FLUCTUATION THEOREM, INFORMATION AND BIOLOGICAL SYSTEMS

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ABSTRACT
Fluctuation theorems in the presence of information as well as the definition and quantification of information have created broad discussions and are constantly evolving. The fluctuation theorem can quantify the hysteresis observed in the amount of the irreversible work of unfolding and refolding of a macromolecule in nonequilibrium regimes. It also describes how the probability of violations of the second law of thermodynamics becomes exponentially small as the time or the system size increases. Functional information may lead to self-organizing capabilities of living systems, while instructional information is a physical array. The informational entropy is applicable to describe of objects of any nature. Developed dissipative structures are capable of degrading more energy, and of processing complex information through developmental and environmental constraints. Within this trend, control information is defined as the capacity to control the acquisition, disposition, and utilization of matter, energy, and information flows in purposive processes. On the other hand, maximum entropy production and the fluctuation theorem are seen as the properties of maximum entropy distributions.. This review brings out some critical turning points in describing living systems with the help of fluctuation and information theories.

INTRODUCTION

For a system in contact with a heat bath, symmetry of the probability distribution of entropy production in the steady state is known as the fluctuation theorem. Crook's fluctuation theorem compares probability distributions for the work required in the original process with the time-reversed one. The probabilistic approach reached the broader appeal due to advances in experimental techniques for tracking and manipulation of single particles and molecules [1-7].

An overdamped motion $x(\tau)$ of a system in contact with a heat bath and a single continuous degree of freedom can be described by the Langevin equation: $\dot{x} = \mu F(x,\lambda) + \zeta$ .The systematic force $F(x,\lambda)$ can arise from a conservative potential and/or be applied to the system directly as a nonconservative force , while ζ is the stochastic force, which is not affected by a time-dependent force, and μ is a positive constant. The Langevin dynamics generates trajectories $x(\tau)$ starting at x_0. For an arbitrary number of degrees of freedom, x and F become vectors. The Langevin equation is the generic equation of motion for a single fluctuating thermodynamic quantity such as the concentrations of the chemical species in the vicinity of equilibrium [6-8].

Definition and quantification of information have created broad discussions. 'Information system' with its role in living systems is a constantly evolving field [2,6]. This short review addresses some cirtical discussions on the associaton of information theory with fluctuation theorem and entropy production in living systems.

FLUCTUATION THEOREM

The fluctuation theorem relates the probability $p(\sigma_\tau)$ of observing a phase-space trajectory with entropy production rate of σ_τ over time interval τ, to that of observing a trajectory with entropy production rate of $-\sigma_\tau$

$$\frac{p(\sigma_\tau)}{p(-\sigma_\tau)} = \exp(\tau\sigma_\tau / k_B) \qquad (1)$$

where k_B is the Boltzmann constant. This result describes how the probability of violations of the second law of thermodynamics becomes exponentially small as τ or the system size increases. FT relates the work along nonequilibrium trajectories to the thermodynamic free energy differences, and applicable to single molecule force measurements. The FT depends on the following assumptions. The system is finite and in contact with a thermal bath. The dynamics are required to be stochastic, Markovian, and microscopically reversible. The probabilities of the time-reversed paths decay faster than the probabilities of the paths themselves and the thermodynamic entropy production arises from the breaking of the time-reversal symmetry of the dynamical randomness. Since the statistics of fluctuations will be different in different statistical ensembles.

Crook's FT can be used to determine free energies of folding and unfolding processes occurring in nonequilibrium systems. For that, the unfolding and refolding process need to be related by time-reversal symmetry, i.e. the optical trap used to manipulate the molecule must be moved at the same speed during unfolding and refolding [3,5,6].

In processes that are microscopically reversible, Crook's FT predicts a symmetry relation in the work fluctuations for forward and reverse changes a system undergoes as it is driven away from thermal equilibrium by the action of an external perturbation. A consequence of Crook's FT is Jarzynski's equality: $\exp(-\Delta G / k_B T) = \langle \exp(-W / k_B T) \rangle$. However, for processes that occur far from equilibrium the applicability of Jarzynski equality is hampered by large statistical uncertainty arising from the sensitivity of the exponential average to rare events [3].

