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The landscape and flux of a minimum network motif, Wu Xing*

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Wu-Xing theory is an ancient philosophy that serves as a guiding principle in the traditional Chinese medicine (TCM). It has been used to explain the unbalance among the TCM organ systems in disease states and provide treatment philosophy qualitatively. Until now, it is still a challenge to explore the Wu-Xing theory beyond its philosophical nature. In this study, we established a quantitative framework using the landscape and flux theory to characterize the nature of the Wu-Xing theory from a perspective of a minimal network motif and leave certain specific functional aspects of Wu-Xing theory for future exploration. We uncovered the irregular ring shape of projection landscape for the Wu-Xing network with several local basins and barriers. We found that the dynamics of the self-organized Wu-Xing system was determined by the underlying negative landscape gradient force and the nonequilibrium rotational flux. While the shape of the Wu-Xing landscape determines the stabilities of the states, the rotational flux guarantees the persistent periodic oscillation and the stability of the flow. This provides a physical and quantitative basis for Yin–Yang duality of the driving forces for determining the dynamics and behaviors of the living systems. Applying landscape and flux analysis, we can identify the key parameter for the dynamics/function of Wu-Xing network. These findings allow us to have a deeper understanding of the scientific merits of the ancient Wu-Xing theory from the network motif perspective.

Keywords: traditional Chinese medicine, nonequilibrium, landscapes, flux

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1. Introduction

Wu-Xing theory, also known as Five Elements Theory,[1] is an ancient philosophy originated in China more than two thousand years ago. The words, Wu Xing (五行), first appeared in *Shangshu* (《尚书》, 476 BC–221 BC).[2] Water, fire, wood, metal, and earth were used as metaphors to describe five properties of nature phenomena, *i.e.*, water sinks down, fire flares up, wood can be curved and straightened, metal can be used to cut things and earth is where grain can grow from (“五行: 一曰水, 二曰火, 三曰木, 四曰金, 五曰土. 水曰润下, 火曰炎上, 木曰曲直, 金曰从革, 土曰稼穡”). Later, Dong Zhongshu (董仲舒 , 179 BC–104 BC) stated in his book *ChunqiuFanlu* (《春秋繁露·五行相生》) about the relationships among the Wu Xings as “the immediate neighbors are inter-promoting each other but the next neighbors are inter-overcoming each other.” (“比相生而间相胜也”[3]). The Wu-Xing diagram shown in Fig. 1 indicated the normal direction of the Wu-Xing connectivity with the outside circle of inter-promotion and the inner star of inter-overcoming. In ancient Chinese history, the Wu-Xing metaphors had been used in many areas of Chinese culture including predicting star movement, weather changes, social and political events and so on. The most successful application of Wu-Xing theory was its integration into the traditional Chinese medicine (TCM). It has been an important guiding principle and a fundamental methodology in TCM for disease etiology, diagnosis and treatment.[4]

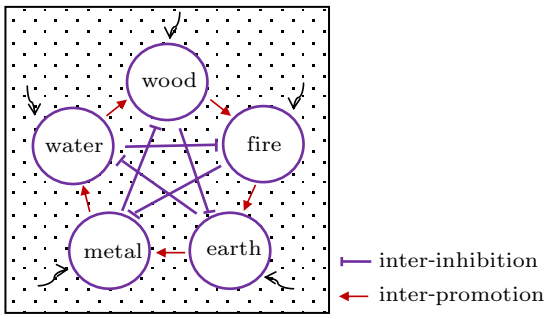


Fig. 1. Wu-Xing diagram. The five elements are wood, fire, earth, metal, and water. The outside circle connects with inter-promoting relationships and the inner star connects with inter-inhibitory relationships.

In *Huangdi Neijing* (《黄帝内经》), the five metaphors of Wu Xing were referred as five Zangs (viscera), five directions, five colors, five musical notes, five flavors, five odors, five sounds, five emotions, five tissues, *etc*.[4,5] The Chinese character “Xing” can have many meanings. In addition to the meanings we mentioned, it can also mean, for example, the principles of evolution of things in the universe, the orbits of trajectories of the objects’ motions, the ways of how things work, *etc*. Such as in “《周易·复卦》: 反复其道, 七日来复, 天行也 ”; 《诗经·小雅·十月之交》: 日月告凶, 不用其行 .

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"Wu Xing" sometimes is translated as "five ways" for this reason."

In *Nan Jing* (《难经》), another TCM classical literature, relationships of Wu-Xing theory was explained from the perspective of a person. As a person, 'my relationship' with 'my mother' is who gives me my life (生我, Sheng Wo) and 'my relationship' with 'my child' is whom I give the life to (我生, Wo Sheng).[4] This unique perspective puts one Xing, 'Wo' or 'me' as the reference to define its relationships with the other four Xings. When Wu-Xing theory is applied to TCM, two steps are the keys for disease diagnosis: (i) identifying the problematic Xing as the center for considerations, and (ii) evaluating its relationships with other Xings. Once the problem is identified and the excessive or suppressive nature is classified, the treatment plan is to adjust the problematic center Xing and manipulate its related Xings in order to achieve the whole-body harmonization. In addition, the direction of the interactions of Wu Xings in TCM does not always go one direction according to the normal flow. Under abnormal conditions, the relationships can be reversed. In those cases, special names are used for the abnormal relationship, it was called Xiang Wu (相侮, inter-insult[6] or disrespectfulness).[4]

Reflecting on the application of Wu-Xing theory in TCM, we believe that Wu-Xing theory is not simply the Four Elements Theory of Empedocles (Greek, 490 BC–430 BC) plus one more element. Wu-Xing theory uses five well-known metaphors to illustrate the fundamental functions and their relationships of complex world. It is an ancient methodology to analyze, understand and manage complex systems.

Modern complex systems science or complexity science was officially established in early to late 20th century.[7] It emerged from many fields of science such as mathematics, physics and economics. Complex system science has been applied to understand biomedical systems. The concepts of attractors,[8] nonequilibrium landscape-flux theory,[9] and immune states and its transitions[10] shed new lights on understanding heart rate regulation and development of skin lesions. Wu-Xing network structure and associated simulations were considered previously.[11] Self-stabilization feature of the network was reported and potential perturbation-recovery strategies were suggested. However, the multiple state complexity, limited cycle oscillations, and the full functions of the network were not revealed. Here, we explore the network aspect of the Wu-Xing theory with a statistical physics framework via landscape and flux analysis and leave certain specific functional properties of Wu-Xing theory for future exploration.

2. Wu-Xing network motif

The concept of Wu-Xing network motif was hidden in the mother-me-child relationship stated in *Nan Jing* (《难经》). We extract the Wu-Xing network motif from the well-known Wu-Xing diagram shown in Fig. 1 as follows: (i) Wu Xing theory has four fundamental types of relationships that tie the five nodes together. These four types of relationships are the combination of the two opposite forces, Yin and Yang, and two directions of the interactions, input and output; *i.e.*, Yin–Input, Yang–Input, Yin–Output, and Yang–Output (Fig. 2(a)). We believe these four types of relationships or interactions are the core universal relationships of any element or subsystem functionally connecting with other elements or subsystems in self-organized dynamical systems.

