PHYSICAL REVIEW E **94**, 052150 (2016)

Mesoscopic kinetic basis of macroscopic chemical thermodynamics: A mathematical theory

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(Received 11 April 2016; revised manuscript received 11 October 2016; published 30 November 2016)

Gibbs' macroscopic chemical thermodynamics is one of the most important theories in chemistry. Generalizing it to mesoscaled nonequilibrium systems is essential to biophysics. The nonequilibrium stochastic thermodynamics of chemical reaction kinetics suggested a free energy balance equation $dF^{(\text{meso})}/dt = E_{\text{in}} - e_p$ in which the free energy input rate E_{in} and dissipation rate e_p are both non-negative, and $E_{\text{in}} \leqslant e_p$. We prove that in the macroscopic limit by merely allowing the molecular numbers to be infinite, the generalized mesoscopic free energy $F^{(\text{meso})}$ converges to φ^{ss}, the large deviation rate function for the stationary distributions. This generalized macroscopic free energy φ^{ss} now satisfies a balance equation $d\varphi^{\text{ss}}(\mathbf{x})/dt = \text{cmf}(\mathbf{x}) - \sigma(\mathbf{x})$, in which $\mathbf{x}$ represents chemical concentration. The chemical motive force $\text{cmf}(\mathbf{x})$ and entropy production rate $\sigma(\mathbf{x})$ are both non-negative, and $\text{cmf}(\mathbf{x}) \leqslant \sigma(\mathbf{x})$. The balance equation is valid generally in isothermal driven systems and is different from mechanical energy conservation and the first law; it is actually an unknown form of the second law. Consequences of the emergent thermodynamic quantities and equalities are further discussed. The emergent "law" is independent of underlying kinetic details. Our theory provides an example showing how a macroscopic law emerges from a level below.

DOI: 10.1103/PhysRevE.94.052150

I. INTRODUCTION

Ever since the work of Gibbs and the influential treatise of Lewis and Randall [1], chemical thermodynamics has been one of the most important theoretical cornerstones of chemical science. The Gibbs free energy and related chemical potential govern complex chemical kinetics towards equilibrium state. While temperature is one of the key concepts in the theory, its origin resides in the mechanical movement of atoms and molecules, as already clearly articulated by Boltzmann in his mechanical theory of heat [2]. The notion of chemical potential, however, cannot be understood from Newtonian mechanics. This is best illustrated through its definition in Gibbs' equation:

$$dU = TdS - pdV + \sum_{i=1}^{n} \mu_i dN_i, \tag{1}$$

in which

$$T = \left(\frac{\partial U}{\partial S}\right)_{V,\{N_i\}}, \qquad p = -\left(\frac{\partial U}{\partial V}\right)_{S,\{N_i\}},$$
$$\mu_i = \left(\frac{\partial U}{\partial N_i}\right)_{S,V,\{N_{j,j\neq i}\}}. \tag{2}$$

In graduate texts on Newtonian mechanics, there is a demonstration that [3] $\partial U/\partial S$ is the mean kinetic energy if one identifies the $S \equiv k_B \ln \Omega$ as the phase volume of a Hamiltonian dynamics; and $-\partial U/\partial V$ as the momentum transfer on the wall of a box that contains gas particles. While these demonstrations are not general, they have provided definitive *mechanical* interpretations of the two emergent thermodynamic quantities. On the contrary, there is no mechanical interpretation for the $\partial U/\partial N$ in (2). It is widely felt that a "mechanistic" interpretation of the chemical potential μ_i has to be a probabilistic one. We hasten to mention that a large portion of living organisms are sustained as nonequilibrium systems mainly driven by $\Delta\mu$, not a difference in T or p. Therefore, a fundamental understanding of the irreversibility of life requires a deeper understanding of μ, which is still lacking a rigorous submacroscopic foundation.

We report here, mathematically, the chemical potential μ has an origin in the mesoscopic description of chemical kinetics, as an emergent macroscopic quantity. We reserve the lengthy rigorous mathematical analysis in a much longer manuscript [4], and report here the physics and mathematical discovery for a broader audience.

