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# FRACTIONAL COOPERATIVITY
# OF A FEW-STATE SYSTEM IN THE ENVIRONMENT

*Cooperativity represents a type of the not well-defined quantities implemented in different fields ranging from physics to chemistry, biology, informatics, etc. In the present work, we define the cooperativity from the physical point of view by relating it to the stability of a few-state system with respect to the irreversibility. First, we reduce this system evolving in time to the pair of fluctuating energy levels of different dimensionalities with the initial population of one level, different probabilities of microscopically reversible transitions between the levels, and some probability of irreversible decay of another level. Then we make an average of the reduced system over the energy level fluctuations to provide between-level transition rates with the explicit impacts of external controls on levels' positions and dimensionalities. Finally, we demonstrate the emergence of the cooperativity of a fractional degree ranging between 2/e and unity when normalized in this system and observe that, at the lower bound of such degree, the system becomes unstable, so that, to restore the stability, one needs either to decrease the irreversible decay rate or to make the reversible backward transitions faster.*

*K e y w o r d s: irreversible kinetic processes, energy fluctuations, dissipating environment, cooperativity, Hill's coefficient, ligand-receptor assembly.*

## 1. Introduction

There is no single definition of cooperativity which can equally be applicable to all situations in natural, life, social, economic, and information sciences. Historically, the concept of cooperativity has been introduced as far as the Enlightenment, perhaps when human beings of different ownerships were managed to organize themselves in collectives for a mutual benefit [1]. At these times, people could roughly be differentiated by those who strongly interact with one another to form the collectives of cooperatively coupled persons and others which contact each other much weaker to remain the uncoupled individuals. For the former, it was quite likely to think of cooperativity as of a synonymous of collectivity, by simply relating the emergent collective property with the number of persons present at the cooperative workplace [2], thus regarding that the bigger the collective, the greater would be its benefit.

Later on, it became obvious that too much cooperativity is not always better for collective's stability [3]. Indeed, any multistate many-particle system, to be well-controlled with respect to the

environment-induced exchange of energy and particles, would likely be much stable than more cooperative ones. Therefore, in treating the cooperativity, the use of additive (extensive) parameters like the number of states or particles and the form or size of the modular configurations within the system might be insufficient. Instead, to be certain in frameworking the cooperativity, one should rather employ the ensemble-averaged (intensive) properties of the system like its stability and flexibility.

Far later on, with advances in the investigation of biological [4–6], physical [7–9], and chemical [10–13] systems at the molecular level, different measures describing the cooperative properties of molecular structures in equilibrium have been proposed. These measures were mostly reduced to the degree, to which fitting system's saturated responses to external stimuli by a sigmoidal curve deviates from the two-state Boltzmann distribution [4–6, 10–13]. Three types of such a degree have been especially noticed: the Hill coefficient describing the binding of ligands to multisite proteins [14]; the elasticity coefficient relating to the response of target state variables of a system to a change in its control variables [15–17]; and the strength of intermolecular bond interactions,

to the either structurally promoted, by a stabilization, or structurally constrained, by a concerted reaction, high level of target state population with respect to the population of initial and intermediate states [18–25] (cf. also [26, 27]). It was established that, for a one-ligand few-state system, there exists a sigmoidal Boltzmann distribution of the equilibrium target state population, which is approximated by the normalized rational function of degree 1 [6, 11]. In this case, the degree of cooperativity defined with respect to the control parameter involved in the integral power series in the distribution denominator (via equilibrium constants) is identified as the maximum power of a series greater than or equal to one and less than the number of states minus one [22, 23]. However, in the more general case of a multistate many-ligand system, similarly assessing the degree of cooperativity becomes inappropriate since the shape of the distribution function greatly deviates from that of a sigmoidal type [16]. Rather, for the simplest two-state system, there was a common consensus that the cooperativity degree equals one and only one irrespective of to which control parameter it would be defined [26]. This coincides with the idea that the states of an equilibrium two-level system reveal themselves as statistically independent ones so showing no correlations (or cooperativity) beyond ones imposed by the Boltzmann statistics [28]. So the main corollary is that, if being in equilibrium, any two-state system should be regarded stable, noncooperative, and characterized by the cooperativity of a conventional degree 1 [23, 25].

However, most real molecular systems are not static in time and space. Rather, depending on external controls, they constantly evolve from the nonequilibrium to equilibrium states, by undergoing the irreversible relaxation transitions between different energy levels. These transitions occur due to the nonadiabatic coupling of a system with the environment, leading to the transient changes of level's populations with time. As a result even in the two-state case, such non-stationary nonequilibrium systems, when being unstable, could demonstrate the cooperativity of a fractional degree. Therefore, to describe the kinetics of these systems, one should revisit some of the prescripts from equilibrium statistical mechanics [28], particularly in application to the case of irreversibly damped nonequilibrium systems which have a few microscopically fluctuating quantum energy levels [29].