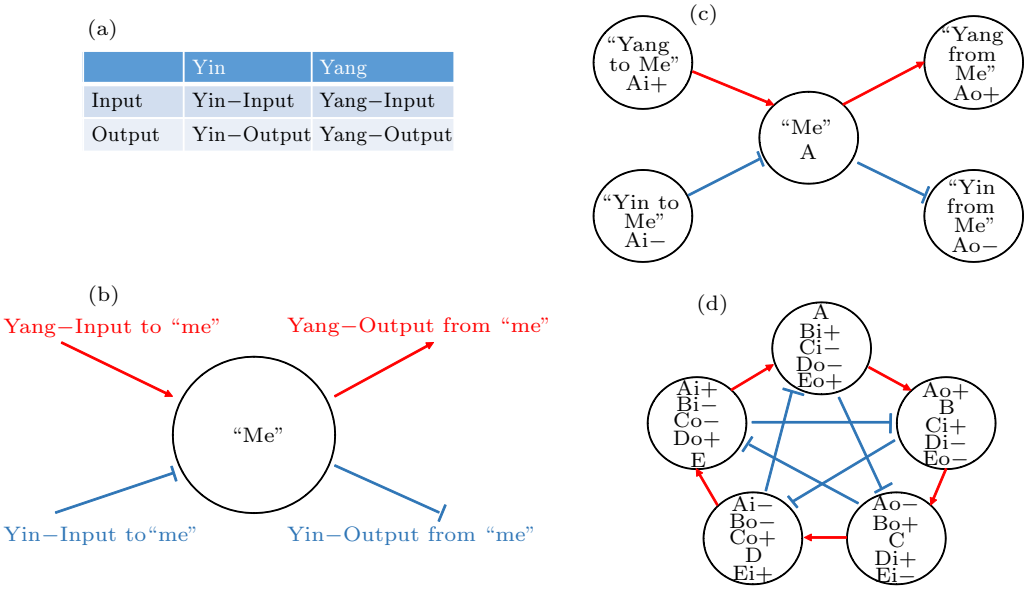


Fig. 2. (a) Four types of relationships are the combination of the two opposite forces, Yin and Yang, and two directions of the interactions, input and output; (b) the four relationships of a subsystem "Me" as a fundamental network motif; (c) four types of relationships with non-repeating nodes; (d) the classic Wu-Xing diagram.

(ii) Yin–Yang and directions of in and out are relative terms. A reference point is necessary to correctly define them. We borrowed Wo (我) or 'me' used in *Nan Jing* (《难经》) as the reference point. From the center node, 'me', four relationships are shown in Fig. 2(b). (iii) In order to describe these four types of relationships with non-overlapping nodes, five is a minimum number of nodes required (Fig. 2(c)). Figure 2(c) is the core unit of the Wu-Xing network motif. (iv) All four types of relationships exist for all five nodes in the system. Therefore, the classical Wu-Xing diagram is revealed, where the outside circle connects five nodes with inter-promotion and inner star connects the five nodes with inter-inhibition (Fig. 2(d)).

We believe that human body is very complicated. It is hard to restrict our understanding on human physiology into a five-node-network of Wu-Xing theory. However, the 'me' and its four types of fundamental relationships (Fig. 2(c), *i.e.*, the Wu-Xing motif, can serve as a framework for problem solving in a complex system.

3. The Wu-Xing network

The Wu-Xing network is different from naturally occurring biological, social or ecological network. It is hypothetical with basic relationships and minimum nodes. It not only captures the directions of the network with input and output, but also the functional impacts of the interactions with Yin and Yang. In addition, it reflects a reference point when defining the interaction. We believe that these unique features of Wu-Xing Theory are hidden in this ancient philosophy. Our work aims to explore the dynamics globally via the landscape of this ideal network. This work was inspired by other published efforts.[12–16] However, we are not studying centrality, degree of connectivity, and power law of degree distribution.[12] We are also not trying to map Wu Xing and other TCM concepts to specific genes regulatory network, protein-protein interaction network, or biological processes as proposed by others.[17,18] The well-known concepts of the gene or the protein interaction networks mentioned in our work was used to explain the underlying meaning of the mathematic equations. We believe that the hidden meaning of Wu-Xing theory is universal, and its significance is far beyond TCM.

Landscape-and-flux theory has recently been developed for quantifying the global driving force and thermodynamics for general dynamical systems.[19] We are interested in using the landscape and flux analysis to learn the Wu-Xing network model in a global and physical way, *e.g.*, its potential systematic states and how those states could relate to human health or diseases hypothetically. Furthermore, we hope that the quantitative landscape and flux analysis can enlighten us about the pathways leading from a disease state to a healthy state[20–22] and shed light on why and how the Wu-Xing theory is so useful beyond its philosophical impact.

4. Materials and methods

Landscape and flux theory was introduced to uncover global nature of dynamical systems including physical, biologic, and chemical systems. In general, the systems can be classified as the equilibrium (close system without exchange with outside) or non-equilibrium systems (open system with exchange with outside). The potential function of an equilibrium system is a priori known if the underlying interaction potentials are known. However, the potential landscape of the non-equilibrium system is not known a priori. A non-equilibrium system can continually exchange energies, materials and information with the environments. For example, the typical biologic system as a self-organized dynamic system is often a non-equilibrium open system.[23–26] Wu-Xing network motif highlighted the dynamic interactions in non-equilibrium open system. We can explore its underlying nonequilibrium dynamics with its landscape and flux.

The conventional dynamics of the open system has often been represented by a set of ordinary differential equations. For the stochastic system involving the intrinsic fluctuations and the external fluctuations from the environments,[27–30] one should explore the underlying stochastic dynamics. The stochastic dynamics with a set of Langevin equations can be represented as: $\mathrm{d}\boldsymbol{x}/\mathrm{d}\boldsymbol{t} = \boldsymbol{F}(\boldsymbol{x}) + \eta$, where $\boldsymbol{x}$ represents a vector form of all the elements or nodes, $\boldsymbol{F}(\boldsymbol{x})$ represents the deterministic or averaged part of the driving force that causes the changes of the motion, while the η term represents the stochastic part of the driving force from the environments. The deterministic force $\boldsymbol{F}(\boldsymbol{x})$ represents a macroscopic force for the underlying observables at the coarse grained level. In other words, the x represents the degree of freedom of the interest or the ones which are observables. The rest of the degrees of the freedom for the system is coarse grained or averaged out. If this macroscopic coarse grained driving force can be represented by the negative gradient of a potential function, then the system will preserve the detail balance condition. The system can then reach the equilibrium state at long times. If the driving force cannot be represented by the negative gradient of the potential alone, then in general the detail balance will be broken. The system at long times then reaches the non-equilibrium state. η is Gaussian white noise term with zero mean and its autocorrelation function is given by $\langle \eta(\boldsymbol{x},t)\eta(\boldsymbol{x},0)\rangle = 2\boldsymbol{D}\delta(t)$. $\boldsymbol{D}$ is the diffusion coefficient. It characterizes the intensity of the variable fluctuations from the external fluctuations of the environments or intrinsic statistical fluctuations, or both. The external fluctuations represent the effect of the environment on the network while the internal fluctuations represent the effect of the size of the system.