II. MESOSCOPIC CHEMICAL KINETIC SYSTEMS

The mesoscopic description of a well-mixed chemical kinetics is based on a system of elementary chemical reactions with arbitrary complexity; reactions occur one at a time in a stochastic fashion, as now clearly demonstrated in single-molecule studies [5]. The general setting has N chemical species and M reactions in a fixed volume of V [6]:

$$\nu_{\ell 1}^{+} X_1 + \nu_{\ell 2}^{+} X_2 + \cdots \nu_{\ell N}^{+} X_N \rightleftharpoons \nu_{\ell 1}^{-} X_1 + \nu_{\ell 2}^{-} X_2 + \cdots \nu_{\ell N}^{-} X_N, \tag{3}$$

in which $1 \leqslant \ell \leqslant M$. $\nu_{ij} = (\nu_{ij}^{-} - \nu_{ij}^{+})$ are the *stoichiometric coefficients* relating species to reactions. In a reaction vessel with rapidly stirred chemical solutions, the numbers of species i at time t is denoted by $n_i(t)$. Our theory assumes the following:

(i) Each reaction is microscopically reversible, with forward rate $r_{+\ell}[\mathbf{n}(t)]$ and backward rate $r_{-\ell}[\mathbf{n}(t)]$ where $\mathbf{n} = (n_1, \ldots, n_N)$ denoting the copy numbers of all the species. Both $r_{\pm\ell}$ are non-negative, but their dependencies on $\mathbf{n}$ can essentially be arbitrary.

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(ii) As an elementary reaction, each occurs as a Markov process with exponential waiting time following the distribution $r(\mathbf{n})e^{-r(\mathbf{n})t}$, in which $r(\mathbf{n})$ is the corresponding rate function.

(iii) The mesoscopic rate $r_{+\ell}(\mathbf{n})$ is the number of occurrences of the ℓth forward reaction per unit time in the volume V. Therefore, for a macroscopic system with extremely large $\mathbf{n}$ and V: $(x_1,\ldots,x_N)\equiv\mathbf{x}=\mathbf{n}/V$ are the concentrations, and $R_{\pm\ell}(\mathbf{x})=\lim_{V\to\infty}r_{\pm\ell}(V\mathbf{x})/V$ are the concentration-based rates of the reactions.

At finite volume V, the time evolution of probability governing the stochastic trajectory $\mathbf{n}(t)$ can be described by the chemical master equation

$$\begin{aligned}\frac{dp_V(\mathbf{n},t)}{dt} &= \sum_{\ell=1}^{M}[p_V(\mathbf{n}-\boldsymbol{\nu}_\ell,t)r_{+\ell}(\mathbf{n}-\boldsymbol{\nu}_\ell)-p_V(\mathbf{n},t)r_{-\ell}(\mathbf{n})\\ &\quad -p_V(\mathbf{n},t)r_{+\ell}(\mathbf{n})+p_V(\mathbf{n}+\boldsymbol{\nu}_\ell,t)r_{-\ell}(\mathbf{n}+\boldsymbol{\nu}_\ell)]. \quad (4)\end{aligned}$$

The chemical reaction system can be either closed or open. A closed system has no exchange of matter with its surroundings; an open system can exchange various chemical species with its surroundings, which are kept at constant concentrations. If all the "externally buffered" species are themselves at a chemical equilibrium, the situation is like a dialysis system, which ultimately reaches a chemical equilibrium both within and with its surroundings. If, however, there are at least two species that are sustained at a nonequilibrium condition, then the system eventually settles into a nonequilibrium state with stationary concentration fluctuations. This last scenario is the biochemical kinetic setup for modeling a living cell under a continuous chemostat.

Kurtz has shown in 1972 [7] that in the limit of $V\to\infty$, the mesoscopic stochastic description $\mathbf{n}(t)$ of the chemical reaction system (3) becomes the following set of deterministic rate equations for the macroscopic kinetics:

$$\frac{dx_i(t)}{dt}=\sum_{\ell=1}^{M}\nu_{\ell i}[R_{+\ell}(\mathbf{x})-R_{-\ell}(\mathbf{x})], \quad (5)$$

$1\leqslant i\leqslant N$, in which $\mathbf{x}(t)$ is the concentration (particle number per unit volume) of chemical species at time t. Kurtz's theorem paves the way for a unified mathematical theory of chemical kinetics in a rapidly stirred vessel of both small and large size.