If we deal with the thermodynamically closed system (CS) consisted of $M + 1$ levels with energies $E_m$, $m = 0, 1, 2, ..., M$, then, to describe the ensemble-averaged equilibrium level population $P_m^\infty$ in cooperative dependence on the energy (enthalpy) changes, it is sufficient to use $M$ state variables, say the between-state energy differences $\Delta E_{mm'} = E_m - E_{m'}$ counted from the lower level bound often let equal zero: $E_{m'=0} = 0$. Since, in the CS, every microscopic action is reversible, these quantities form the oscillatory dynamics of non-averaged populations with the enthalpically driven frequencies $\Omega_{mm'} = \Delta E_{mm'}/\hbar$, whose controllable variation, however, does not lead to system's cooperativity ($\hbar$ is the Planck constant). Rather, to describe transient kinetics of the non-oscillatory behaviors of populations, one should use a concept of open system (OS) [30, 31], which allows the non-stationary irreversible transitions to occur on the quantum-level scale [32]. In this concept, the OS is considered as a few-level nonequilibrium part of an infinite-level CS that treats its rest part as the equilibrium environment (EE). Therefore, to analyze the time-dependent dynamics of the nonequilibrium level population $P_m(t)$, one needs to expand the set of state variables to $2M$ independent parameters, say, the probabilities $W_{mm'}$ of leading-order transitions from a level $m$ to the neighboring level $m' \neq m$ constrained by the condition of detailed balance (a principle of microscopic reversibility) [33, 34]. These relaxation transitions are caused by perturbations of the OS on the specific transient time scale $\tau_{\mathrm{tr}}^{(W)} = \{W_{mm'}^{-1}\}$ formed due to the relaxation interaction between the OS and the EE.

However, for the so-defined OS, the number of energy levels does not conserve. For example, this is the case if the OS being in contact to the EE exchanges with it as energy as well particles, whose concentration is controlled, or, if the OS is decomposed into parts, due to the energy level fluctuations [35]. Hence, it is necessary to regard such number as an entropically driven parameter related to the effective level dimensionality. Furthermore, that number can even be uncertain when, along with the microscopically reversible forward-backward transitions between the levels, their depopulation kinetics in the OS comprises also the macroscopically irreversible decays [36, 37]. In effect, the latter specifies the loss of stability of microscopic states, which directly points, relating to the problem of irreversibility in quantum

mechanics [38], to the possibility of violation of the lower (zero) boundedness of the state energy spectrum just for a few-level OS [39].

In the aforementioned cases, one problem is to exactly solve the set of $M + 1$ ordinary differential equations for non-conserved level populations $P_m(t)$, given initial conditions. To simplify this commonly hard problem, one usually does not try to analytically find or numerically calculate the overall kinetics in every microscopic detail. Instead, one intends to understand how the levels of potentially large (variable or uncertain) number $M + 1$ are correlated (or cooperated) in their reversible dynamics and irreversible kinetics so that to be adequately described within an effective few-level system. Moreover, how has one to control the degree of correlations between (or cooperativity of) these few levels such that to be consistent in associating the transient population peaks with the thermodynamic quasiaverages like levels' dimensionalities and particles' concentration? Note that this directly corresponds to a reduced description of the OS originally formulated by Bogolyubov as the principle of weakening of correlations in the initial value problem for the non-ergodic multilevel systems and, equivalently, as a procedure of contraction of the number of system's independent variables in the boundary condition problem in a distant past, both basing on the idea of a hierarchy of relaxation times [40, 41].

Another problem is to define the highly contracted energy spectrum of the OS when to perform a coarse-graining of the CS consisting of macroscopically many states. To provide this correctly, there is the Nakajima–Zwanzig method, which allows one to observe an evolution of the CS through its projection on state variables of a few-level OS only [42, 43]. However, this method has a price such that the eigenenergy levels found for the so-reduced OS cannot be represented deterministically at every time instant but rather only functionally with the random and unresolved dynamics [44, 45]. In these situations, one substitutes the latter for the well-known stochastic processes, e.g. a Gaussian white noise or dichotomous colored noises. This allows one to take on the procedures of stochastic averaging of the functionals introduced to be analytically unapproximated [46–51], particularly by using the stationary Lorentzian distribution for the stochastic realizations of fluctuating energy levels in the OS and the equilibrium Boltz-

mann distribution for the occupation numbers of harmonic vibrations in the EE [52].

In the present paper, the above-presented coarse-graining methodology contained, in part, in our recent work [51] is applied here to show the role of energy level fluctuations for quantifying the degree of cooperativity of a few-state irreversible OS and defining the possible ways of its control. Especially, we aim at modeling the cooperative behavior of the nonequilibrium OS in the equilibrium while noisy EE. We restrict ourselves to the case where the noise adds to the eigenenergies of the stochastic Hamiltonian of the OS rather the Hamiltonian of the EE is time-independent. In Section 2, we outline the microscopic model of evolution of the OS in detail. We make accent on the adiabatic and nonadiabatic interactions of the OS and the EE in the weak coupling limit as well as provide an averaging of the stochastic master equation with properly balanced probabilities of transitions between the states. In Section 3, we calculate these transition probabilities by reducing the OS to the simplest case of two irreversibly decaying and randomly fluctuating energy levels of different dimensionalities, provide the output level population with the dependence on the input, backward, and output rates, determine the degree of cooperativity of this OS, and establish the bounds of variation of that degree. Finally, in Section 4, we analyze the results obtained, discuss some consequences, and sum up with the conclusion.