In the absence of the initial of final correlations, entropy production satisfies the integral of FT (or the Jarzynski

equality): $\langle \exp(-\sigma) \rangle = 1$ where $\langle .. \rangle$ is the ensemble average over all microscopic trajectories. In the presence of information (I) processing with initial and final correlations, the integral FT with energy dissipation and energy cost of information exchange becomes [5]

$$\langle \exp(-\sigma + \Delta I) \rangle = 1 \qquad (2)$$

where ΔI is the change in the mutual information. Convexity of $\exp\langle x \rangle \le \langle \exp(x) \rangle$ leads to $\langle \sigma \rangle \ge \langle \Delta I \rangle$ [5]. With the correlation remaining after a feedback control ($I_{\rm rem}$) by Y on X, Eq. (2) becomes

$$\langle \exp(-\sigma - (I - I_{\rm rem})) \rangle = 1 \text{ so } \langle \sigma \rangle \ge -\langle I - I_{fb} \rangle \qquad (3)$$

where $\langle I - I_{\rm rem} \rangle$ may be an upper bound of the correlation that can be used.

The detailed FT in the presence of information processing is

$$\frac{p_b[X_b, y]}{p_f[X_f, y]} = \exp(-\sigma + \Delta I) \qquad (4)$$

with the constraint $p[x, y] \neq 0$ (x and y are initial phase-space points), p_b and p_f are the joint probability distributions of the backward and forward processes, respectively, and $(-\sigma + \Delta I)$ shows the total entropy production of the composite system XY and the baths. Here system x evolves from x to x' along a path x_f in such a manner that depends on the information about y, which does not evolve in time [5].

FT allows a general orthogonality property of maximum information entropy (MIE) to be extended to entropy production (EP). Maximum entropy production (MEP) and the FT are generic properties of MIE probability distributions. Physically, MEP applies to those macroscopic fluxes that are free to vary under the imposed constraints, and corresponds to the selection of the most probable macroscopic flux configuration [9,10]. The constrained maximization of Shannon information entropy (H) is an algorithm for constructing probability distributions from partial information. MIE is a universal method for constructing the microscopic probability distributions of equilibrium and non-equilibrium statistical mechanics. The distribution of the microscopic phase space trajectories over a time τ satisfies $p_\alpha \propto \exp(\tau\sigma_\tau / 2k_B)$.

INFORMATION THEORY

Information may be defined as the capacity to reduce statistical uncertainty in the communication of messages between a sender and a receiver. Consider the number of ways in which N distinguishable entities can be assigned to M distinguishable states such that there are n_i entities in state i

$$W = \frac{N!}{n_1!n_2!..n_M!} \qquad (5)$$

Maximum probability is related to maximum entropy in the limit of large N and n_i and the asymptotic result from Stirling's approximation ($\ln N! \approx N \ln N$) yields

$$\frac{1}{N} \ln W = -\sum_i^M p_i \ln p_i = H \qquad (6)$$

where the occupation frequency of state i is: $p_i = n_i/N$ [10].

In Shannon's theory, entropy represents the amount of uncertainty one particular observer has about the state of this system [11]. This uncertinty is not information. For a variable X with the x_1, x_2,.., x_N of its N posible states, the probability of finding X in state x_i would be p_i and the Shannon's entropy H of X is $H(X) = -\sum_i^N p_i \ln p_i$. If nothing is known about X, we have $H(X) = \ln N$, which is the maximum value that $H(X)$ can be; this occurs if all the states are equally likely $p_i = 1/N$. However, for example, if $X = x_5$ then the uncertainty about X becomes smaller, and therefore $H(X)$ represents the quantity of the closest description of X. The probability distribution using prior knowledge or measurements can teach us something about a system. The difference between the maximal and the actual entropy after our measurements or analysis is the amount of information we have for the system. As it mesaures the difference of uncertainty, information is a relative quantity [11].