Due to the effect of the stochastic nature, the dynamics is not deterministic along with the time evolution. More appropriate quantitative description of the dynamics can be utilized by the probability distribution. In order to study the evolution of the probability distribution that reflects the global nature of the non-equilibrium system rather than a single trajectory, we can perform statistical analysis and obtain the probability distribution at steady state from the simulation of the underlying stochastic dynamics. Although the single trajectory in time is stochastic and nonlinear and therefore unpredictable, the corresponding probability evolution is linear and predictable.

Moreover, the probability evolution follows the diffusion equations in continuous case.[31] The equation can be written in the form of probability conservation: $\partial P/\partial t + \nabla \cdot \boldsymbol{J} = 0$ where $\boldsymbol{J}$ is defined as the probability flux $\boldsymbol{J} = \boldsymbol{F}P - \boldsymbol{D}\nabla P$. This equation is usually called Fokker–Planck diffusion equation describing the system probability evolution under a deterministic force F and stochastic force characterized by the fluctuation strength $\boldsymbol{D}$. The Fokker–Planck equation in this conservation form states that the change of the local probability is equal to the net input flux. When the divergence of the probability flux $J_{\rm ss}$ is zero ($\nabla \cdot \boldsymbol{J} = 0$), the system reaches the steady state ($\partial P/\partial t = 0$). The probability distribution of steady state plays a key role in characterizing the system. On the one hand, we can obtain the probability distribution $P_{\rm ss}$ of the steady state by directly solving the Fokker–Planck equation. However, it is difficult to solve the diffusion equations for multi-variables model. On the other hand, the probability distribution can also be calculated through collecting the joint statistics (histogram or distribution) from the longtime trajectories of the variables in the stochastic Langevin dynamics simulations. In order to simulate the stochastic trajectories, we can transform the Langevin equation into the following discrete form

$$\boldsymbol{x}(t+\Delta t) = \boldsymbol{x}(t) + \boldsymbol{F}(\boldsymbol{x}(t))\Delta t + u\sqrt{2D\Delta t}.$$

Here, Δt is the simulation time step, D is diffusion strength constant, and u is a random number drawn from the Gaussian distribution with zero mean and unit variance. We set the initial conditions $\boldsymbol{x}(t=0)$ and with small time intervals, then the trajectories can be obtained. The algorithm applied for the stochastic simulation is called the Euler or Euler–Maruyama algorithm. The simulated stochastic trajectories are different from time to time, but the distribution $P_{\rm ss}(\boldsymbol{x})$ of the steady state remains the same for the long time evolution.

We define the potential function $U = \ln P_{\rm ss}$ which resembles the Boltzmann law under equilibrium condition. Therefore, U quantifies the weight of the emergent state of the system. Only high weight states are important and functional, which should be the ones we pay attention to. If the steady state flux is equal to zero, then the system is in equilibrium state and the detailed balance condition is satisfied. When the steady state flux is not equal to zero, the detailed balance is broken and the system is in non-equilibrium steady state, we can see that $\boldsymbol{F} = -\boldsymbol{D}\cdot\nabla U + \boldsymbol{J}_{\rm ss}/P_{\rm ss}$ from the flux definition. Thus, we can decompose the force driving the dynamics of the system into two parts. The first is related to the gradient of the potential U, the second term is the steady state probability flux $\boldsymbol{J}_{\rm ss}$ (velocity current) divided by the steady-state probability $P_{\rm ss}$ (density). The part of the gradient force can attract the system down to the basin of the potential function and stabilize the point attractor. The rotational curl force can drive the stable oscillation cycle flow. The steady state flux is divergent free and therefore rotational which can be termed as rotational flux. The difference between the equilibrium state and nonequilibrium state is that for equilibrium systems, the dynamics is determined by the gradient of the potential. This is in analogy of the motion of a charged particle moving in an electric field. However, for nonequilibrium systems, the dynamics is determined by both the potential and the additional rotational flow force, in analogy to a moving electron in the electric and magnetic field.[19,23–25,32] The presence of this rotational flow force is the source of the detailed balance breaking. The origin of this rotational flow force is from the input of the energy from the environment which is usually not explicitly represented in the coarse grained representation of the equation of motion. However, if we go into the microscopic details of the underlying process, for example, taking all the chemical reactions into account of a biological process of interests, then we can clearly see although the overall system is isolated, only part of it or limited degrees of freedom can be observed in the experiments. These limited observable degrees of freedom not only have the force generated among themselves but also the force from the interactions with the degrees of freedom from the other parts of the system. This is the microscopic origin that in general the force has two components, one from the within observables or limited degrees of the freedom characterized by the potential gradient while the other one from the outside or the degrees of the freedom from the other parts of the system characterized by the rotational flow. For thermodynamics, the action of this rotational force is often in the form of the energy flow from the environment to the system of interests. In this sense, if we focus on the limited degree of the freedom or observables while averaging out the rest of the system, then the limited degrees of the freedom can be treated as an open system while the rest of the degrees of the freedom of the system can be treated as the environments exchanging the energy with the system.

The Wu-Xing network motif is an open non-equilibrium system with exchanges in energy, materials and information to the environments. Therefore, the deterministic driving force for the dynamics is determined by both the negative gradient of the potential and the curl probability flux. The emergence of the flux indicates the degree of nonzero exchange of the

energy and material with the environments, a signature of an open system.[19,23–25,32]

The dissipation as a global physical characteristic for this open system can be used to measure the degree of the non-equilibriumness away from the equilibrium. As mentioned in pervious section, the dissipation is closely related to the EPR in the steady state of non-equilibrium system.[19,23–25,32–34] The system entropy is defined as $S = -\int P(\boldsymbol{x},t)\ln P(\boldsymbol{x},t)\,\mathrm{d}\boldsymbol{x}$. By performing the derivative of the above expression with respect to time t, the change rate of the system entropy can be represented as follows: $\dot{S} = \int (\boldsymbol{J}\cdot\boldsymbol{D}^{-1}\cdot\boldsymbol{J})/P\mathrm{d}\boldsymbol{x} - \int (\boldsymbol{J}\cdot\boldsymbol{D}^{-1}\cdot(\boldsymbol{F}-\nabla\cdot\boldsymbol{D}))\,\mathrm{d}\boldsymbol{x}$, where $\int (\boldsymbol{J}\cdot\boldsymbol{D}^{-1}\cdot\boldsymbol{J})/P\mathrm{d}\boldsymbol{x} = e_{\mathrm{p}} = \dot{\boldsymbol{S}}_{\mathrm{tot}}$ is the entropy production rate. This represents the total entropy change rate (including both system and environment). $\int (\boldsymbol{J}\cdot\boldsymbol{D}^{-1}\cdot(\boldsymbol{F}-\nabla\cdot\boldsymbol{D}))\,\mathrm{d}\boldsymbol{x} = h_{\mathrm{d}} = \dot{\boldsymbol{S}}_{\mathrm{env}}$ is the rate of the heat dissipation or the entropy change rate from the environment. When the non-equilibrium system stays at the steady state, the derivative of the system entropy with respect time t is equal to zero. Therefore, the EPR is equal to the heat dissipation from the environment at the steady state. According to the equation, the dissipation cost quantified by entropy production e_{p} and heat dissipation h_{d} is directly connected with the rotational flux $\boldsymbol{J}$. The equation can also be expressed as $\dot{S}_{\mathrm{tot}} = \dot{S} + \dot{S}_{\mathrm{env}}$. This provides the first law of non-equilibrium thermodynamics. The entropy production is always larger or equal to zero. This provides the second law of non-equilibrium thermodynamics.[33]