## 2. Microscopic Model of a Multilevel System in Contact to the Environment

Consider the closed system which can be decomposed into two weakly interacting parts such as the nonequilibrium open system and the equilibrium environment. Suppose that there exists some perturbation technique to introduce a microscopic model of the CS on a countable state space, which renormalizes the OS state basis ($|m = = 0, 1, 2, ..., M\rangle$) such that to eliminate all direct (resonant) couplings of states from explicit consideration. In second-order perturbation theory on the rest indirect (relaxation) interactions between states, this allows us to represent the Hamiltonian $H_{\mathrm{CS}}(t)$ of the CS in the form

$$H_{\mathrm{CS}}(t) = H_{\mathrm{OS}}(t) + V + H_{\mathrm{EE}}. \qquad (1)$$

Here,

$$H_{\text{OS}}(t) = \sum_m E_m(t)|m\rangle\langle m| \qquad (2)$$

is the time-dependent stochastic Hamiltonian of the OS in the adiabatic approximation with the eigenenergy levels $E_m(t) = E_m + \epsilon_m(t)$, where $E_m$ and $\epsilon_m$ are the mean and stochastic level positions at the time $t$, respectively,

$$H_{\text{EE}} = \sum_\lambda \hbar\omega_\lambda(b_\lambda^\dagger b_\lambda + 1/2) \qquad (3)$$

is the time-independent Hamiltonian of the EE modeled as a set of equilibrated harmonic oscillators playing a role of the infinite state thermal bath for the OS with $b_\lambda^\dagger$ and $b_\lambda$ being the operators of creation and annihilation, respectively, of a normal vibration (phonon) of the mode $\lambda$ with frequency $\omega_\lambda$ in the EE,

$$V = \sum_{mm'}(\delta_{mm'} - 1)\sum_\lambda \chi_{mm'}^\lambda(b_\lambda^\dagger - b_\lambda)|m\rangle\langle m'| \qquad (4)$$

is the operator of bilinear nonadiabatic coupling of the OS to the EE with the parameters $\chi_{mm'}^\lambda$ provided the energy balance holds within the total CS at every instant.

Given the representation of Hamiltonians (1)–(4), the next step is to suppose a hierarchy of fundamental time scales for the dynamics of the density matrix $\rho_{\text{CS}}(t)$ of the CS due to the Liouville–Neumann quantum evolution equation

$$\dot{\rho}_{\text{CS}}(t) = -\frac{i}{\hbar}[H_{\text{CS}}(t), \rho_{\text{CS}}(t)]. \qquad (5)$$

Let this hierarchy be as follows:

$$\tau_{\text{ch}} \ll \tau_{\text{st}} \ll \tau_{\text{tr}}. \qquad (6)$$

Here, on the short time scale $\Delta t \leq \tau_{\text{ch}}$ for the chaotic phase of the dynamics, the state basis of two parts of the CS is completely formed. This factorizes $\rho_{\text{CS}}(t)$ by the nonequilibrium density matrix $\rho_{\text{OS}}(t)$ of the OS and the equilibrium density matrix $\rho_{\text{EE}}$ of the EE like

$$\rho_{\text{CS}}(t) = \rho_{\text{OS}}(t)\rho_{\text{EE}}, \qquad (7)$$

where $\rho_{\text{EE}} = \exp\{-H_{\text{EE}}/k_{\text{B}}T\}/\text{Tr}_{\text{E}}\exp\{-H_{\text{EE}}/k_{\text{B}}T\}$ with $T$ and $k_{\text{B}}$ being the absolute temperature and Boltzmann's constant, respectively. Moreover, at

the times $t \geq \tau_{\text{ch}}$, applying the diagonal Nakajima–Zwanzig projection operator $T_d$ according to the rule $\rho_{\text{OS}}^{(d)}(t) = T_d\rho_{\text{OS}}(t)$ for the diagonalization of the density matrix of the OS transforms the Liouville–Neumann equation (5) to its diagonal form

$$\dot{\rho}_{\text{OS}}^{(d)}(t) = -\frac{1}{\hbar^2}\int_0^t d\tau T_d[V, U(\tau)[V, \rho_{\text{OS}}^{(d)}(t-\tau)]U^\dagger(\tau)], \qquad (8)$$

where $U(\tau) = \hat{D}\exp\{-\frac{i}{\hbar}\int_0^\tau dt'[H_{\text{OS}}(t') + H_{\text{EE}}]\}$ is the stochastic operator of evolution ($\hat{D}$ is Dyson's operator of chronological ordering). So, Eq. (8) decoheres the dynamics of the OS, by making impossible for the off-diagonal elements $\rho_{\text{OS}}^{(nd)}(t)$ of $\rho_{\text{OS}}(t)$ to oscillate with the defined phase in unison to possibly produce the interference effects. Meanwhile, on the long-time scale $\Delta t \geq \tau_{\text{tr}}$, the evolution of $\rho_{\text{OS}}(t)$ becomes averaged with respect to the random trajectories, assigning the slowest time $\tau_{\text{tr}} \gg \tau_{\text{st}}$ of occurring the nonadiabatic relaxation transitions between the different yet already steady-state levels of the OS. Rather, on the stationary time scale $\Delta t \approx \tau_{\text{st}}$, there occur any relaxation transitions between the OS states, as well as there are no corresponding processes of phonons' creation and annihilation in the EE. Nevertheless, there exists essentially the adiabatic stochastic dynamics of the energy levels of the OS. This requires to provide the averaging over random realizations of trajectories of $\rho_{\text{OS}}(t)$ for the stochastic energy shifts at the level of the evolution equation (8) (usually designated as $\langle\langle...\rangle\rangle$), in particular, for finding the averaged populations of states $P_m(t) = \langle\langle p_m(t)\rangle\rangle$, where $p_m(t) = \langle m|\rho_{\text{OS}}^{(d)}(t)|m\rangle$ are the non-averaged populations, as well as the averaged probabilities $W_{mm'}$ of transitions between states.