If we define another random variable Y with its states y_1, y_2,..,y_M and probabilities p_1, p_2,..,p_M, then the joint entropy $H(X,Y)$ measures our uncertainty about the joint system XY in $N \cdot M$ states. If X and Y are somehow connected, such as two molecules that can bind to each other, the information that one molecule has about the other is

$$I(X:Y) = H(X) + H(Y) - H(XY) \qquad (7)$$

Here ':' shows that information is symmetric; X and Y equally know each other. If the state of Y is known, then the so called 'conditional entropy' becomes

$$H(X/Y) = H(XY) - H(Y) \qquad (8)$$

For independent variables: $H(XY) = H(X) + H(Y)$. With the conditional entropy, Eq. (7) becomes

$$I(X:Y) = H(X) - H(X/Y) \qquad (9)$$

Eq. (9) shows that information measures deviation from independence that is the amount by which the entropy of X or Y is reduced by knowing the other (Y or X) [11].

Maximization of the information entropy (IE) determines the probability of a particular state of the system. This leads to the relation between the probability of a nonequilibrium process and the number of microscopic trajectories [12,13].

Information and Thermodynamics

Maximum entropy and maximum entropy production are two essential properties in equilibrium and nonequilibrium thermodynamics, respectively. MEP may be an organizational principle applicable to physical and biological systems. Various derivations of MEP by using the MIE procedure by Jaynes [14] exist in the literaure [2]. In these derivations the IE is not defined by a probability measure on phase space, but on path space for the stationary nonequilibrium systems [10].

Consider M sites with a variable $n_i(t)$ (i = 1,2,.,M) at each site with t = 0,1,.,τ. The flux (time asymetric) occurring

randomly at every time step, $J_{ij} = -J_{ji}$ from i to j depends on a parameter $c_{ij} = c_{ji}$, such that $J_{ij}(t) = \pm c_{ij}$ with stochastic sign. A miscroscopic path a is a set of values $\pm c_{ij}$ so that: $n_{i,a}(t+1) - n_{i,a}(t) = -\sum_j J_{ij,a}(t)$. The path dependent time average is $\bar{J}_{ij,a} = (1/\tau)\sum_t J_{ij}(t)$ and $n_i(0)$ does not depend on the complete path. With the miscroscopic path dependent probability p_a, the path ensemble averages are $\langle \bar{J}_{ij} \rangle = \sum_a p_a \bar{J}_{ij,a}$. By using Jayne's information theory and maximizing path information entropy

$$S_I = -\sum_a p_a \ln p_a \tag{10}$$

with the constraints

$$1 = \sum_a p_a \tag{11}$$

$$\langle n_i(0) \rangle = \sum_a p_a n_{i,a}(0) \tag{12}$$

$$N_{ij} = -\sum_a p_a \bar{J}_{ij,a} \tag{13}$$

the most likely probability on path space is estimated as

$$p_a = \frac{1}{Z} \exp A_a \tag{14}$$

where N_{ij} is the numerical value of the time and path ensemble average of the flux J_{ij}, A_a the path action: $A_a = -\sum_{ij} \lambda_i \, \mathrm{n}_{ia}(0) + \sum_i n_{ij} \bar{J}_{ij,a}$ in which λ_i and $n_{ij} = -n_{ji}$ are the Lagrange multipliers of constraints (12) and (13), respectively, and Z is the partition function [2,9,14].

However, a trajectory of a quantity possesed by a system may fluctuate wildly (far from equilibrium) or weakly; than they would not have the same probabilities as long as they have the same initial and final states. Here a path trajectory is a sequence of p over some time interval:

$$a \equiv [p(0), p(dt), p(2dt), .., p(Mdt)] \tag{15}$$

where $M = \tau/dt$. And dt is the coarse graining corresponding to the time scale of experimental observations [8].

