a literature work, rather than a blueprint for a building or a machine; while individual proteins in a proteome are more like words and phrases in a prose other than nodes in a mechanical or electronic network (1).

This gives us an insight into the nature of the difficulties we are facing in our attempts to integrate our bio-molecular level observation into gene or protein regulatory network and then reach organism level medical understanding. Such difficulties are more philosophic than technical. Even if advancement in silicon technology can provide more powerful simulative environment, a huge lot of dynamic, interactive, environmental and context information that are needed for a successful and accurate simulation has been deprived in the structure dissecting process for the sake of physical accuracy and clarity.

The physical dissection caused loss of dynamic, interactive, environmental and background information is common in scientific researches; it is not a big deal for a mechanical system whose main function at various levels are controllable and predictable. However, for adjustable complex systems like social groups, districts or countries, as well as multicellular organisms such kind of information loss is fatal for the functional integration process.

In some research fields especially social sciences where physical accuracy is a minor factor and the focus of research is function and activity of the subjective system people naturally dissect the function/activity of the system into several interrelated, even overlapped functional subunits and at the same time keep maximum dynamic, interactive, environmental and background factors in their consideration. For example, when we are studying current state of a country, we may divide it into several aspects such as politics, culture, industry, agriculture, nature resources, financial system, and defence power. All of these aspects are naturally interrelated and interdependent, and they form a holistic model to evaluate the situation of the country.

Since most life scientists have already agreed on that multicellular organism could be considered as a community of different types of cells, then using the function dissecting methodology on human body is not totally groundless from modern scientific point of view. Of course, a medicine branch based on such methodology has to trade anatomical accuracy and clarity for vast dynamic, interactive and environmental documentation. TCM is exactly the case. According to Yellow Emperor’s Inner Classic (Huang Di Nei Jing), a book about TCM fundamentals, the function of human body are enunciated by five theories: Yin Yang, Five Element, Qi (air/energy) Xue (blood), Ying (nutritive Qi) Wei (protective Qi), and Meridians (2). Each theory interprets a different aspect of body function, and almost all of them are inter-containing and interdependent with the exception that Meridian theory seems parallel with the other four.
First, the Yin Yang theory (2) claims that like any other objects in universe, body function are the collaborative results of two dynamically interdependent aspects. Body’s physical substance belongs to Yin, while body’s activity or function belongs to Yang. Yin and Yang are not mutually exclusive. There is Yin in Yang, and vice-versa. Each supports the other. Yin and Yang use each other. They cannot exist without each other. Yin nourishes, prompts, and restricts Yang; Yang instructs, transforms, and leads Yin. The normal vital activities of the human body are the results of the interaction and relative balance between Yin and Yang. The above description is mystical enough to annoy any curious scientific reader, but a proper analogue will solve the difficulty immediately. Say we are studying a working group consisted of several members, and every activity of the group as a whole is the result of cooperation of all the members. The members use various methods to coordinate their action, including words, facial expressions, gestures, and other body languages. Then all these informational components of this group should be assigned Yang property, and the actual members should be Yin. And relatively say, the members who mainly send out instructions are more Yang, while the members who mainly receive instructions and respond to them are more Yin.

Second, according to the five element theory (2), all functions of the body can be dissected into five inter-containing and interdependent compartments which are represented by metal, wood, water, fire and earth respectively. The five compartments maintain a dynamic balance by constantly interacting with each other in certain generating or restricting way among themselves. The content of five element theory is shown in figure 2.

The water compartment is called T-kidney (as for TCM kidney) which is a totally different concept from modern anatomical kidney. In TCM, T-kidney is the most important compartment of the body function; it is viewed as the root of life activities and the origin of our congenital (inherited) foundation. It is so said that T-kidneys is in charge of the Yin and Yang of the entire body. Physiologically, T-kidney is the main support for growth, development, maturation, and reproduction.

The earth compartment is called T-spleen (as for TCM spleen) which is not an anatomical concept either. In TCM, T-spleen rules transformation and transportation, ascends pure essence, and governs the blood. Physiologically, T-spleen performs the function of digestion, absorption, transportation, movement and metabolism of the body.