Averaging Eq. (8) with the use of (1)–(4) gives

$$\dot{P}_m(t) = -\frac{2}{\hbar^2}\text{Re}\sum_{m'}\int_0^t d\tau\langle\langle Q_{mm'}(\tau)p_m(t-\tau) - Q_{m'm}(\tau)p_{m'}(t-\tau)\rangle\rangle. \qquad (9)$$

Here, $Q_{mm'}(\tau) = \sum_\lambda |\chi_{mm'}^\lambda|^2 f_{mm'}(\tau)R_\lambda(\tau)e^{i\Omega_{mm'}\tau}$ are the time-dependent transition coefficients, $\Omega_{mm'} = (E_m - E_{m'})/\hbar$, $f_{mm'}(\tau) = \exp[i\int_0^\tau \omega_{mm'}(t') \times dt']$ are stochastic functionals of the random frequency shifts $\omega_{mm'}(t) \equiv [\epsilon_m(t) - \epsilon_{m'}(t)]/\hbar$, $R_\lambda(\tau) =$

$= n(\omega_\lambda)e^{i\omega_\lambda\tau} + [1 + n(\omega_\lambda)]e^{-i\omega_\lambda\tau}$ is the one-phonon correlation function, and $n(\omega_\lambda) = [e^{\hbar\omega_\lambda/k_{\rm B}T} - 1]^{-1}$ is the Bose distribution function for vibrations.

In Eq. (9), the main difficulty is to treat a non-Markovianity of integrands and to average the stochastic functionals $\langle\langle Q_{mm'}(\tau)p_m(t-\tau)\rangle\rangle$ in the explicit form. However, if the random energy level fluctuations in the OS are stationary, then, on the transition time scale $\tau_{\rm st} \ll \Delta t \le \tau_{\rm tr}$, averaging the right-hand side of (9) can be factorized provided that $\langle\langle f_{mm'}(\tau)p_m(t-\tau)\rangle\rangle = F(\tau)P_m(t)$. To do so, we must take into account that, in the second-order perturbation theory, the non-Markovianity of population of states does not reveal $P_m(t-\tau) \approx P_m(t)$. In addition, we introduce a stochastically averaged characteristic functional in the form

$$F_{mm'}(\tau) = \langle\langle f_{mm'}(\tau)\rangle\rangle = \langle\langle e^{i\int_0^\tau \omega_{mm'}(t)dt}\rangle\rangle. \qquad (10)$$

The latter can easily be calculated for many stochastic processes, e.g., for the di- and trichotomous ones or Gaussian white noise [46–51]. In such cases, one reduces (10) to the simple exponential form

$$F_{mm'}(\tau) = e^{-\gamma_{mm'}\tau} \qquad (11)$$

with $\gamma_{mm'}$ meaning the effective half-width of the $m, m'$-pair of levels. Such a quantity is also associated with the friction coefficient for the movement of particles within the OS, which has to be linearly proportional, in direct accordance with the Stokes law, to the viscosity of the EE. Physically, the values of $\gamma_{mm'}\tau_{\rm ch}$ are referred to as the squares of the reduced amplitudes of energy level fluctuations of the OS being introduced in the Hamiltonian $H_{\rm OS}(t)$ as it ad hoc adiabatic stochastic additions to its eigenenergies (2). Therefore, the inverse root of these in fact forms the range for a stochastic time scale $\Delta t \approx \tau_{\rm st} = \{\gamma_{mm'}\tau_{\rm ch}\}^{-1/2}$ within the assumed hierarchy of time scales (6).

Using (10) and (11) reduces the integral differential equation (9) to the master equation

$$\dot{P}_m(t) = -P_m(t)\sum_{m'} W_{mm'}(t) + \sum_{m'} P_{m'}(t)W_{m'm}(t), \qquad (12)$$

where the normalized populations $\sum_m P_m = 1$ are supposed Markovian on the longer (transition) time scale, but can retain the memory about their initial values via the time-dependent transition probabilities

$$W_{mm'}(t) = \frac{2}{\hbar^2}{\rm Re}\int_0^t d\tau e^{(i\Omega_{mm'} - \gamma_{mm'})\tau} \times$$

$$\times \sum_\lambda |\chi_{mm'}^\lambda|^2\{n(\omega_\lambda)e^{i\omega_\lambda\tau} + [1 + n(\omega_\lambda)]e^{-i\omega_\lambda\tau}\} \quad (13)$$

on the shorter (stochastic) time scale. This type of generalization of the master equation is just typical in using the Golden Rule approaches for the phenomenological or microscopic description of nonadiabatic nonequilibrium processes in the condensed phase systems [53, 54]. It appears here as a result of the stochastic averaging over random fluctuations of the energy levels of the OS and necessitates the accounting for cooperative effects in a wide range of transition probabilities including the very small ones, where the non-Markovianness of the OS is particularly apparent. Importantly, the assumed hierarchy of fundamental time scales (6) in the OS does not explicitly enter the master equation (12), but is especially necessary for its strict derivation so being represented in it in the form (13) most convenient for the sequel. Moreover, information about the time scales is neither lost nor filtered out, but rather is correctly taken into account by the corresponding averages: equilibrium occupation phonon numbers $n(\omega_\lambda)$ formed at chaotic times in the EE, intensities $\gamma_{mm'}$ of stationary adiabatic energy level fluctuations established at stochastic times in the OS, and parameters $2\hbar^{-2}|\chi_{mm'}^\lambda|^2|\Omega_{mm'}|^{-1}$ of nonadiabatic coupling between the OS and the EE responsible for occurring the relaxation processes at transition times, respectively.