5. Results and discussions

5.1. The Wu-Xing motif

In order to quantitatively understand the Wu-Xing network model, we introduce a mathematical model with five variables to characterize the network. The five nodes (wood, fire, earth, metal, and water) are respectively represented as the symbol x_i ($i = 1, 2, \ldots, 5$). The interactions among the fundamental elements are known as the "inter-promotion" (相生) and "inter-inhibition" (相克) in ancient literature. We represent them mathematically as the activation and repression in biological system using the Hill equation, a mathematical model of ligand-receptor binding, which is a fundamental relationship in biological system. Here, we do not pinpoint to specific genes or proteins. We generalize to biological processes that depend on biomolecular interactions to carry out their functions, which is a different approach from other network-based approach for integration TCM with modern science.[17,18]

The Hill equation was also used to characterize other types of interactions in biological system, such as gene expression regulation and the relationship between the product and the substrate. For example, in the gene transcriptional regulatory network,[35,36] a gene X is regulated with transcription factors Y by binding to multiple binding sites. If the expression of gene X is activated by the transcription factor Y, then the rate of production of protein X can be formulated as a Hill equation, $\mathrm{d}X/\mathrm{d}t = aY^n/(S^n + Y^n) + b$. In this case, the low concentration of protein Y results in the low production (or output) rate of protein X due to the activated regulation and therefore gives rise to low concentration of protein X. Conversely, the high concentration of protein Y will produce the high concentration of protein X. If the expression of gene X is repressed by the transcription factor Y, then the rate of production of protein X can be formulated as a Hill equation, $\mathrm{d}X/\mathrm{d}t = aS^n/(S^n + Y^n) + b$. In this case, the low concentration of protein Y leads to high production (or output) rate of protein X due to the repressive regulation and therefore gives rise to high concentration of protein X, and *vice versa*. Hill equation can also represent the relationship between the product and the substrate. But the chemical reaction is composed of many fundamental chemical reactions. The coarse grained description of the chemical reactions preserves only the observables while averaging out many other fundamental reactions. This makes it essentially an open system for the observables or limited degrees of freedom we are studying while the degrees of the freedoms from the other parts of the system are treated as the environments. The coarse grained form of the interactions can be represented by the Hill equation. Therefore, the Hill equation can depict an open system. However, this equation describes the average dynamics of the macroscopic variables such as the concentrations. For the macroscopic system, the averaged description is approximately right because the fluctuations can be ignored.

Here we extend the Hill equation to characterize complex interactions with above interactions to symbolize the four types of relationships in a fundamental network motif. Interactions from multiple sources, with different time scales, acting on different targets, but having the same direction of actions to a biological function are considered to act in a cooperative manner, activation or repression. Using this strategy of dimensional reduction, the interactions among the five elements can be reasonably expressed with the Hill equation. According to the analogy, we can represent the Wu-Xing network with the nonlinear ordinary differential equations as follows:

$$\begin{aligned}
\frac{\mathrm{d}x_1}{\mathrm{d}t} &= \left(\frac{a_1 x_5^n}{S_1^n + x_5^n} + b_1\right)\left(\frac{a_2 S_2^m}{S_2^m + x_4^m} + b_2\right) - kx_1,\\
\frac{\mathrm{d}x_2}{\mathrm{d}t} &= \left(\frac{a_1 x_1^n}{S_1^n + x_1^n} + b_1\right)\left(\frac{a_2 S_2^m}{S_2^m + x_5^m} + b_2\right) - kx_2,\\
\frac{\mathrm{d}x_3}{\mathrm{d}t} &= \left(\frac{a_1 x_2^n}{S_1^n + x_2^n} + b_1\right)\left(\frac{a_2 S_2^m}{S_2^m + x_1^m} + b_2\right) - kx_3,\\
\frac{\mathrm{d}x_4}{\mathrm{d}t} &= \left(\frac{a_1 x_3^n}{S_1^n + x_3^n} + b_1\right)\left(\frac{a_2 S_2^m}{S_2^m + x_2^m} + b_2\right) - kx_4,\\
\frac{\mathrm{d}x_5}{\mathrm{d}t} &= \left(\frac{a_1 x_4^n}{S_1^n + x_4^n} + b_1\right)\left(\frac{a_2 S_2^m}{S_2^m + x_3^m} + b_2\right) - kx_5. \qquad (1)
\end{aligned}$$

Here a_1, a_2, b_1, b_2, k are positive parameters that denote the strength of the following interactions or processes: The expression into first bracket represents an activation (activation strength $a_1$and the basal expression strength b_1) that obeys a "sigmoidal" transfer function(monotonic function with a threshold). The second expression of the next bracket represents inhibition (inhibition strength a_2 and the basal expression strength b_2); and the last term is the first-order inactivation (degradation) of either factor with the rate k. S is the half-maximum effective concentration value of x_i. n, and m is the Hill coefficient.

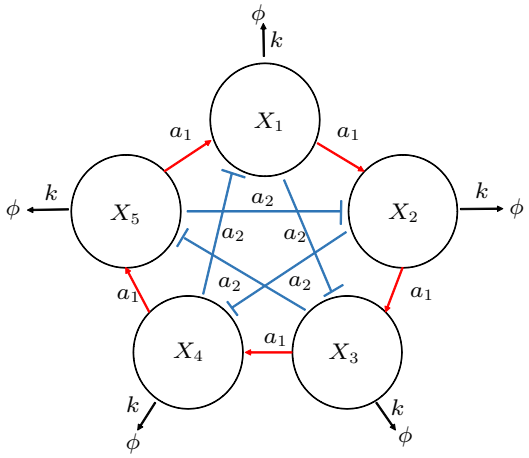


Fig. 3. The diagram of Wu-Xing model with the parameters.

However, for the mesoscopic system which is often of our interests, the fluctuations typically cannot be ignored and often become important. Therefore, the fluctuations can be easily observed and need to be taken into account by the noise term. This is the rational behind employing the Langevin equation to quantify the underlying stochastic dynamics. The Langevin equation is composed of the two driving forces, $F(x)$ on the RHS of equation (1) represents the deterministic or averaged part of the driving force, while the η term represents the stochastic part of the driving force from the environments. This is the whole model of ours using the Langevin equation.