The wood compartment is called T-liver (as for TCM liver) which is more like the extended functional aspect of the anatomical liver and its products. In TCM, T-liver rules flowing and spreading. And by this flowing and spreading activity, it regulates Qi and emotions, enhances the transformation properties of the spleen, and spreads necessary substances to the entire body. T-liver is also responsible for storing and regulating blood flow.

The metal compartment is called T-lung (as for TCM lung) which seems including the function of anatomical lung and the diffusion effects of various small molecules especially oxygen and water all over the body. In TCM, T-lung rules Qi and administer respiration, directs movement in a disseminating, descending and liquefying manner, moves and adjusts the water channels, collects blood vessels, and rules Qi regulation.

The fire compartment is called T-heart (as for TCM heart) which is another compartment that shows great discrepancy with the anatomical concept. In addition to regulating the cardiovascular system, T-heart seems also responsible for maintaining part of CNS and part of the endocrine system’s function. In TCM, T-heart rules the blood and blood vessels, as well as spirit. The spirit refers to a person's mental, cognitive and intellectual abilities. T-heart takes charge of mental activities by mastering other functional compartments.

The generating and restricting interaction among the five compartments does not perform on an even ground. Of the five compartments T-kidney is like the root, it lays foundation for all the other compartments, so it is called the body’s congenital foundation. T-spleen is called the acquired foundation of our body; it plays a key role in assimilating external nutrition into the body. Whenever we decide to treat a disorder of the body, we have to pay close attention to these two compartments, protect them from being harmed, and enhance their activities to guarantee treatment of other compartments will be effective. T-heart is the ruler among the five compartments; it gives out higher level instructions to coordinate the activities of all the compartments, and thus it has more Yang properties than the other compartments.

Qi Xue theory (2) describes the energy and material production and consumption process of the entire body. Qi and Xue represent the energy and material aspect of the process respectively. Significantly, the production and consumption of energy inside the body are companied with diffusion and consumption of oxygen as well as production and diffusion of carbon dioxide, so the energy condition and the gas (O_2 and CO_2) diffusion pattern inside the body are always intertwined and usually described as Qi totally. Each compartment has its unique way to acquire Qi, which allows it to perform its unique function thus maintains dynamic balance with other compartments. Xue is usually translated as blood, but it is just an approximate concept in TCM related to material metabolism in physiological function, not the same blood of anatomical accuracy.

Balance between Ying and Wei (2) deals with the diagnosis and treatment of epidemic febrile diseases (infectious diseases in western term). Ying and Wei represent two interdependent aspects of body’s defense system. Because of the universal existence
of the defense system over the entire body, Ying and Wei are considered part of the body’s Qi constitution. Ying (Nutritive qi) mainly comes from food essence derived by the T-spleen's transformation and transportation properties and also provides the needed nutrients to support the physiological function of the body. Wei (protective Qi) also comes from the activities of T-spleen, and shows comparatively more Yang property than Ying. It not only guards against various disease-causing environmental factors but also regulates the sweat glands and pores and provides nourishment for the skin, hair and muscles.

Meridian theory (2) uses a different way to dissect the body function. Meridians work like a network system, transporting and distributing Qi and Xue throughout the body. They link up organs, limbs, joints, bones, tendons, tissues and skin, and provide communication between the body's interior and exterior. Seems Meridians are invisible channel network in human body through which cells of different spots communicates with each other by exchange of chemical information, thus meridians are essential way to coordinate various aspects of the body function, and have great significance in disease diagnosis and treatment.

The idea –Fundamentals of micro-holistic body model

People have been attempting to integrate TCM with western medicine and modern sciences for decades in China. The main obstacle for this endeavour is that the functionally dissected TCM body model cannot match the physically dissected body model of western medicine physiologically and pathophysiologically at all. Now with the new recognition that multicellular organism can be considered as a community of different types of cells, and the detailed cellular and molecular observations about human body, we can try a different strategy to dissect human body at cellular and molecular level.

Cells are the basic functional units of a multicellular organism. When we are talking about the growth, development, and maturity of an individual we are referring to the growth, proliferation and differentiation of each single cell that composes the individual. We can consider a single cell as basic member of a cell community, and scrutinize its constitution and activities under the context of the whole community. We study the universal internal structure and processes of the cell, and at the same time we have to consider the specific functional role that the cell serves in the whole community, as well as what kind of services it has to receive from its fellow members in order to live and properly function inside the community.