III. MESOSCOPIC NONEQUILIBRIUM THERMODYNAMICS

On the other hand, based on the Markov jumping processes associated with Eq. (4), a mesoscopic statistical (or stochastic) thermodynamic theory has been developed in recent years in the field of nonequilibrium statistical physics. The most celebrated result from this theory is the Jarzynski-Crooks equality [8,9]. The mesoscopic theory also, for the first time, demonstrated a free energy balance equation: One can introduce a generalized, nonequilibrium free energy $F^{(\mathrm{meso})}$ for any chemical reaction system at the mesoscopic level. Then it can be mathematically shown that this $F^{(\mathrm{meso})}$ satisfies an instantaneous balance relation [10–14]:

$$\frac{dF^{(\mathrm{meso})}}{dt}=E_{\mathrm{in}}-e_p, \quad (6)$$

in which

$$F^{(\mathrm{meso})}[p_V(\mathbf{n},t)]=\sum_{\mathbf{n}}p_V(\mathbf{n},t)\ln\left(\frac{p_V(\mathbf{n},t)}{p_V^{\mathrm{ss}}(\mathbf{n})}\right), \quad (7)$$

the free energy input rate, also called housekeeping heat [15]

$$\begin{aligned}E_{\mathrm{in}}[p_V(\mathbf{n},t)] &= \sum_{\ell=1}^{M}\sum_{\mathbf{n}}[p_V(\mathbf{n},t)r_{+\ell}(\mathbf{n})-p_V(\mathbf{n}+\boldsymbol{\nu}_\ell,t)r_{-\ell}(\mathbf{n}+\boldsymbol{\nu}_\ell)]\\ &\quad\times\ln\left(\frac{p_V^{\mathrm{ss}}(\mathbf{n})r_{+\ell}(\mathbf{n})}{p_V^{\mathrm{ss}}(\mathbf{n}+\boldsymbol{\nu}_\ell)r_{-\ell}(\mathbf{n}+\boldsymbol{\nu}_\ell)}\right), \quad (8)\end{aligned}$$

and the free energy output rate, i.e., entropy production rate

$$\begin{aligned}e_p[p_V(\mathbf{n},t)] &= \sum_{\ell=1}^{M}\sum_{\mathbf{n}}[p_V(\mathbf{n},t)r_{+\ell}(\mathbf{n})-p_V(\mathbf{n}+\boldsymbol{\nu}_\ell,t)r_{-\ell}(\mathbf{n}+\boldsymbol{\nu}_\ell)]\\ &\quad\times\ln\left(\frac{p_V(\mathbf{n},t)r_{+\ell}(\mathbf{n})}{p_V(\mathbf{n}+\boldsymbol{\nu}_\ell,t)r_{-\ell}(\mathbf{n}+\boldsymbol{\nu}_\ell)}\right). \quad (9)\end{aligned}$$

$p_V^{\mathrm{ss}}(\mathbf{n})$ is the stationary distribution for $\mathbf{n}$ at volume V.

Since we only consider the isothermal case, we assume that $k_BT=1$ throughout the article. Therefore $F^{(\mathrm{meso})}$ has the dimension of energy, and E_{in} as well as e_p has the dimension of energy per unit time.

Both E_{in} and e_p are non-negative, and $dF^{(\mathrm{meso})}/dt$ is never positive. When applied to the chemomechanics of a single ATPase motor protein, the E_{in} is the amount of chemical energy input per unit time, e.g., ATP hydrolysis, and e_p is the minimal amount of heat dissipation [16]. If the motor is actually performing mechanical work against an external elastic force $f^{(\mathrm{ext})}$ and moving with velocity v, then both E_{in} and e_p contain the mechanical power $f^{(\mathrm{ext})}v$.

For a closed chemical reaction system, or an open system in contact with a single external chemical potential μ^{ext}, it can be shown that $E_{\mathrm{in}}=0$. In this case, the $F^{(\mathrm{meso})}$ is indeed the free energy of the molecular system approaching equilibrium [17,18].

So far, Eq. (6) is only established in the mesoscopic setting. So all three non-negative quantities, entropy production rate e_p, free energy input rate E_{in}, and free energy dissipation rate $-dF^{(\mathrm{meso})}/dt$ are functions of the volume parameter V.