In Fig. 3, we show the diagram and relationship of the five fundamental elements with the related parameters. In the different parameter space, we obtain different phases of the Wu-Xing model. In Figs. 4(a) and 4(b), we show the phase diagram of Wu-Xing model for the parameter space (a_1, b_1) and parameter space (a_1, a_2) using the deterministic equation (1). We can see the model has different types of the solutions. It has a solution of limit cycle in the region I. The model has five stable states in the region II, and a mono-stable state in the region III. The model also has the mixture solution of mono-stable state and limit cycle in the regions IV and V. Therefore, when the parameters are given by $a_1 = 1.8$, $a_2 = 1$, $b_1 = 1$, $b_2 = 0$, $k = 1$, $n = 4$, $m = 4$, $S_1 = 0.5$, $S_2 = 0.5$, the former Wu-Xing model produces an oscillation solution of the limit cycle. When the parameters are given by $a_1 = 1.8$, $a_2 = 1$, $b_1 = 0.5$, $b_2 = 0$, $k = 1$, $n = 4$, $m = 4$, $S_1 = 0.5$, $S_2 = 0.5$, the deterministic model generates a multi-stable solution of the five steady states.

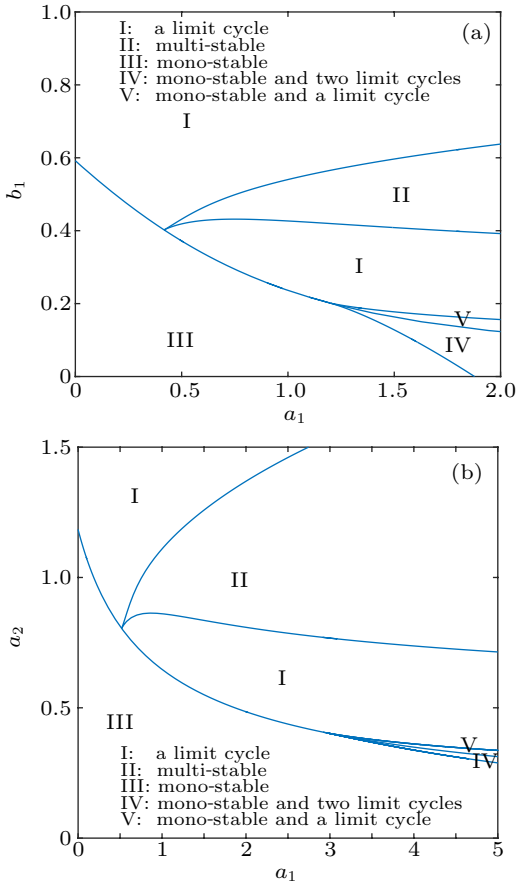


Fig. 4. The phase diagrams on the (a_1, b_1) parameter space (a) where $a_2 = 1$, $b_2 = 0$, $k = 1$, $n = 4$, $m = 4$, $S_1 = 0.5$, and $S_2 = 0.5$ and on (a_1, a_2) parameter space (b) where $b_1 = 0.5$, $b_2 = 0$, $k = 1$, $n = 4$, $m = 4$, $S_1 = 0.5$, and $S_2 = 0.5$.

5.2. Landscape and flux of multi-stability for the Wu-Xing network

According to the underlying differential equations of Wu-Xing network, we can explore the associated dynamics behavior. Furthermore, through introducing the stochastic nature and investigating the probabilistic evolution, we can quantify the steady state probability distribution in the state space.[19,23–26,37] We can first quantify the landscape and flux with the parameters set as $a_1 = 1.8$, $a_2 = 1$, $b_1 = 0.5$, $b_2 = 0$, $k = 1$, $n = 4$, $m = 4$, $S_1 = 0.5$, $S_2 = 0.5$. In the deterministic model, the system gives arise to multi-stable steady state attractors. According to the landscape and flux theory,[19,24] figure 5 shows the two-dimensional projection of the potential landscapes of Wu-Xing network. We found the underlying potential landscape of Wu-Xing network has five different attractor basins. The five basins reflect the five different phases in the Wu-Xing system. They correspond to the five solutions or five steady states of the deterministic model. They are $(0.5, 1.4, 1.14, 0.035, 0.018)$, $(0.018, 0.5, 1.4, 1.14, 0.035)$, and $(0.035, 0.018, 0.5, 1.4, 1.14)$, $(1.14, 0.035, 0.018, 0.5, 1.4)$,

$(1.4, 1.14, 0.035, 0.018, 0.5)$. In each steady state, the concentrations of the three adjacent nodes are higher and those of the rest of the two nodes are almost equal to zero. This denotes that a stable state is located in the region of the coexistence of the three adjacent nodes. It is important to note that although the 5 nodes in our model are symmetric by construction due to the symmetric connections, the 5 states generated are not identical. They represent distinct states with the clustered 3 non-zero nodes. The five distinct states could be correlated to the five functionally stable states of Wu Xing. For example, in TCM, seasonal changes were mapped to Wu Zangs: the spring is the season of growth initiation and Gan (肝) is in charge; the summer is the season of full growth and Xin (心) is in charge; the late summer is the season of harvesting and Pi (脾) is in charge; the autumn is the season of retrieving and Fei (肺) is in charge; and the winter is the season of restoring and Shen (肾) is in charge.[38] The seasonal transition is associated with the transitions in dominant Zangs. The more detailed connection between these 5 stable states with TCM is the topic that we would like to address deeper in our future work.

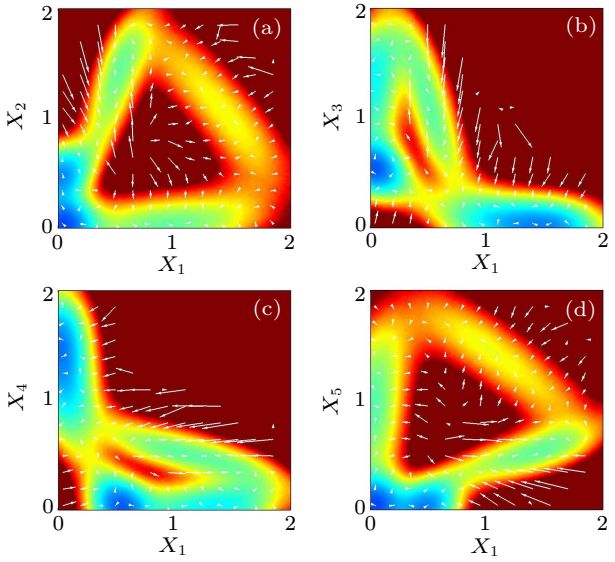


Fig. 5. The two-dimensional projection of Landscape and flux of multi-stable Wu-Xing model, where $a_1 = 1.8$, $a_2 = 1$, $b_1 = 0.5$, $b_2 = 0$, $k = 1$, $n = 4$, $m = 4$, $S_1 = 0.5$, and $S_2 = 0.5$.