Lipid bilayer membrane and associated proteins are the basic constructive substances of an eukaryotic cell, and the cell is elaborately subdivided into functionally distinct, membrane-enclosed compartments. An animal cell contains about 10 billion protein molecules of perhaps 10,000 kinds, the blueprints (genes) of almost all of them hide as chromosomes inside the nucleus, and the synthesis of almost all of them begins in the cytosol. Each newly synthesized protein is then delivered specifically to the cell compartment that requires it (1). To make the decision of proliferation, differentiation, apoptosis, and so on the cell needs specific proteins to receive and relay signals from the exterior; and those specific proteins are called receptors. To perform all the activities of synthesis, delivery, signal-relaying, division etc. the cell needs to cost specific form of energy, thus it has to produce the usable energy itself from certain materials available inside the cell.

Thus the intracellular organelles, machineries, and processes can be divided into three basic compartments according to their specific function.

The first compartment called the signalling and manufacturing compartment, includes: (a) Nucleus that contains most of the cell’s genetic material (genome), organized as multiple long linear DNA molecules in complex with a large variety of proteins, such as histones, to form chromosomes. (b) Ribosomes that combine to a messenger RNA molecule, which they use as a guide to join the correct sequence of amino acids into polypeptide chains. (c) Endoplasmic reticulum (ER) includes rough ER and smooth ER. The walls of rough ER are studded with protein-making ribosome; the ribosomes only attach to the ER once it starts to manufacture of bile acids and proteins also. (d) Peroxisomes are enclosed by only a single membrane, grow off from the ER, not the Golgi apparatus (that is the source of lysosomes), and contain oxidative enzymes, such as catalase and D-amino acid oxidase. Certain enzyme utilize molecular oxygen, eliminate hydrogen atoms from specific organic substrates, in an oxidative reaction, creating hydrogen peroxide. Catalase in sequence utilizes this H$_2$O$_2$ to oxidize other substrates, including phenols, formaldehyde, formic acid, and alcohol, through the peroxidative reaction which is crucial in liver and kidney where the peroxisomes detoxify different toxic substances that enter the blood. Beta-oxidation within peroxisomes decomposes fatty acid into acetyl-CoA. First steps in the creation of plasmalogen which is abundant in heart and nerve cells also occur in peroxisomes. They play a role in the manufacture of bile acids and proteins also. (e) Intracellular signal relaying system is not a membrane-enclosed organelle, but it is the main instructor or information processing module in the signaling and manufacturing compartment, and there are scaffold proteins confine certain pathways in
cytosol. The signal relaying process include: (extracellular signal) → membrane/nuclear receptor → intracellular mediators → effector proteins → cell behavior → negative feedbacks control cell behavior (1).

Signaling and manufacturing compartment is composed of DNA replication, repair, recombination, transcription, RNA splicing and translation, protein folding and other macromolecule biosynthesis machineries, as well as proteins produced by these machineries that relay extracellular signals into intracellular activities mostly lead to cell behaviors like protein turnover, secretion, cell growth, proliferation, differentiation or apoptosis. All these behaviors are basic characteristics of a living cell, the essence and nature of life, and exhibited as growth, development, maturity, and other basic life activities at the whole multicellular organism level.

The second compartment called the intracellular logistics compartment that includes: (a) Golgi apparatus is central in modifying, sorting, and packaging macromolecules (proteins and lipids) from ER for cell secretion (exocytosis) or use within the cell (vesicular traffic inside the cell). (b) Endosomes are membrane-enclosed vesicles, developed via a complex family of procedures jointly known as endocytosis, and located in the cytoplasm of practically every animal cell. Many endocytotic vesicles, originated from the plasma membrane, are either transferred to a pre-existing endosome and mingled with it or are acidified via proton pump to turn into an endosome. Some endocytosed material went through endosomes on its way to lysosomes. (c) Lysosomes are small, spherical single membrane organelles containing digestive enzymes (acid hydrolases), derived from Golgi apparatus. They digest surplus or shattered organelles, food particles, and absorbed viruses or bacteria. (d) Cytoskeletons are dynamic assemblies including intermediate filaments, actin filaments, and microtubules. They uphold cell shape, protect the cell, enable cellular motion using assemblies such as flagella, cilia and lamellipodia, and play vital function in both intracellular transport—the travel of vesicles and organelles for instance, and cellular division. (e) Centrosome is an organelle that acts as the chief microtubule-organizing center (MTOC) of the animal cell plus a regulator of cell-cycle progression. (f) Proteasomes are compartmentalized proteases situated in the nucleus and the cytoplasm. They purposely tear down aberrant proteins that are marked for degradation with a small protein named ubiquitin. Their objects contain denatured and misfolded proteins plus those short-lived normal proteins that serve particular cell physiological goals (1).