## 3. Fractional Cooperativity of a Reduced Two-Level Irreversible System

In the previous section, starting from the microscopic model for the Hamiltonians of a set of adiabatically fluctuating energy levels of the nonequilibrium open system and their weak nonadiabatic coupling to the equilibrium environment (2)–(4), we get the probability of relaxation transitions between these levels (13) averaged over both the equilibrium vibrations in the EE and the stationary fluctuations in the OS. By its form, the expression for the transition probability (13) appears as some kind of the Fermi Golden

Rule where, however, the main attention is paid not to summing over a proper dense set of energy levels of the final state of the OS, but rather to providing a correct averaging on stochastic trajectories for transitions with their different contributions according to a Cauchy distribution [52]. Moreover, the transition probability (13) includes stochastic additions to the fluctuating energy levels in a nonperturbation manner [49–51]. This allows us to analyze the different regimes for transition processes in the OS in dependence on the stochastic $\{\gamma_{mm'}\}$ and natural $\{|\Omega_{mm'}|\}$ frequencies that can potentially vary in wide limits. However, there are two problems in practically calculating the otherwise strict expression (13). First, the order of taking on the calculation of (13) is of crucial importance: at first, to take a sum over the infinite number $\Lambda \to \infty$ of phonon modes $\lambda = 1, 2, ..., \Lambda$, which generally diverges, and only then to integrate over the time $\tau$ in the interval from 0 to $t$. Therefore, to sufficiently change the orders of summing and integrating and further to provide these operations most accurately necessitate to make additional assumptions about a specific relation between the parameters $\{\gamma_{mm'}\}$ and $\{|\Omega_{mm'}|\}$, as well as the possible dependence of the couplings $|\chi_{mm'}^{\lambda}|^2$ on $\lambda$. Second, the transition probability (13) assumes that to cover the difference between energy levels involved in relaxation of the OS is mainly the process of creation or annihilation in the EE of only a one phonon, while the role of multiphonon processes is minor. However, this assumption is not very critical for describing the transition processes caused by the weak coupling of states of the OS to the vibrations in the EE and can safely be relaxed in the Born approximation over the nonadiabatic operator (4) used above (cf., e.g., [53–55]).

Exceptionally interested in that how to give a simple but adequate description of the degree of cooperativity of the OS, we restrict ourselves to only the calculable cases for the time-dependent transition probability (13). These are basically the two: nonadiabatic transitions with $|\Omega_{mm'}| \gg \gamma_{mm'} \to +0$ and adiabatic transitions with $\gamma_{mm'} \gg |\Omega_{mm'}| \to +0$. In both cases, the upper limit of the integral on the right-hand side of (13) can be turned to infinity $t \to \infty$, which is equivalent to neglecting the time-dependence of (13) within the hierarchy of time scales (6). Furthermore, since $\hbar\gamma_{mm'} \approx k_\mathrm{B}T$ [49, 50], as usual, those correspond to the quantum $\hbar|\Omega_{mm'}| \gg$

$\gg k_\mathrm{B}T$ and classical $\hbar|\Omega_{mm'}| \ll k_\mathrm{B}T$ limits, respectively. Consequently, in these cases, introducing the rate limit factors

$$\Phi_{mm'} = \Phi_{m'm} =$$

$$= \begin{cases} (2\pi/\hbar^2) \sum_\lambda |\chi_{mm'}^\lambda|^2 \delta(|\Omega_{mm'}| - \omega_\lambda), \\ |\Omega_{mm'}| = \omega_\lambda \gg k_\mathrm{B}T/\hbar, \\ (2\pi/\hbar^2) \sum_\lambda (|\chi_{mm'}^\lambda|^2/\omega_\lambda), \\ |\Omega_{mm'}| \le \omega_\lambda \ll k_\mathrm{B}T/\hbar \end{cases} \quad (14)$$

leads to the following reduced expressions for relaxation transition probabilities:

$$W_{mm'} =$$

$$= \begin{cases} \Phi_{mm'}[\theta(\Omega_{mm'}) + e^{-\hbar|\Omega_{mm'}|/k_\mathrm{B}T}\theta(\Omega_{m'm})], \\ |\Omega_{mm'}| = \omega_\lambda \gg k_\mathrm{B}T/\hbar, \\ \Phi_{mm'}, \quad |\Omega_{mm'}| \le \omega_\lambda \ll k_\mathrm{B}T/\hbar \end{cases} \quad (15)$$

with $\theta(x)$ being the Heaviside step function, which is 0 for $x < 0$ and 1 for $x \ge 0$. So, if quantifying the degree of cooperativity of the few-level OS most simplistically but correctly, we can classify the probabilities of transitions between the fluctuating energy levels by the two likely types: mechanistic type of activationless temperature-independent transitions and Arrhenius's type of activation-like exponentially temperature dependent transitions. In (15), these correspond to the case $W_{mm'} = \Phi_{mm'}$ of either classical $\hbar|\Omega_{mm'}| \to 0$ (the lower line) or highly exoergic quantum $\hbar\Omega_{mm'} \gg k_\mathrm{B}T > 0$ (the first term in the upper line) limits and to the case $W_{mm'} = \Phi_{mm'} e^{-\hbar\Omega_{m'm}/k_\mathrm{B}T}$ of the highly endoergic quantum limit $\hbar\Omega_{m'm} \gg k_\mathrm{B}T > 0$ (the second term in the upper line), respectively.