In the two-dimensional projection of the potential landscapes, the depths of the 5 steady states appear to be different, which is an illusion. In fact, due to the symmetry of the model, the 5 steady states have the same depth in the five-dimensional potential landscape or the same weight in the steady state probability distribution. Around the five attractor basins, the dynamics is spontaneously attracted to the near basin by the negative potential gradient force, which guarantees the relative stability of these attractor basins or phases. Meanwhile, we can quantify the barriers between the adjacent attractors. All attractors are connected with the barriers and the systemic dynamics can be switched from one attractor to another by the stochastic noise, flux and input. The barrier heights can be used to measure the landscape topography and represent the capability of communicating from one attractor to another. Therefore, it can be used to correlate the escape time for the attractor and thus be used as a measure of the stability of a specific state represented by the basin of attraction.

5.3. Landscape and flux of limit cycle for the Wu-Xing network

By setting the parameters as $a_1 = 1.8$, $a_2 = 1$, $b_1 = 1$, $b_2 = 0$, $k = 1$, $n = 4$, $m = 4$, $S_1 = 0.5$, $S_2 = 0.5$, we can also explore another case with the landscape and flux theory. In the deterministic model, this system has only one unstable solution (0.64, 0.64, 0.64, 0.64, 0.64) and generates a limit cycle oscillation. Figure 6 shows the two-dimensional projection of the potential landscapes with the limit cycle. In this case, we found the underlying potential landscape of Wu-Xing network has an irregular ring shape with the center high potential island surrounded by a closed ring valley and outer high potential cliff. Outside the oscillation cycle ring, the dynamics is attracted to the ring by the negative landscape gradient force, which gives arise to the stability of the oscillation ring path. Once on the oscillation ring, the driving force is mainly dominated by the rotational flux along the oscillation cycle path. The flux can guarantee the stability of the directional flow of the oscillations. In addition, we also notice the 5 local basins with the barriers in between on the closed ring valley. These basins are not stable states. Due to the presence of the curl flux force, the switching between the states will be coherent and follow specific sequence of periodic oscillations. Our findings yield results that have not been seen before in Wu-Xing study. Potential correlations to the relative stable states could associated with the concepts of seasonal associations with Five Zangs[38] and *Zi Wu Liu Zhu* (子午流注)[4] in TCM and the circadian rhythm in modern medicine,[39–42] where different functions of organs and bioprocesses are more dominant at specific season or time of the day. These seasonal and daily patterns oscillate in a limited cycle manner. At the cellular level, the behavior of the cell cycle may also correlate with these results, which was not observed by TCM but is a well-studied area of research in modern science.[43–45]

This activated self-organizational phenomenon of state transition and flux was qualitatively described in the Wu Zang (the Five Organ theory) of TCM. The driving forces of the flux could correlate with the innate Shen Qi (肾气,先天之气) and acquired Pi Qi (脾气, 后天之气).The innate Shen Qi refers to the driving force of growth inherited from embryogenesis to birth and through the life. The acquired Pi Qi refers to nutrients and energy taken from living environment that nurture the life. These two forces of life drive directional flow in the

network to maintain the oscillations and architectural stability of the network.

We also found some local basins and barriers between the basins along the cycle ring path. The local basins are similar to the previous discussed case of coherent and stable oscillation flow, the rotational flux has to be large enough to overcome the local barriers. In fact, if the rotational flux is not large enough, the system will likely be trapped to an attractor by the potential gradient force. We can also uncover the potential landscapes of the Wu-Xing network with similar characteristics in certain different parameter regions. Some local basins and barriers between the basins can give arise to an irregular ring valley. TCM concepts of Yin/Yang deficiencies and excessiveness may refer to pathological states that are trapped in those irregular ring valleys. It would be very interesting to study those parameters of irregular rings and explore their potential correlations with clinical conditions described in TCM. Such exploration may lead to further understanding of TCM diagnosis and treatment principles in a more quantitative manner.

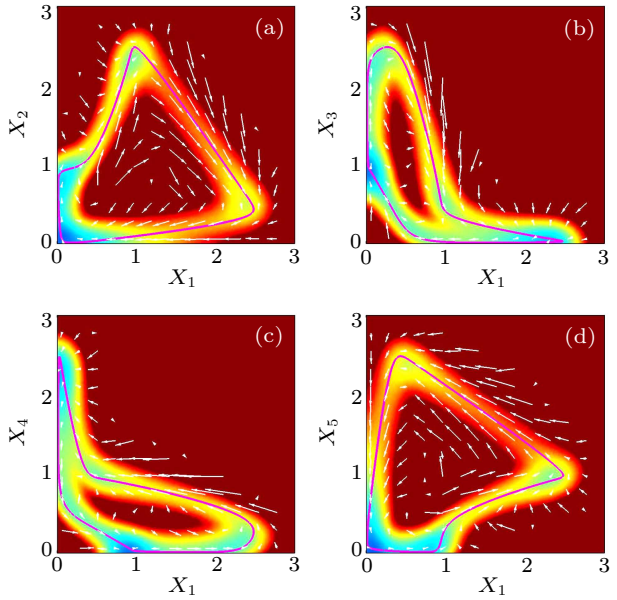


Fig. 6. The two dimensional projection of landscape and flux of Wu-Xing model of limit cycle, where $a_1 = 1.8$, $a_2 = 1$, $b_1 = 1$, $b_2 = 0$, $k = 1$, $n = 4$, $m = 4$, $S_1 = 0.5$, and $S_2 = 0.5$.

It is important to realize that the system dynamics is determined not only by the negative landscape gradient force but also by the rotational flux. The system has the stronger rotational flux for limit cycle to maintain the periodic oscillation flow. Moreover, the direction of the rotational flux is consistent with the direction of the limit cycle. The system dynamics present the irreversibility for the time evolution.

In the case of multi-stable state, the system has the stronger gradient force which guarantees the multi-stability. It is important to note that the complex system dynamics is determined by the two driving forces. One is the gradient of the potential landscape and the other is the curl probability flux. While the potential landscape tends to attract the system down the stable states, the curl flux tends to destabilize the individual states and drive the stable flow.[19,23–25,32] In fact, this applies to any complex system. These two driving forces for complex systems can be viewed as Yin and Yang representing two different aspects of the driving forces of the universe acting together to shape the behaviors. Therefore, the potential landscape and curl flux together provide the physical and quantitative foundations for the Yin–Yang duality as the driving force for determining the complex system behaviors.[19,23–25,32]

In summary, the combination of the negative landscape gradient force and the rotational flux force dominated the self-organized dynamics of Wu-Xing network.[46,47]

5.4. Flux direction of Wu-Xing network

In the TCM classics *Huangdi Neijing* (《黄帝内经》), the interactions of five Xings with reversed directions were described to be associated with abnormal conditions. We found the phenomena of reversed flux when evaluating the relationship between a_1 and a_2, the strength of promotion and repression among the Wu-Xing interactions. Figure 7 shows that when setting $a_2 = 0.5$ and varying a_1 in 2, 2.5, and 3, the network landscapes stay in a limit cycle and the curl flux is in the anti-clockwise direction. However, when setting a_2 in 1.5, the same range of variation in a_1 results in the landscapes of the other limit cycle and the resulting flux is in the clockwise direction.