The intracellular logistics system includes all kinds of macromolecules which are dealing with (a) the physical movement involved in all intracellular processes, (b) modifying, packaging, delivering, storing semi-finished and finished cell products, (c) acquiring, and processing raw materials to supply for manufacture or other purpose, (d) destroying, recycling damaged or outdated parts, components, and information (signalling mediators). The activities of intracellular logistics are emphasized in cells that are in charge of strength and motion such as muscle cells, and also are exhibited more obviously in the epithelium tissues that are lining the gastrointestinal tract, which contain vast amount of proteins that are engaged in the transcellular transportation of digested food components.

The third compartment is the intracellular power compartment that is in charge of the energy supply and consumption of cells. It is mainly composed of mitochondria which are membrane-enclosed organelles that are described as "cellular power plants" because they consume oxygen and generate most of the cell's supply of adenosine triphosphate (ATP), used as a source of the chemical energy. The central sets of reactions involved in ATP production are jointly known as the citric acid cycle. Moreover, mitochondria have many crucial functions in cellular metabolism other than energy manufacturing: (a) Provide NADPH and carbon bones for the biosynthesis in cytosol, required for cell growth; (b) Receiving electrons from NADH in cytosol thus keep a proper NAD+ concentration necessary for glycolysis; (c) Transitory storage of calcium ions and calcium signalling association including calcium-evoked apoptosis; (d) Mitochondria contain tissue-specific proteins that are encoded in the cell nucleus. For instance, mitochondria in liver cells contain enzymes to detoxify ammonia, a waste of protein metabolism. (e) Heat production in brown cells, which detach mitochondria respiration from ATP synthesis (1). Furthermore, there are two forms of energy existing in the cell. One is the ATP produced mainly through mitochondria by respiratory chain; the other is the ion gradient across the membranes of the cell that is produced by different ion pumps through the hydrolysis of ATP. While ATP provides general energy and material supply for cell activity, the different ion gradients facilitates longer-distance, faster and more accurate behaviour control for specialized cells such as electric excitable nerve cells and muscle cells. Thus the intracellular power system of the organism should include all the energy generating and converting machineries inside all kinds of cells.

Though the signalling and manufacturing compartment makes all the functioning macromolecules of the cell its function must be supported by the logistics system at every step, and must consume energy in the form of ATP which is produced by the intracellular power system. The cell life activities depend on the efficient and accurate coordination of the three intracellular systems. The signalling and manufacturing compartment makes all the decision and provides the other two systems with personnel, while the other two supplies the signalling and
manufacturing compartment with energy and logistics services.

Almost every cell type is composed of the three functional subunits described above. The proper coordination of the three functional subunits is the basic requirement of a healthy and living cell. However, being a specialized member of a multicellular organism, the cell needs to get nutrients and oxygen as well as coordinative information from adjacent as well as far away cells so that the whole organism can properly live, grow and develop. It has to get all the nutrients and information from its immediate environment and also emits its own signal and other products into the immediate environment. This means the multicellular organism must have a systematic extracellular logistics compartment that performs the corresponding task outside the cells for the whole organism: (a) Processing raw materials into cellular acceptable nutrients and storing them transiently; (b) Making carrier proteins for nutrients and signal molecules, carrying and distributing them properly; (c) Carrying and distributing oxygen and collecting carbon dioxide; (d) Destroying and recycling damaged and outdated circulating proteins and other molecules including outdated signal molecules based on the timing of the whole organism.