The partition and constitutive (phenomenological) equation of motion have the relations

$$\frac{\partial \ln Z}{\partial n_{ij}} = N_{ij} \tag{16}$$

$$X_{ij} = \frac{n_{ij}}{\tau} \tag{17}$$

The forward and backward components of the time and ensemble averaged fluxes are

$$N_{ij} = N_{ij}^f - N_{ij}^b = \frac{c_{ij} e^m}{e^m + e^{-m}} - \frac{c_{ij} e^{-m}}{e^m + e^{-m}} \tag{18}$$

where $m = X_{ij} c_{ij}$ and $2 c_{ij} X_{ij} = \ln\left(N_{ij}^f / N_{ij}^b \right)$.

The entropy production of a microscopic path a is [2]

$$\sigma_a = \sum_a p_a \sigma_a = \sum_{ij} X_{ij} N_{ij} \tag{19}$$

By using Eq. (14) in Eq. (10), the maximum information entropy as a function of the forces becomes

$$S_{I,\max}(X) = \ln Z(X) - \langle A(X) \rangle \approx \ln W\left(\langle A(X) \rangle \right) \tag{20}$$

where $W\left(\langle A(X) \rangle \right)$ is the density of paths.

The entropy curvature (response) matrix is

$$A_{ij,kl}(N) = \frac{\partial X_{ij}}{\partial N_{kl}} = -\frac{\partial^2 S_{I,\max}(X(N))}{\tau \partial N_{ij} \partial N_{kl}} \tag{21}$$

The probability distribution for the time averaged flux is

$$p(\bar{J}) \propto \exp\left(-\frac{\tau}{2} \sum_{ij,kl} [\bar{J}_{ij} - N_{ij}] A_{ij,kl}(N) [\bar{J}_{ij} - N_{kl}] \right) \tag{22}$$

Combining the equation above with the FT yields [2]

$$\frac{p(\bar{J})}{p(-\bar{J})} = \exp(2\tau\sigma(\bar{J})) \tag{23}$$

In near equilibrium regime, the maximum path information is

$$S_{I,\max}(X) = \ln(W) \approx \ln 2^{\tau(M^2 - M)} + \tau\sigma/2 \tag{24}$$

The first part on the right side of the equation above is the logarithm of the total number of paths for uniform probability distribution, while the second term is the entropy production. In the MEP, the assumption was that the number of paths W should be an increasing function of the averaged action [10]. Here for higher entropy production, the SI is minimum [2].

MEP principle states that if thermodynamic forces X_i are preset, then the true thermodynamic flows J_i satisfying the condition $\sigma = \sum_i J_i X_i \geq 0$ yield the maximum value of the $\sigma(J)$. This can be written using the Lagrange multiplier λ

$$\delta_j [\sigma(J_k) - \lambda(\sigma(J_k) - \sum_i J_i X_i)]_X = 0 \tag{25}$$

and at fixed forces, the relationship between the fluxes and forces become

$$X_i = \frac{\sigma(J)}{\sum_i J_i (\partial\sigma / \partial J_i)} (\partial\sigma / \partial J_i) \tag{26}$$

and indicates that the relationship between the thermodynamic forces and fluxes can be both linear and nonlinear [12].

The same entropy production can be both maximum and minimum depending on the constraints used in the entropy production variation. However, it is widely published that the MEP principle may be a critical link in the explanation of the direction of the biological evolution under the imposed constraints of the environment [9,10,12,13]. If X is fixed, the MEP leads to maximum J that is the selection of fastest process. MEP principle has proved to be valuable for understanding and describing of various nonequilibrium processes in physics, biology, and environment. The local equilibrium of a nonequilibrium system and the representation of the EP as a bilinear form of flows and forces are a

mandatory condition for the use of MEP principle [11,14].

In the cortex, populations of neurons continuously receive input from other neurons, interpret it their ongoing activity, and generate output destined for other neurons. This information processing and transmission is limited by the repertoire of different activated configurations available to the population. The extent of this repertoire may be quantified by its entropy H characterizing the information capacity as the upper limit on aspects of information processing of the population. When the information transmitted from the input to the output by a population that has only two states in its repertoire (H = 1 bit), then regardless the information the input contains, the output information content cannot exceed 1 bit. Therefore, a network with low entropy population may limit information transmission. Activity in the cortex depends on the ratio of fast excitatory E to inhibitory I synaptic signals to neurons. This E/I ratio remains fixed at an average in various events during highly fluctuating activity levels, yet a small E/I raio, caused by weak axcitation drive, may reduce the correlations as well as the overall level of activity [16].