To illustrate how such a clear else rigorous result of calculation of the probability of transitions (15) can affect the emergence of the cooperativity within the OS, let us constrain ourselves to considering that elementary model for its energy levels, in which this is only possible. Being specific (cf. [51]), let the energy levels of the OS be distinguished according to the contact positions of a particle of the one sort, referred to as a ligand (L), with respect to both the particles of the other sort in the bulk and the binding center of a molecule referred to as a receptor (R). To model the R, let us restrict it to have only two contacts with the L corresponding to either the metastable L-R bound state $|1\rangle$ with the energy

level of $E_1$ or the stable L-R bound state $|0\rangle$ with the energy level of $E_0$. The latter state is assumed to be the most long-lived one in the OS of modeling, for instance, the ground state of the R or the state, where the integrity of the L as individual particle is broken down due to irreversible mechanisms so that the energy spectrum of the OS becomes formally unbounded from the below with $E_1 - E_0 \to \infty$. On the other hand, concerning the particles in the bulk, the number of their contacts with the L can be macroscopically large. Moreover, the energies $E_{2,3,...,M}$ of these contacts can be considered equal to one another forming the quasiisoenergetic levels. In this case, one should distinguish between the number $Z$ of partitions among contacts of the L with a particular particle and the number $N = 1/C$ of independent particles per one L of concentration $C$ in the bulk. Hence, for the number of states $\{|m = 1, 2, ..., M\rangle\}$, one obtains $M = 1 + ZN \equiv 1 + Z/C$, where the dimensionless concentration $C$ of the L, if being small $C \ll 1$, serves as a running control parameter that can vary in wide limits, when we define the degree of cooperativity in the OS.

To reduce the generally large number $M$ of states of the OS, we combine the degenerate contacts in the bulk into the one level of energy $E_2$ and dimensionality $ZN$ and then count only the two remaining energy levels supposing them largely extended from one another with respect to the thermal energy $E_2 - E_1 \gg \gg k_B T$. It is common to use the ergodic approximation to model the *a priori* unknown probabilities of transitions between the bulk states. In this case, one may regard every state in the bulk to be connected to every other state such that to approximate all probabilities of transitions between these states with one the same rate constant $W \equiv W_{\mu\mu'}(\mu \neq \neq \mu' = 2, 3, ..., M)$ to be the most rapid one in the OS to remove from consideration. Substituting the assumptions made into the master equation (12) coarse-grains it to the system of two ordinary differential equations for nonconserved populations

$$\dot{P}_2(t) = -aP_2 + bP_1;$$
$$\dot{P}_1(t) = aP_2 - (b+k)P_1 \tag{16}$$

equipped with effective transition probability rates $(\Phi \equiv \Phi_{12})$:

$$a = W_{21}/ZN = C\Phi/Z \equiv \Phi/d;$$
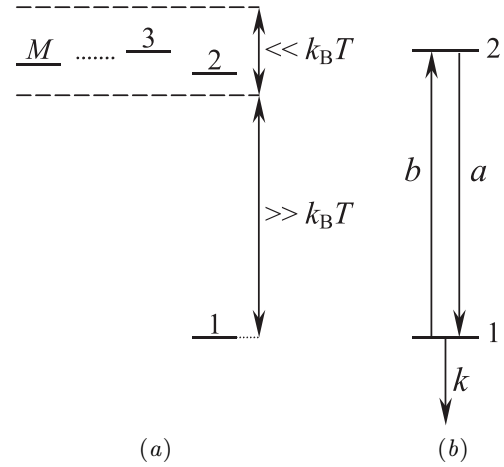$$b = W_{12} \equiv \Phi e^{\hbar\Omega_{12}/k_B T}; \quad k = W_{10} \gg W_{01} \to 0. \tag{17}$$

**Fig. 1.** A diagram of $M$ energy levels (numbers) distinctly distant each other (in thermal energy units) (*a*) and its coarse-grained reduction by a two-level scheme with effective rate constants $a$, $b$, and $k$ (*b*)