The extracellular logistics system is composed of certain specialized cell types, tissues, their specialized products, and the function they imparted to the organism. The main related anatomical organ with this system is liver.

Compared to human society, if the intracellular logistics compartment is like the local logistics inside a city, the extracellular logistics compartment is the national or interstate logistics that handles the material and information supply collectively and distributes them to each city efficiently.

In addition to necessary nutrients, an aerobic organism has special needs for oxygen that is utilized in every cell to generate energy for life activity and produce carbon dioxide. The oxygen uptake from exterior world and the exhalation of carbon dioxide are performed by a set of special instruments (respiratory system) includes blood vessels and specialized epithelial tissues in lung that directly contact with the exterior air. This system is in charge of gas exchange (mainly by diffusion) at two terminals (lung with exterior air, every cell with its immediate environment) and thus has major influence in the utilization of oxygen and energy generation inside every individual cell of the organism. Or it can be considered that the molecules/components/cells that are involved in diffusive function in the body compose the oxygen pumping and distributing compartment (the diffusion compartment). If we make a metaphor, the oxygen in human body works like the oil in our modern society. The oxygen pumping and distributing compartment plays the role like Oil Industry in human society.

The major life activities of a multicellular organism such as a human being include interactions with the outside world and with other individuals, as well as its own programmed growth, development, and maturation. How do all the cell members of a human body coordinate their individual behaviours to respond to or perform the activities mentioned above? There are specialized cell types and tissues that are wired to receive stimulations from the outside world, generate and send signals to other cells include themselves. In addition, some cell types will gradually grow into a state according to a naturally programmed schedule, send out signals to cells in the whole organism, and lead to the growth and maturation of the whole organism. Tissues and cells that are in charge of these aspects of the organism can be considered as the governing compartment of the organism. This compartment obviously resembles the role of government or politics in human society, and anatomically relates to CNS and endocrine system.

Aside from all the functional compartments discussed above, the cells that compose a multicellular organism also need a very important system to provide protection against physical, chemical, and microbial damages from the external environment and maintain a suitable, clean internal environment for all bodily processes to function properly. This can be considered as defence compartment of the organism that corresponds to the innate immune defences of an organism in molecular biology.

Generally, there are three lines of innate immune defences in vertebrates (1).

First, the skin and epithelial surfaces of other kind, containing those coating the respiratory, intestinal, and urinary tracts, offer a physical and chemical barrier between the interior of the body and the exterior world. The ordinary floras also have a position in shielding body surfaces against invaders by contending for the same ecological niche and thus limiting colonization. The first line also takes a big part in upholding homeostasis (temperature, water, PH, ion regulation) of an organism. The second line includes cell-intrinsic responses, by which an individual cell realizes that it has been contaminated and takes processes to destroy or cripple the invader. The third line relies on a dedicated set of proteins and phagocytic cells that indentify preserved features of pathogens and become rapidly stimulated to help annihilate invaders (1).

Overall, this is the theoretical system obtained by dissecting the cell community body model using sociological strategy. It is obviously a micro-holistic body model based on intertwined cellular and molecular function. It includes two aspects and seven compartments:

Two aspects: 1. The various information flows that are produced, released, received, and interpreted by each cell of the body and lead to coordinated cell behaviours that are basic for a multicellular life; 2.
The basic life units (cell) that produce, release, receive, and interpret combined information and finally perform the correct conducts coordinately. In a more practical expression, the two inseparable aspects of life are the extracellular signalling molecules and the cells that communicate with each other using the extracellular signalling molecules.

Seven compartments include three universal compartments that are running within almost every cell in the body and four specific systems that are comprised of particular cell groups and molecules that provide particular services needed generally by all the cell members in the body. The three universal compartments: (a) the intracellular signalling and manufacturing compartment; (b) the intracellular logistics compartment; (c) the intracellular power compartment. The four specific compartments: (d) the extracellular logistics compartment of the organism; (e) the oxygen pumping and distributing compartment of the organism; (f) the governing compartment of the organism; (g) the defence compartment of the organism.

Among the seven compartments, the three universal compartments are fundamentals for life, while the four specific compartments are regulative modules in a multicellular system. In addition, the internal relationship among the seven compartments can be derived from the analogy with human society.