IV. MACROSCOPIC NONEQUILIBRIUM THERMODYNAMICS

Now if we perform the limit of $V\to\infty$, Kurtz's theorem tells us that $\mathbf{x}(t)=\lim_{V\to\infty}\mathbf{n}(t)/V$ is the solution to the nonlinear rate equation (5). Furthermore, the probability theory also suggests that for a wide class of chemical reaction models, a macroscopic chemical energy function $\varphi^{\mathrm{ss}}(\mathbf{x})$ naturally emerges from the limit of $-\frac{1}{V}\log f(\mathbf{x}|V)$ when V is large, in which $f(\mathbf{x}|V)$ is the stationary probability density $f(\mathbf{x}|V)=Vp_V^{\mathrm{ss}}(V\mathbf{x})$ [19].

Since we have set $k_BT=1$, $\varphi^{\mathrm{ss}}(\mathbf{x})$ actually is also the limit of $-\frac{k_BT}{V}\log f(\mathbf{x}|V)$ which has the dimension of energy per unit volume (energy density).

Then we can approximate the probability density as

$$f(\mathbf{x}|V) \approx \frac{\Omega(\mathbf{x})e^{-V\varphi^{\mathrm{ss}}(\mathbf{x})}}{\Xi(V)}, \tag{10}$$

where

$$\Xi(V) = \int \Omega(\mathbf{x})e^{-V\varphi^{\mathrm{ss}}(\mathbf{x})}d\mathbf{x}.$$

Here $\Omega(\mathbf{x})$ is analogous to the "degeneracy" in a partition function calculation. As a part of the mathematical theory of large deviations within probability distributions, Eq. (10) and alike have been considered as the mathematical foundation of equilibrium statistical thermodynamics [20].

What is the mechanistic force corresponding to the emergent chemical energy function $\varphi^{\mathrm{ss}}(\mathbf{x})$? More specifically, how does this "force" affect the macroscopic kinetics? First, one needs to consciously recognize the vast separation of time scales in the mesoscopic and macroscopic kinetics. That is why the dynamics of the latter is partially dictated by the stationary behavior of the former, in the form of $\varphi^{\mathrm{ss}}(\mathbf{x})$. It is clear that $\varphi^{\mathrm{ss}}(\mathbf{x})$ is a consequence of a global, infinitely long time behavior of the mesoscopic system.

The emergent chemical energy function $\varphi^{\mathrm{ss}}(\mathbf{x})$ satisfies the following equation first derived by Hu in 1986 [21]:

$$\begin{aligned}\sum_{\ell=1}^{M}\{R_{+\ell}(\mathbf{x})[1 - e^{\boldsymbol{\nu}_\ell\cdot\nabla_{\mathbf{x}}\varphi^{\mathrm{ss}}(\mathbf{x})}]\\ +R_{-\ell}(\mathbf{x})[1 - e^{-\boldsymbol{\nu}_\ell\cdot\nabla_{\mathbf{x}}\varphi^{\mathrm{ss}}(\mathbf{x})}]\} = 0,\end{aligned} \tag{11}$$

where $\boldsymbol{\nu}_\ell = (\nu_{\ell 1},\ldots,\nu_{\ell N})$.

Based on the fact that $R_{\pm\ell}(\mathbf{x}) = \lim_{V\to\infty} r_{\pm\ell}(V\mathbf{x})/V$, the probability of the mesoscopic chemical kinetics $\mathbf{n}(t)$ becomes concentrating at $\mathbf{x}(t)$ at time t and $\frac{1}{V}\log p_V^{\mathrm{ss}}(V\mathbf{x}) \approx -\varphi^{\mathrm{ss}}(\mathbf{x})$ at large V, one can prove that in the "macroscopic limit," i.e., $V\to\infty$,

$$V^{-1}F^{(\mathrm{meso})} \to \varphi^{\mathrm{ss}}(\mathbf{x}), \tag{12a}$$

$$\frac{d\varphi^{\mathrm{ss}}(\mathbf{x})}{dt} = \mathrm{cmf}(\mathbf{x}) - \sigma(\mathbf{x}), \tag{12b}$$

$$V^{-1}e_p \to \sigma(\mathbf{x}) = \sum_{\ell=1}^{M}[R_{+\ell}(\mathbf{x}) - R_{-\ell}(\mathbf{x})]\ln\left(\frac{R_{+\ell}(\mathbf{x})}{R_{-\ell}(\mathbf{x})}\right), \tag{12c}$$

$$\begin{aligned}V^{-1}E_{\mathrm{in}} &\to \mathrm{cmf}(\mathbf{x})\\ &= \sum_{\ell=1}^{M}[R_{+\ell}(\mathbf{x}) - R_{-\ell}(\mathbf{x})]\ln\\ &\quad\times\left(\frac{R_{+\ell}(\mathbf{x})}{R_{-\ell}(\mathbf{x})}e^{\boldsymbol{\nu}_\ell\cdot\nabla_{\mathbf{x}}\varphi^{\mathrm{ss}}(\mathbf{x})}\right).\end{aligned} \tag{12d}$$