Flux direction changes by varying a_1 and a_2 quantitatively indicate that the balance and optimal actions of promotive and repressive interactions in the Wu-Xing network are critical in maintaining functional dynamics of the network. This finding could be used to quantitatively guide TCM practice of balancing Yin Yang and the Five Zangs in maintaining good health, preventing and treating diseases.

5.5. The effects of regulations on Wu-Xing system dynamics and thermodynamics

To study the thermodynamics and dissipation cost of the non-equilibrium open system, we can calculate the entropy production rate (EPR) under different conditions. As shown in Fig. 8, we plotted the relationship among the entropy production rate, the activation strength a_1 and repression strength a_2. We can see the entropy production rate increases with the increase of activation strength a_1 and repression strength a_2. This illustrates that the system requires more dissipation cost upon increasing the activation strength or repression strength. Meanwhile, we can find the EPR of the limit cycle phase is larger than the EPR of the multi-stable state phase. The generation and progression of the limit cycle oscillations require more energy input to maintain.

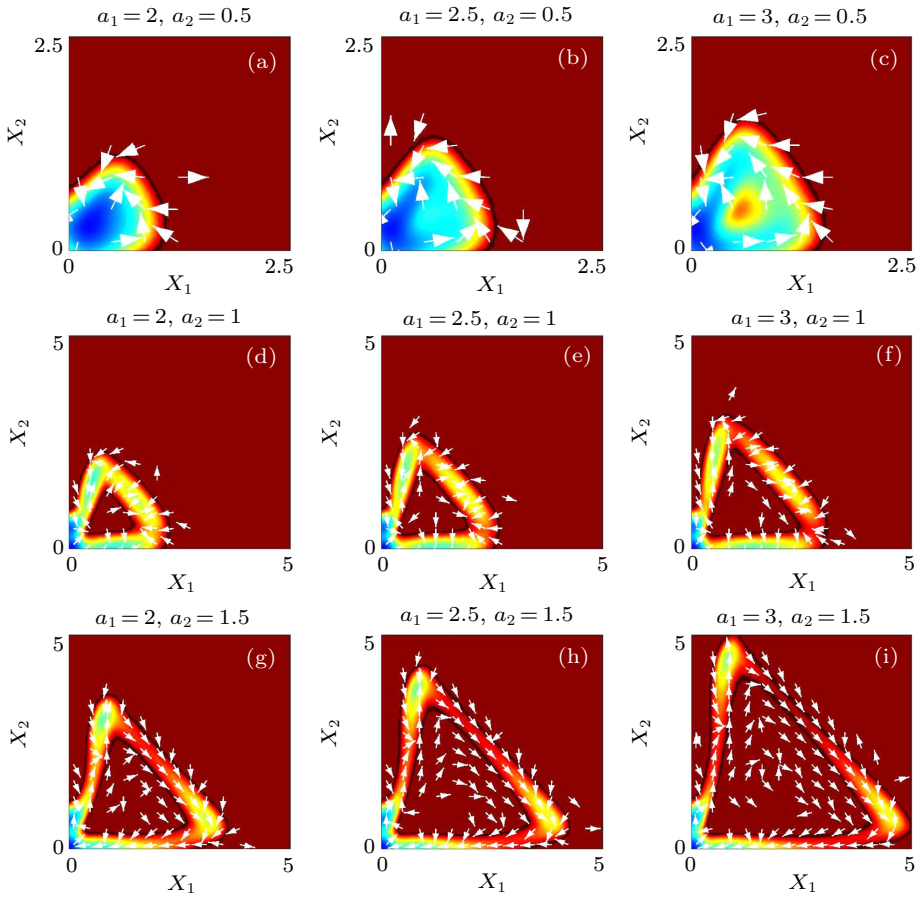


Fig. 7. The landscape and the direction of flux. The direction of flux (region I of limit cycle) is anti-clockwise below the region II of Fig. 4(b), see panels (a)–(c). The direction of flux (region I of limit cycle) is clockwise above the region II of Fig. 4(b), see panels (g)–(i).

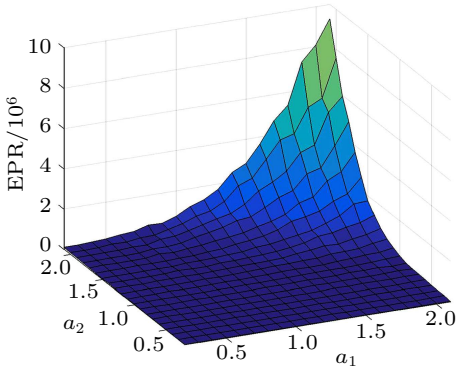


Fig. 8. The entropy production rate *versus* the activation strength a_1 and repression strength a_2.

5.6. The relationship among entropy production rate, flux, and oscillation period

In Fig. 9, we show the relationship between the EPR and the period of the limit cycle. We can see the EPR increases with the increase of the period. In this case, the amplitude of the oscillation is larger, and this leads to more dissipation cost for the completion of periodic oscillation. In Fig. 10, we show the change of EPR with the flux along the cycle path(a loop integral along the limit cycle $\oint J\mathrm{d}l/\oint \mathrm{d}l$). We find that EPR increases with the increase of the flux. This indicates the thermodynamic dissipation cost of the system is due to the rotational flux as one of the driving force for dynamics along the limit cycle.

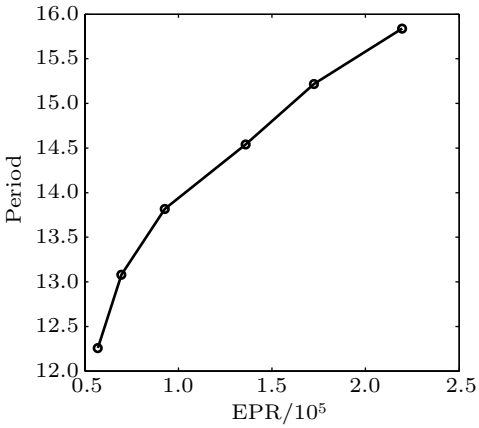


Fig. 9. The entropy production rate *versus* the period of limit cycle.

Limit cycle oscillations are essential for the birth and replication of cell life or in the broad sense life itself in the organism level. The combination of alternative activation and repression regulations in Wu-Xing network motif can lead to the limit cycle oscillations (birth or replications). This oscillation is boosted by the nutrients such as oxygen recognized in modern gene and metabolic network studies. The entropy production rate EPR quantifies the thermodynamic cost asso-

ciated with such boost. The more the EPR cost or the energy input cost is, the faster the limit cycle is or the smaller the period is.[44,48] This corresponds to stronger alternative activation and repressions among the five-node regulations in Wu-Xing theory.