The main achievement of the “micro-holistic body model” is that it is a bottom-up, holistic and functional body model. It integrates molecular, intracellular and intercellular level processes inside a multicellular organism into organismal level functions and activities. Everyone knows that cell is the functional and structural unit of a multicellular organism. However, how to translate cellular and intercellular processes and experimental facts into organismal level phenomena, and then turn the laboratory result of molecular biological studies into actual clinical practices is the bottleneck of development of current molecular medicine and systems biology. The micro-holistic body model presented in the manuscript provides the philosophical and methodological tool for scientists engaging in the related area of molecular medicine, systems biology, and TCM modernization etc. Especially, it might overcome the philosophical obstacle between western medicine and TCM, makes the fundamental comparison between the two systems feasible.

Evaluation of the idea and discussions

The micro-holistic model of human body and TCM fundamentals are supposedly of the same philosophic system, so the two should match each other very well. Table 1 provides how perfectly the theoretical frame of micro-holistic body model and TCM fit into each other with the exception of meridian theory that is considered a parallel system with other TCM fundamentals.

This comparison provides very strong support for TCM theoretical system in modern scientific sense. TCM theories usually are considered pure empirical because the Yin Yang and five element theories as the basic constructive philosophy of TCM system have never been explicitly interpreted or tested by modern culture and sciences and are often considered as “pseudoscientific”.

It is the first time that we construct a dynamic theoretical body model de novo based on cellular and molecular constitution of human body using holistic methodology. The result is surprising, the micro-holistic body model exactly reflect the TCM holistic body model at molecular level (see Table1.). It not only confirms the rationale and reliability of TCM therapeutics in healthcare practice but also set the foundation for TCM modernization, systematic integration of modern medicine and TCM (3), and development for new strategy of drug and therapy discoveries.

Of course, there are many other aspects like etiology, pathology, diagnostics, and so on in TCM system other than the basic theories. Once the fundamentals gain modern scientific scope through the micro-holistic body model, the other contents of TCM will get a solid ground for open debate among scientists of various related fields and will finally be renewed by modern scientific terms without losing its philosophic advantages. For example, pulse taking as one of TCM main diagnostic techniques is often ridiculed by western doctors. They do not believe that just by taking pulse one can tell the global status of an individual’s health. Pulse is the reflection of how heart continuously pumps blood into blood vessels and how blood vessels relay the blood to the whole body until the very last terminal of capillaries. It is a hugely important physiological activity of human body, so it must intensively exhibit the functional status of each holistic compartment. The patterns of pulse should be affected by those factors like: 1. The quality and texture of the big vessels – T-kidney; 2. the cellular skeleton of cells composing the vessels especially smaller vessels – T-spleen; 3. the blood viscosity and other properties– T-liver; 4. the diffusion function status of capillaries – T-lung; 5. the strength, speed, and rhythms etc. of heart beat – T-heart. Though T-heart does not equal to the anatomical heart, the status of anatomical heart is the indication of how T-heart system (nerve, brain, and hormone control) running in an individual body. Thus, it is pretty rational to decode pulse patterns to diagnose the imbalance or disharmony among the holistic compartments in human body. How to make it objectively measurable other than the subjective standards in TCM diagnosis documents will be a very interesting topic.

With the help of the micro-holistic body model the results of pathophysiological examination of modern medicine also can get into TCM theoretical system. Thus, more area of traditional therapeutics can be explored and tested. For example, in the case
of some complex diseases such as Alzheimer’s disease (AD), hypertension and depression, western pathological studies can describe the abnormal phenomena happened to related tissues, cells and their function. However, it is very hard to reduce various phenomena into causal mechanism of the disease (table 2). With TCM and micro-holistic body model, the diagnostic procedure will naturally explain the mechanism of the complex disease. For example, people feel confused about the accumulation of amyloid protein in the brain cell of the AD patients, wondering whether it is the consequence or cause of AD (4). In TCM diagnosis, it is clear that the deficiency of T-kidney Yin makes the quality control in protein synthesis procedure loosened, and yields more aberrant proteins. The deficiency of T-spleen Yin means that the cell does not have enough capacity to dispose aberrant proteins efficiently. Thus the accumulation of amyloid protein appears. 