The macroscopic chemical thermodynamics is formulated here under "per unit volume." $\mathrm{cmf}(x)$ and $\sigma(x)$ have the dimension of energy per unit volume per unit time.

Equation (12b) is a macroscopic chemical (free) energy balance equation, in which the emergent *chemical motive force* (cmf) characterizes the force the environment puts upon the kinetic system, and entropy production rate $\sigma(\mathbf{x})$ characterizes the amount of free energy that is dissipated from the system.

Similar to the mesoscopic situation, both $\sigma(\mathbf{x})$ and $\mathrm{cmf}(\mathbf{x})$ are non-negative, while $d\varphi^{\mathrm{ss}}(\mathbf{x})/dt$ is never positive, showing that the deterministic macroscopic trajectories of Eq. (5) always go downhill of $\varphi^{\mathrm{ss}}(\mathbf{x})$.

$\sigma(\mathbf{x}) = 0$ if and only if the *strong detailed balance condition* is satisfied at $\mathbf{x}$, i.e., for each reaction ℓ, $R_{+\ell}(\mathbf{x}) = R_{-\ell}(\mathbf{x})$. This is the thermodynamic equilibrium state.

$\mathrm{cmf}(\mathbf{x}) = 0$ if and only if the *weak detailed balance condition* is satisfied at $\mathbf{x}$ based on (11) and the inequality $\log x \leqslant x - 1$, i.e.,

$$\ln\left(\frac{R_{+\ell}(\mathbf{x})}{R_{-\ell}(\mathbf{x})}\right) = -\boldsymbol{\nu}_\ell\cdot\nabla_{\mathbf{x}}\varphi^{\mathrm{eq}}_{\mathbf{x}}(\mathbf{x}), \qquad \forall\ell. \tag{13}$$

Equation (13) formalizes the fundamental insights of Lewis on the importance of detailed balance in chemical kinetics [22]. In this case there is *a chemical equilibrium between the local kinetics and its environment that is created by the other reactions in the same kinetic system.*

The validity of the weak detailed balance condition for any $\mathbf{x}$ and ℓ is equivalent to the well-known Wegscheider-Lewis cycle condition [4,22–24]. In this case, any stable fixed point of Eq. (5), i.e., local minimum of $\varphi^{\mathrm{ss}}(\mathbf{x})$, satisfies the strong detailed balance condition, which is at thermodynamic equilibrium. Hence once the open, driven kinetic system eventually settles into a nonequilibrium steady state $\mathbf{x}^{\mathrm{ss}}$ (or some more complex behaviors like oscillations), Eq. (13) should not always hold for any $\mathbf{x}$, which is equivalent to say that $\mathrm{cmf} \neq 0$. At any nonequilibrium steady state $\mathbf{x}^{\mathrm{ss}}$, $\mathrm{cmf}(\mathbf{x}^{\mathrm{ss}}) = \sigma(\mathbf{x}^{\mathrm{ss}}) > 0$.

The macroscopic chemical energy function $\varphi^{\mathrm{ss}}(\mathbf{x})$ can further give rise to a general fluctuation-dissipation theorem for the chemical reaction models discussed here. Denote $\mathbf{q}$ as a stable fixed point of Eq. (5), and define three matrices Ξ, A, and B, in which $\Xi_{ij} = \frac{\partial^2\varphi^{\mathrm{ss}}(\mathbf{q})}{\partial\mathbf{x}_i\partial\mathbf{x}_j}$, $A_{ij} = \sum_{\ell=1}^{M}[R_{+\ell}(\mathbf{q}) + R_{-\ell}(\mathbf{q})]\nu_{\ell i}\nu_{\ell j}$, and $B_{ij} = \frac{\partial F_i(\mathbf{q})}{\partial\mathbf{x}_j}$ where $F_i(\mathbf{q})$ is the right-hand side of Eq. (5) at $\mathbf{x} = \mathbf{q}$. Just taking the second derivative to both sides of Eq. (11), we can have the equality

$$\Xi A\Xi = -\Xi B - B\Xi. \tag{14}$$

If Ξ is invertible, then $A = -B\Xi^{-1} - \Xi^{-1}B$.