For a number of unique binary patterns, p_i the probability that pattern i occurs, the entropy of the set of patterns is

$$H = -\sum_{i=1}^{n} p_i \log_2 p_i \qquad (27)$$

Eq. (27) estimates the occurrence probability for each pattern. Maximization of entropy may be an organizing principle of neural information processing systems [16].

The information capacity I_C in binary units may be expressed as a function of the probability p

$$I_C = \frac{1}{\ln 2}\left(\sum_{j=1}^{\Omega} p_j \ln p_j - \sum_{j=1}^{\Omega} p_j^o \ln p_j^o \right) \qquad (29)$$

where Ω is the number of possibilities, p^o is the probability at equilibrium (i.e., no knowledge), and p is the probability when some information are available about the system. Information here is used as a measure of structure [1,7].

BIOLOGICAL SYSTEMS

Ribonucleic acid (RNA) translates the genetic codes in the nucleic acids of deoxyribonucleic acid (DNA). The codes consisting of four different bases (nucleotides) are adenine (A), guanine (G), cytosine (C) and thymine (T, DNA only) or uracil (U, RNA only). During the gene expression, RNA serves as the template for the translation of genes into proteins by transferring amino acids to the ribosome to form proteins, which may undergo posttranslational conformational changes, folding, and association with other polypeptide chains. All these steps can be regulated, therefore, the dynamical object of a gene is to produce functional, folded, and chemically modified protein [17].

Information and Biological Systems

DNA is a code, and codes from sequence alone do not reveal information. The nonconditional entropy for DNA sequence or proteins is about two bits per base; a random protein would have $\log_2(20)$ = 4.32 bits of entropy per site. Due to repetitions, pair, and triplet correlations the actual entropy would be lower [11]. This entropy per symbol only allows us to quantify our uncertainty about the sequence identity; it will not reveal the 'function' of the genes.

In equilibrium thermodynamics, isolated systems have the maximum entropy and there are no correlations; hence there is no information. The information as the amount of correlations between two systems stored in living system (biological genomes) points out that they are far away from equilibrium. Consequently, information theory becomes a part of nonequilibrium thermodynamics in living cells. Information measures the amount of entropy shared between two systems; so it is the information that one system has about the other. if it cannot be specified what the information is about, then it would be entropy. Also informations enables us to make predictions about other systems; only in reference to another ensemble entropy can become information. Therefore, what is described by the correlations between the seqences stores information not the sequence itself. On the other hand, what information a genomic sequence represents depends on the interpreter environment. If a sequence means someting it can create a function necessary for its environment [11,17].

The information theory introduced 'functional information' that leads to self-organizing capabilities of living systems, and 'instructional information' that is a physical array. However, linkages with the field of semiotics established a much more compatible approach to biological information [17]. Within this trend 'control information' is defined as the capacity to control the acquisition, disposition, and utilization of matter, energy, and information flows functionally.

Each position on the genome is four-base code and the uncertainty at each position is two bits; then the maximum entropy becomes

$$H_{\max} = -\sum_{i=G,C,A,T} p(i) \log_2 p(i) = \log_2(4) = 2 \text{ bits} \qquad (30)$$

since $p(i)$ = ¼. The actual entropy is obtained from the actual probabilities $p_j(i)$ for each position j on the sequence. In N sequences, we have $p_j(i) = n_j(i)/N$ by counting the number of $n_j(i)$ occurences of nucleotide i at position j (this will be done for all positions j = 1,..,M on the sequence length M). When we ignore correlations between positions j, the information stored in the sequence becomes

$$I = H_{\max} - H = 2M - H \text{ bits} \qquad (31)$$

where

$$H = -\sum_{j=1}^{M} \sum_{i=G,C,A,T} p_j(i) \log_2 p_j(i)$$

The thermodynamics of protein structures implies that sequence and structure are related. If a structural entropy of proteins H(str) is obtained for a given chain length and for a given environment, the the mutual entropy between structure and sequence becomes [11]