The deficiency of T-liver Yin indicates that cells cannot get enough nutrition support from extracellular logistics system. So the production and delivery of normal substance in the brain cells must also have been greatly impaired and cause the collapse of brain function as well as its structure. Though it is incurable, the TCM therapeutics for AD designed according to the above diagnosis can help patients maintain a nearly normal life till the end (Because the crude style of TCM herb therapy cannot be admitted by conventional academic standards, few reports about full TCM treatment of AD can get published. However, in some TCM clinics in China, there are AD patients receiving TCM treatment who can maintain a nearly normal life to the end.). The dialectic relationship of the TCM compartments can explain almost every complicated phenomenon of complex human diseases, while micro-holistic body model can bring all the explanations to molecular and cellular level and expand the molecular research scope of medicine.

The match of TCM with micro-holistic body model also has very important indications in human genome anatomy, gene regulation and drug discovery strategy. We know that some functionally related genes are organized as an operon(7) and are transcribed together into mRNA strand and either translated together in the cytoplasm, or undergo trans-splicing to create monocistronic mRNAs that are translated separately. An operon is made up of several structural genes arranged under a common promoter and regulated by a common operator. A set of operons (functionally related or unrelated--according to the context of this concept, “related or unrelated” should be judged by if they take part in the same or related cellular pathway.) scattered throughout the chromosome, but subject to the regulation by the same regulator is called a regulon (8). A modulon (9) is a regulon concerned with multiple pathways or function, in which operons/regulons may be under individual controls as well as common, pleiotropic regulatory protein. The global control of gene expression is subject to the intricate cross-link of the operons, regulons and modulons. In modern biological field, the prevalent opinion among researchers is to treat organisms as chemical factories. So the identification and descriptions of operons, regulons and modulons are mainly focused on chemical or metabolical pathways (10). It is still hard to get a dynamic global picture of the chemical manufacturing aspect of a multicellular organism from all the fragmental studies up to now. However, with TCM and micro-holistic body model, the global molecular sociality of an organism is very clear. TCM theories and practices indicate that identification of regulons and modulons according to the seven compartments of the micro-holistic body model will get a tangible multilevel gene regulatory network in which the operators of different operons, regulators of various regulons and modulons serve as control nodes at different level and provide safer and more efficient drug design targets as well as explicit principles for design of compounded drug formula. For example, in TCM there are herbs and other drugs acting as enhancers of T-kidney, T-spleen and other compartments respectively. The T-kidney enhancers must act on regulators/operators inside the T-kidney modulons, and so do the enhancers of other compartments. The regulators/operators will be the significant drug design targets for many complex diseases. The abundant long-history TCM clinical documents can provide instructions for rationally composing of the compound for treatment of complex diseases.

The overall hypothesis derived from above discussion would be: The gene expression profile can be approximately divided into three kinds of modulons (T-kidney, T-spleen, Qi Xue) within a common cell; there should be countable control points subjected to influences of environmental and personal factors at different level inside each modulon. There are also a lot of documents in TCM system (2) indicate organ and tissue specification of those control points and its significance to the performance of the entire body.

**Conclusion**

Integrating modern and traditional medicine is a very challenging and important topic throughout the world (3, 11). In China there have been decades of efforts in integrating Western medicine and TCM together, and people have nailed down that the key problem in this area is the philosophical obstacle between modern western science and TCM. Modern western medicine is mainly based on reductionism, while TCM fundamentals are macro-holistic and functional. It is totally impossible to compare or match the two systems directly at physiology and pathophysiology level. The main achievement of the “micro-holistic body model” is that it is a bottom-up, holistic and functional model. It overcomes the philosophical obstacle between western science and
TCM, establishes an analogical relationship between cell physiology and fundamentals of TCM, and makes the comparison between the two systems feasible. However, the large scale comparative study of overall physiological and pathological mechanisms between western medicine and TCM under the guidance of the micro-holistic model is only possible through close collaboration of TCM scholars, doctors practising modern and traditional medicine, scientists of bioinformatics, and experimental biologists etc. Thus, the micro-holistic body model is just the initiative point of a set of hugely complex medical hypotheses, a beginning that may lead to some breakthroughs in therapeutics of complex disease. Thus, it is very important to make the model and idea known and discussed in related academic fields.