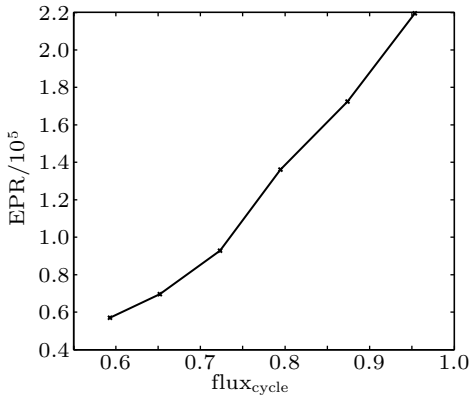


Fig. 10. The entropy production rate *versus* the integral of flux along the limit cycle.

The landscape and flux perspective provides a global and balanced view of life. In the example of a single cell, the life itself including the birth, growth and proliferation is determined by the cell cycle. While the Mexican hat shaped landscape ring valley determines the stability of the different functional phases such as G1, S, G2, and M phases, the curl flux drives the stable limit cycle oscillation flows. This does not come for free. There is a cost which is a thermodynamic manifestation of the dynamical flux quantified by the entropy production rate for maintaining the cell cycle function of cell birth, growth and proliferation. This thermodynamic cost is provided by the nutrition in the form of chemical energy supply such as ATP hydrolysis. Not enough thermodynamic cost will have the weak flux or drive for the oscillations and therefore influence the quality of the cell function such as birth and growth. On the other hand, too much energy supply giving larger flux or drive for the cell cycle will render the oscillations without any check points or resistance, leading to uncontrollable birth and growth, a signature of cancer. In order to maintain the normal function of life at the cellular level, one has to have the appropriate balance between the two Yin and Yang driving forces in terms of the landscape and flux with a suitable thermodynamic energy or nutrient supply. This dynamical and thermodynamic analysis is consistent with the Ying–Yang and Wu-Xing theory as well as the TCM practice for life, providing a physical and quantitative basis for the above ancient theories and practices.

5.7. Global sensitivity analysis of key regulations for Wu-Xing system

Wu-Xing system can be sustained by the interactions among five fundamental elements and inter-regulations. To find the key regulatory elements in the Wu-Xing network, we perform a global sensitivity analysis for the oscillation period and EPR.

In Fig. 11, we show the results of the global sensitivity analysis. We analyzed the sensitivity of the EPR and the oscillation period upon changes of the 8 parameters in the Wu-Xing network. We found the basal expression strength b_1 (parameter 2) of self-activation and inhibition strength a_2 (parameter 3) can have significant more effects on the EPR and oscillation period.

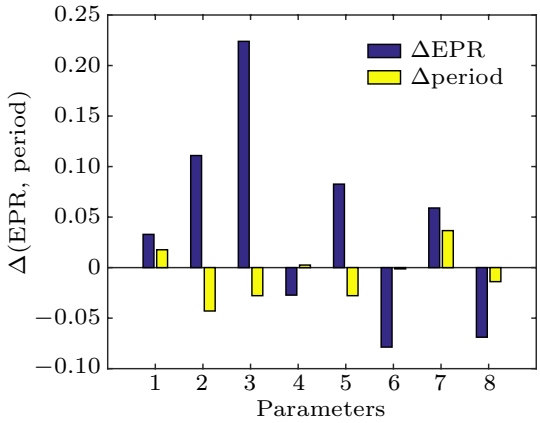


Fig. 11. Global sensitivity analysis in term of the EPR and oscillation period when regulations are changed. The x coordinates (1 to 8) correspond to the 8 regulation parameters. 1: a_1, 2: b_1, 3: a_2, 4: n_1, 5: n_2, 6: S_1, 7: S_2, 8: k.

The landscape and flux analysis of Wu-Xing motif network reveals dynamic features of the network topologies, which are hard for human mind to comprehend without the mathematic revelation and simulation. The multi-target treatment plan is often used as TCM treatment principles. For example, when treating one organ's deficiency, the organ that has negative input to will be suppressed and the organ that have positive input to will be strengthened in addition to strengthen the deficient organ. Knowing the dynamic features of the Wu-Xing motif network, this ancient practice can be quantitatively understood from the perspective of valley, barrier and flux of the landscape.

In the post genomic era, a specific gene regulatory network motif can be constructed with the synthetic biology methodology.[49–52] One can experimentally explore the dynamical behavior of a regulatory network under specific conditions, which enables the comparison of the network behavior observed in an experiment and theoretical predictions.[50,51] We hope our findings can be validated with a synthetic biological network in the future.

6. Conclusion

As a significant guiding principle, Wu-Xing theory of ancient China has been integrated into TCM for disease etiology,

diagnosis and treatment, especially in configuration of treatment strategy. For example, when treating deficiency of the Pi (脾), the Earth organ, the herbal formula not only contains herbs supplement the deficiency of Pi (脾), but also has herbs to calm the Gan (肝), the Wood organ that suppresses the Pi (脾). For thousands of years, Wu-Xing theory has been used in TCM conceptually. In this work, we applied a landscape and flux framework to quantify the Wu-Xing network based on a minimum network motif. First, we established a mathematical model of Wu-Xing network on the basis of the regulatory similarity between the Wu-Xing network and the biochemical network. Second, we quantified the underlying landscape of the Wu-Xing network. The potential landscape of the Wu-Xing network shows an irregular ring shape for oscillation dynamics under certain conditions or multiple attractors under other conditions. Third, we uncovered the driving forces for the dynamics of Wu-Xing network, the underlying landscape and the rotational flux. These features measure the degree (of detailed balance breaking) away from equilibrium. Meanwhile, the landscape topography of the barrier height can give rise to the stability of the steady state attractors and the rotational flux drives the persistent oscillation and guarantee the stability of the flow. Therefore, the landscape and flux provide the physical and quantitative basis for Yin–Yang duality of the driving forces for determining the dynamics and behavior of the living systems. The potential barriers separate the system into different phases and prevent the easy progressions of the phase transformations. Finally, the rotational flux originated from the energy exchange or supply from the environment, and the corresponding dissipation consumption can drive the periodic oscillations across different phases. This provides the thermodynamic basis for the behavior of the living systems. The dynamical and thermodynamic driving forces identified here provide us a guiding principle for the determining the functions of the living systems. This is particularly apparent in the life cycle of a single cell through the cell cycle. With landscape and flux analyses, we identified several key parameters for controlling the network and its phase transitions. These findings were not possible to comprehend without integrating mathematical modeling into the ancient Wu-Xing network. We hope that our work can enlighten an effort to build a quantitative Wu Xing framework and strengthen the guiding principle of Wu-Xing theory in TCM practice.

Current work focuses on characterizing the four fundamental relationships among five Xings. Each Xing in the classic Wu-Xing theory also represented a class of functions, which are combined to form a self-organized, opened, dynamic, adaptive, nonequilibrium system. Current work did not address certain functional specificity of the Wu-Xing theory. We wish to address those aspects in future work.

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