$$I(\text{seq:str}) = H(\text{seq}) - H(\text{seq/str}) \qquad (32)$$

where H(seq) is the entropy of sequences of lenth M and H(seq/str) is the entropy of squences given the structure. If the environment requires a certain structure that will be functional in that environment then $H(\text{seq/str}) \approx H(\text{seq/env})$. Then $I(\text{seq:str})$ is approximately equal to the physical complexity. Assuming that any given sequence produces an exact structure: H(str/seq) = 0, and Eq. (32) becomes

$$I(\text{seq:env}) \approx I(\text{seq:str}) = H(\text{str}) \qquad (33)$$

Therefore, thermodynamic entropy of a protein structure is limited by the amount of information about the environment coded by the sequence. This may imply that sequences that encode more information about the environment may be more functional.

One of the consequences of the Human Genome project has proved that 'biology is an informational science' [16,17]. The communication in living cells is based on the signals, such as electromagnetic-light, mechanical-touch, and chemical, received. In the signal-transduction pathway, a signal on a cell surface converted into a specific cellular response in a series of functional steps [16]. This suggests that information is conceived as the communication of a form from object to interpreter through the sign. The evolution of ways of storing, transmitting, and interpreting information can be seen a major step in the increased capacity for collective behavior and robustness in living systems [4,6,7].

In semiotic understanding of living systems, interpreters of signs and information will often be an interpreter-dependent objective process. Genes should be regarded as signs in DNA, which can only have any effect on a cell function through a triadic-dependent process. The object of sign in DNA is a functional, folded, and chemically configured protein production; when a particular gene product is necessary, a signal from the environment activates the expression of a certain gene. The cell as an interpreter alters its internal states triggered by a collective signal transduction pathway to establish the boundary conditions to processes and perform someting functional with the genetic material [17].

Coupled Biological Systems and Information

Biochemical reactions coupled with diffusion of species can lead to molecular pumps and biochemical cycles in living systems. Here, the coupling refers that a flux occurs without its primary thermodynamic driving force, or opposite to the direction imposed by its primary driving force. This is possible only if a process is coupled with another spontaneous process and is consistent with the second law that states that a finite amount of organization may be obtained at the expense of a greater amount of disorganization in a series of coupled spontaneous processes. An example to that is the adenosine triphosphate (ATP) synthesis coupled to the respiratory electron transport. The ATP synthesis, in turn, is matched and synchronized to cellular ATP utilization. This shows a functional process leading to organized structures where the ATP synthesis ($\sigma < 0$) has been made possible and the whole coupled processes satisfy the condition $\sigma > 0$ [7,19-21].

The general approach for incorporating thermodynamics into the information theory has been to derive probability distributions for nonequilibrium steady states by employing the variational approach. However, composing the appropriate constraints to be used in the variational principle is not clear, since there is no definite extremum quantity to characterize the state space of such steady nonequilibrium states. In the vicinity of equilibrium only, the linear phenomenological laws may be useful in that respect [8]. Therefore a natural question is that how useful such an approach would be to describe the information processeing in functionally coupled and self-organized biochemical cycles of living systems that are mainly far from equilibrium. The probabilistic measure of information derived from Jaynes information theory formalism of statistical mechanics is mainly indifferent to meaning [10].

The unified theory of evolution attempts to explain the origin of biological order as a manifestation of the flows of energy and information on various spatial and temporal scales. Genes originates the information to form the required enzymes, regulatory and structural proteins. The genome is the source of cellular codes; also any cellular structure such as lipids and polysaccharides may store and transmit information. Beside these, thermodynamic forces in the form of transmembrane gradients of H^+, Na^+, K^+, Ca^{2+} and consequent electric potential cause significant displacements from equilibrium, and are therefore, potential sources of information. Genome-protein system may be a component of a large ensemble of cellular structures, which store, encode, and transmit the information [6,7,17].