Conflict of interest

The author has no conflicts of interest with regard to the content of this article.

Overview Box

First Question: What do we already know about the subject?
Currently there are few theoretical models in molecular biological field that try to set up the translation between the molecular level phenomena and organism level systemic properties. The philosophical obstacle between western science and traditional Chinese medicine is the key difficulty in efficiently making use of TCM therapeutics in clinics and medical studies.

Second Question: What does your proposed theory add to the current knowledge available, and what benefits does it have?
This paper is the first one to apply sociological strategy upon molecular and cellular constitution of human body. The micro-holistic body model can match the macro-holistic body model of Traditional Chinese Medicine (TCM) very well, which indicates that future healthcare system may be benefited from extracting scientific essence from TCM theory and therapeutics.

Third question: Among numerous available studies, what special further study is proposed for testing the idea?
This is a very big and unconventional idea, but it will bring great benefits to human healthcare if it is proved. The first step to test the idea should be thoroughly molecular and pathophysiological comparative study of modern medicine and traditional Chinese medicine based on one common complex disease such as Alzheimer’s disease.

Figure 1: The development of knowledge about human body in modern western medicine
Figure 2: Five-element Theory

<table>
<thead>
<tr>
<th>Systems</th>
<th>Micro-holistic Body Model</th>
<th>Traditional Chinese Medicine Fundamentals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two aspects:</td>
<td>The extracellular signalling molecules and the cells that communicate with each other using the extracellular signalling molecules</td>
<td>Yin Yang theory: body’s physical substance belongs to Yin, body’s activities or functions belong to Yang. There is Yin in Yang, and vice-versa.</td>
</tr>
<tr>
<td>Seven Compartments:</td>
<td>Intracellular signalling and manufacturing compartment</td>
<td>Water compartment: T-kidney</td>
</tr>
<tr>
<td></td>
<td>Intracellular logistics compartment</td>
<td>Earth compartment: T-spleen</td>
</tr>
<tr>
<td></td>
<td>Extracellular logistics compartment</td>
<td>Wood compartment: T-liver</td>
</tr>
<tr>
<td></td>
<td>Oxygen pumping and distributing compartment</td>
<td>Metal compartment: T-lung</td>
</tr>
<tr>
<td></td>
<td>Governing compartment</td>
<td>Fire compartment: T-heart</td>
</tr>
<tr>
<td></td>
<td>Intracellular power system</td>
<td>Qi Xue theory</td>
</tr>
<tr>
<td></td>
<td>Defence compartment</td>
<td>Ying Wei theory</td>
</tr>
<tr>
<td>Uncertain part</td>
<td>The relationship between informational and communicative detailed organization and physical connection of various types of cell composing the body (?)ª</td>
<td>Meridian theory</td>
</tr>
</tbody>
</table>

ªMeridian theory describes the physiological combinatory involvement of cell junction, cell adhesion, and extracellular matrix in the cell communication of a multicellular organism. Current knowledge about this aspect remains too dispersed and limited to piece up a whole picture.
Table 2. Pathological comparison about complex diseases between western medicine and TCM (4, 5, 6)

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Western Medical Pathology or Etiology</th>
<th>TCM Dialectic Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s Disease</td>
<td>Toxic levels of amyloid protein build up in the brain.</td>
<td>The deficiency of T-kidney Yin, T-spleen Yin, and T-liver Yin</td>
</tr>
<tr>
<td>Essential Hypertension</td>
<td>Abnormal sympathetic nervous activity, narrowing of the blood vessels and artery stiffness caused by deposition and retention of lipoproteins in the sub-epithelial wall, excessive hormone level etc.,</td>
<td>The deficiency of T-kidney and T-liver Yin, or weakness of T-spleen, or the over-active of T-liver Yang</td>
</tr>
<tr>
<td>Depression</td>
<td>Genetic predisposition, the influence of early childhood experiences, the possible effects of psychological adversity, biological and physiological effects of other physical disease. It is yet not possible to determine the precise effects of factors on neurochemical function.</td>
<td>Deficiency of T-kidney Yin and the weakness of T-heart</td>
</tr>
</tbody>
</table>

*From consultation of TCM practitioners in China

References