The coarse-grained reduction provided by (15)–(17) is depicted in Fig. 1 with mapping the $M$-state scheme in Fig. 1, *a* into the two-state effective scheme in Fig. 1, *b*. The latter represents an age-old paradigmatic case of the Michaelis-Menten reaction scheme of the mass-action enzyme kinetics (see, e.g., [56] and references therein). In more physical terms, it appears as a tetrad evolving in time, that is: a pair of well-separated energy levels $E_2 - E_1 \equiv \Delta E \gg \gg k_B T$ of relative dimensionality $d = ZN$, two probabilities of relaxation transitions between the levels related by a principle of microscopic reversibility $W_{21} = W_{12} e^{\Delta E/k_B T}$, and the probability $k$ of the irreversible decay of one of the levels. In fact, using a coarse-grained reduction implies that to possibly describe the degree of cooperativity could emerge in the two-level OS is the quadruple $\{\Omega, a, b, k\}$ measured in inverse time units, where each of four positive parameters – an oscillation frequency $\Omega \equiv |\Omega_{12}| = \Delta E/\hbar$, an input rate $a$, a backward rate $b$, and an output rate $k$ – independently varies in a semiinfinite interval $[0, \infty)$ serving either the running or tuned control parameter. Note that coarse-graining (16) is correct only subsequent to time $\tau_W = W^{-1}$, at which mixing the transitions between bulk degenerate levels is complete. This forms the specific ergodic-mixing timescale, on which the generic energy levels (12) of the multistate scheme in Fig. 1, *a* are collectively populated almost analogously to the population of the re-
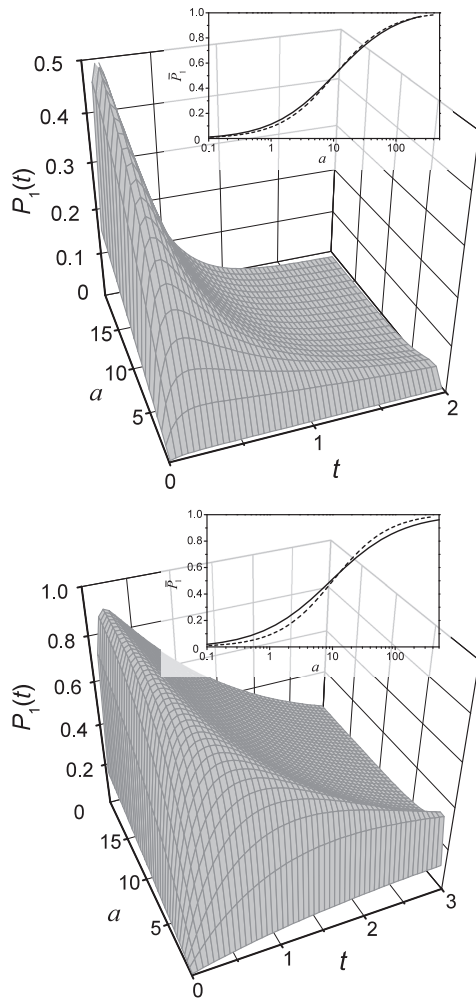
**Fig. 2.** 3D plot of output level populations $P_1(t)$ as a function of the time and the tuned parameters $b$ and $k$ (in inverse time units): $b = 7$; $k = 5$ (in the upper case) and $b = 0.04$; $k = 0.5$ (in the lower case). Inset: Sigmoidal curve fitting of population peaks $\overline{P}_1$ as a function of the running parameter $a$ on the log scale (solid line) in comparison to the Boltzmann curve (dotted line)

duced degenerate energy levels (16) of the two-state effective scheme in Fig. 1, *b*. In essence, the time $\tau_W$ characterizing the recurrent dynamics in the OS is related to the stochastic time $\tau_{st}$, which, however, does not enter any resulting expressions being, hence, insufficient to influence the cooperativity.

Solving (16) is elementary. For the ergodic case where any contact of the L with every particle in the bulk is distributed over contacts almost evenly and at one time, given initial conditions $P_2(0) = 1$; $P_1(0) =$

$= 0$, this yields

$$P_2(t) = (\lambda_2 - \lambda_1)^{-1}[(\lambda_2 - a)e^{-\lambda_1 t} +$$
$$+ (a - \lambda_1)e^{-\lambda_2 t}], \tag{18}$$
$$P_1(t) = a(\lambda_2 - \lambda_1)^{-1}[e^{-\lambda_1 t} - e^{-\lambda_2 t}],$$

where

$$\lambda_{1,2} = \frac{1}{2}\left[(a + b + k) \mp \sqrt{(a + b + k)^2 - 4ak}\right]. \tag{19}$$

According to (18), the time behavior of the population $P_2(t)$ of the input level of the OS is monotonous and, in general, spurious for cooperativity. Rather that, for the output level, $P_1(t)$ is essentially transient, being a good candidate for embodying the cooperativity of the OS. Figure 2 presents a 3D illustration of this effect, by using two different sets of the tuned control parameters: $b = 7$, $k = 5$ (in the upper case) and $b = 0.04$, $k = 0.5$ (in the lower case); with $a$ being the running control parameter. As is seen for both cases, the $P_1(t)$ functions exhibit bell-shaped variations in time. With increasing $a$, they peak at maxima $\overline{P}_1 = \overline{P}_1(a) \equiv \overline{P}_1(t_{\text{peak}}^{(a)})$, as a function of $a$, successively attained at regressive times $t = t_{\text{peak}}^{(a)}$, obeying a sigmoid saturation curve (solid line in the inset), which, depending on the values of tuned parameters, is more (upper case) or less (lower case) close to the Boltzmann distribution (dotted line in the inset). The remoteness of a sigmoid curve from the Boltzmann distribution may point so to the cooperativity qualitatively present in the lower case.

To describe the degree of cooperativity more quantitatively, one firstly considers the odds ratio $\overline{P}_1/(1 - \overline{P}_1)$ for the maximum normalized to 1 of the transient output-level population $\max_{0 \leq a < \infty}[\overline{P}_1(a)] = 1$, then calculates the logarithm of this ratio $\ln[\overline{P}_1/(1 - \overline{P}_1)]$, as a function of the logarithm of the input rate $\ln a$, and finally, associates a slope of this function with the desired degree. In (17)–(19), this is formally equivalent to providing a variation of the logarithm of the L bulk concentration (the L thermodynamic entropy) $\ln C$ or a change of the number of the L local contacts (the L configurational entropy) $\ln Z$, or the choice of the logarithmic dimensionality of bulk states (the L overall entropy) $\ln d$. Using such log-log regressions is common in different types of nonlinear data analyses [57], particularly in cases where the dynamics of levels of a system is regarded to be correlated due to cooperation mechanisms [58].