The use of maximum entropy formalism in biology is growing [4,18] in detecting expression patterns in signal transduction. At the maximum entropy, the probabilities of the different proteins are not equal; each protein will be present in proportion to its partition function, which is the effective thermodynamic weight of a species at thermal equilibrium.

Le Chatelier principle may be applied to analyze how a protein-signalling networks at equilibrium returns to its equilibrium state after being slightly perturbed. For a single cell or small cell colony, cell to cell perturbations are small, while the unperturbed state of a single cell may be unstable in the presence of many other cells. Experiments permits observations of the covariance in the fluctuations and evolution of these fluctuations of different proteins when a single cell is perturbed in the presence of other cells. The information theory helps analyze these covariances to understand the network of interacting proteins [18].

The composite immediate object of a protein coding gene is the sequence of amino acids of a polypeptide, which can be folded in different ways in different cellular contexts and represents dynamical objects. So sign that is a sequence of nucleotides in DNA determines object that is a sequence of amino acids in a polypeptide through interpretant that is a range of possibilities of reconstruction of sequence of amino acids required by the environment (cell).

Dewar [4] suggests that MEP is the unifying optimization for living systems and ecosystem function, in which entropy production might be a general objective function. When a system is away from equilibrium, the nonequilibrium state of MEP is the most probable as it can be realized microscopically in a greater number of ways than any other nonequilibrium state. In this sense, MEP is a statistical principle, rather than a physical principle open to experimental validation. MEP may predict optimal plant behavior from the perspective of natural selection as well as offers a novel statistical reinterpretation of that behavior that is the survival of the likeliest.

For a multicomponent fluid system under mechanical equilibrium with n species and N_r number of chemical reactions and diffusion, the rate of energy dissipation due to local rate of entropy production is [19.20]

$$T\sigma = \int_V \left(-\sum_i \mathbf{J}_i \cdot (\nabla \mu_i)_{T,P} + \sum_{i,j} \mu_i \nu_{ij} J_{rj} \right) dV \geq 0 \qquad (34)$$

where $\mathbf{J}_i$ the vector of mass fluxes, μ_i the chemical potential of species i, and A the affinity $A = -\sum \nu_i \mu_i$. The local mass

balance of chemical species *i* from the continuity equation

$$\rho \frac{\partial w_i}{\partial t} = -\nabla \cdot \mathbf{j}_i + \sum_{i,r} \nu_{ir} J_r \qquad (35)$$

For a steady state system, we have $\nabla \cdot \mathbf{j}_i = \sum_{i,j} \nu_{ij} J_{rj}$ allowing the dissipation to be expressed in terms of affinity

Assuming that we have N number of linear flux-force system expressed in matrix form: $-\mathbf{J} = \mathbf{LX}$, Onsager's reciprocal relations states that the coefficient matrix **L** is symmetrical. The **L** will have $N \times N$ elements and the number of cross coefficients would be $(N^2-N)/2$, which may be on and off based on the biochemical path and its environment. In the absence of pertinent symmetries or invariances, all types of cross-couplings are possible and lead to nonvanishing cross coefficients. If the structure of the system is invariant with respect to some or all of the orthogonal transformations, then the invariance will eliminate certain cross-couplings and their cross-coefficients will vanish.

Thermodynamic coupling may lead to self organized and $(N^2-N)/2$ number of posibility of coupled-uncoupled structures with N biochemical reactions depending on the environmental interpretations. This, in turn, brings out the challenge of implementing the trajectories belonging two or much more coupled processes (recognizing each other) with different inital and end nonequilibrium states into the fluctuationg and information theory.

CONCLUSIONS

Shannon's theory can define both entropy and information and should be used to quantify the information content of sequences by distinguishing information-coding parts from random parts in ensemble of genomes. It can also be used in investigating protein-protein interactions and the association of enzymes and proteins with their binding sites. Also, information theory based biomolecule design may maximize the information shared between the target and biomolecule, such as drug, ensembles. The use of information and entropy in thermodynamically coupled processes in fluctuation theory may be helpful further understanding the concept of functionality in dissipative and self-organized structures of living systems.

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