It is a more rigorous and general version of the fluctuation-dissipation theorem discovered by Keizer in the 1980s [25]. Keizer's original approach is based on the local diffusion approximation, which does not explicitly contain $\varphi^{\mathrm{ss}}(\mathbf{x})$. Also note that the diffusion approximation breaks all the conservation relations of the chemical reaction system (3), while the stochastic chemical reaction model (4) from which the $\varphi^{\mathrm{ss}}(\mathbf{x})$ emerges keeps all of them.

The emergence of $\varphi^{\mathrm{ss}}(\mathbf{x})$ given in Eq. (11) is highly abstract. One example of this, thanks to the recent work of Anderson *et al.* [26], is when the kinetic system is complex balanced, a notion introduced by Horn and Jackson in 1972 [27]. This is a class of models with the law of mass action, which contains detailed balance, all unimolecular reaction networks, as well as many open, driven, nonlinear chemical systems [28]. In this case, it can be shown that the kinetics equation (5) has a unique steady state $\mathbf{x}^{\text{ss}}$ and

$$\varphi^{\text{ss}}(\mathbf{x}) = \sum_{i=1}^{N} x_i \ln\left(\frac{x_i}{x_i^{\text{ss}}}\right) - x_i + x_i^{\text{ss}}, \tag{15}$$

which is a solution to (11), and has actually the same expression as the free energy function $G(\mathbf{x})$ per unit volume (notice that we have set $k_B T = 1$). For complex balanced systems under weak detailed balance condition, Eq. (12b) becomes $dG/dt = -\sigma(\mathbf{x}) \leqslant 0$; and $\boldsymbol{\nu}_\ell \cdot \nabla_{\mathbf{x}} G(\mathbf{x}) = \Delta\mu_\ell(\mathbf{x}) = k_B T \ln[R_{-\ell}(\mathbf{x})/R_{+\ell}(\mathbf{x})]$, in which $\Delta\mu_\ell(\mathbf{x})$ is the free energy difference of the ℓth reaction.

We note that Eq. (15) is a generic, universal expression of the chemical energy $\varphi^{\text{ss}}(\mathbf{x})$, for this large class of complex balanced chemical kinetics, linear and nonlinear, closed and open, equilibrium and nonequilibrium [26]. This illustrates the important idea that macroscopic emergent behavior, such as thermodynamics, should be independent of the underlying details of the kinetics.

In practice, for chemical reaction systems without detailed balance, one can numerically obtain the macroscopic chemical free energy $\varphi^{\text{ss}}(\mathbf{x})$ through the geometric minimum action method [29–31].

V. SUMMARY AND CONCLUSION

In summary, macroscopic chemical thermodynamics, equilibrium or nonequilibrium, can have a rigorous mesoscopic, statistical, reaction kinetic foundation. Macroscopic chemical free energy $\varphi^{\text{ss}}(\mathbf{x})$ per unit volume, which is a generalization of equilibrium free energy, is an emergent quantity in the macroscopic limit. It actually has a free energy balance equation which is different from Newtonian mechanical energy conservation as well as Helmholtz-Boltzmann's derivation of the first law of thermodynamics based on their mechanical theory of heat. This balance equation is actually a form of the entropy balance equation that is pertinent to the second law of thermodynamics of open systems [32]. This free energy balance equation is applicable to closed and driven chemical reaction kinetic systems under isothermal conditions. This chemical theory of reaction kinetics also provides a concrete example for Anderson's structure of scientific laws [33,34]: Macroscopic laws are emergent behaviors from the dynamics of a level below; to a large extent, such laws are insensitive to the details of the dynamics.

Finally, it has not escaped our notice that the mathematical theory presented in this work might suggest possible mechanisms for the entropic theory of gravity and the laws of Newton [35].

ACKNOWLEDGMENTS

H.Q. thanks Professor Miao Li for discussion. This work was supported by National Natural Science Foundation of China under Grants No. 21373021 and No. 11622101 and the 863 program under Grant No. 2015AA020406 to H.G.

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