For the practical use of log-log models, one usually assumes that the log odds ratio scales are as follows:

$$\ln\left[\overline{P}_1/(1-\overline{P}_1)\right] = h_a(b,k)\ln[a/(b+k)], \qquad (20)$$

where $h_a(b,k)$ is the scaling exponent sought as a function of the tuned control parameters $b$ and $k$ with $a$ being the running control parameter. The parameter $h_a(b,k)$ is a commonly regarded equivalent to the Hill coefficient so referring to the cooperativity degree in cases where a change of the input rate $a$ can lead to the saturable variation of $\overline{P}_1$. If $h_a = 1$, then the OS is considered stable and hence non-cooperative (or maximally cooperative, when the increase of $a$ causes the Boltzmann-like change of the normalized $\overline{P}_1$). Rather the case $h_a < 1$ indicates the loss of stability with an emergence of "negative" cooperativity simply attributed as the effect of fractionally lowering its degree. In the limiting case $h_a \to 0$ so-called as a "null" cooperativity, one says that the OS is anti-cooperative, when any change in $a$ causes no change of $\overline{P}_1$. Therefore, calculating the log-log slopes in (20) as functions of the tuned control parameters involved in the kinetic scheme in Fig. 1, $b$ allows us to indicate the emergence of lowering the degree of cooperativity for the non-cooperative or maximally cooperative OS from 1 to fractional values with identifying those intervals of tuning the parameters which make the effect of "negative" cooperativity most salient.

The corresponding 3D graph of $h_a(b,k)$ is depicted in Fig. 3. As expected from (18) and (19), making the two-level OS in Fig. 1, $b$ reversible with $k \to 0$ stabilizes it attributing as non-cooperative for all $b$. This represents the Boltzmann–Gibbs (or Langmuir's isothermal) sigmoid distribution for the population

$$\overline{P}_1 = \frac{a}{a+b} = \left[e^{-\Delta F/k_\mathrm{B}T} + 1\right]^{-1} \qquad (21)$$

of level 1 lying lower than level 2 by the energy difference $\Delta E \gg k_\mathrm{B}T$ with $\Delta F = k_\mathrm{B}T\ln(a/b)$ being the corresponding free-energy difference for levels. The latter, according to $\Delta F = \Delta E - k_\mathrm{B}T\ln d$, will vary in the entire infinite interval by respectively choosing the appropriate values of $\Delta E \gg k_\mathrm{B}T$ and $d \in [1,\infty)$. In the coordinates $\overline{P}_1$ vs. $\ln(a/b)$, the maximum slope of the sigmoid curve (21) attained in a vicinity of $a \approx b$ is $1/4$. This directly refers to just as of non-cooperative case $h_a(b, k \approx 0) = 1$ in (20).
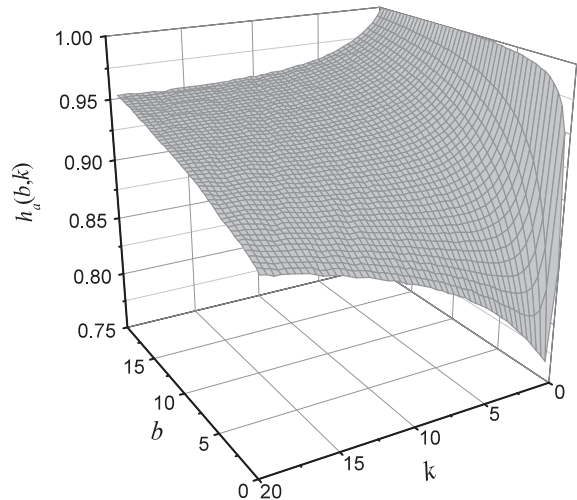


**Fig. 3.** 3D plot of the degree $h_a(b,k)$ of cooperativity (Hill's coefficient) as a function of the tuned parameters $b$ and $k$ (in inverse time units), with $a$ being the entropically driven running parameter, for the case of the irreversible two-level scheme in Fig. 1, $b$

In contrast, enlarging $k > 0$ makes the OS irreversible that conditions the effect of "negative" (i.e., fractional) cooperativity of it. However, this effect appears to be generally dependent on $b$. Indeed, at large $b \gg k$, the larger $k$, the more distinct (i.e., smaller) is the fractional cooperativity. On the other hand, at small $b < k$ there is a critical zone of even smaller $a$ within the region of operationally driven parameters, where the negative cooperativity becomes even more prominent. Such a dip of cooperativity indicates that, in this region, the OS behaves itself as metastable and, as a result, is poorly controllable. Formally, in (20), this corresponds to the lowest fractional values of $h_a(b \approx 0, k) < 1$ determined numerically in Fig. 3. Nevertheless, their bounds can be extracted analytically as well.

In order to sight such a bound, let us note that, in the irreversible case $k > 0$, relations (18) and (19) at $b = 0$ yield $\overline{P}_1(t) = [a/(a-k)][e^{-kt} - e^{-at}]$. This expression cannot be admitted to $\overline{P}_1$ in terms of the running $a$ and the widely tuned $k$ similar to that in terms of $a$ and $b$ for the reversible case (21), but rather only for the limiting case of $a \approx k$ when the $\overline{P}_1(t) = ate^{-(a+k)t/2}$ known of being peaked at the time $t_{\mathrm{peak}} = = [(a+k)/2]^{-1}$ approximately yields

$$\overline{P}_1(a \approx k) = (2/e)\frac{a}{a+k}. \qquad (22)$$

Obviously, in a vicinity of $a \approx k$, the slope of (22) is $1/2e$. Therefore, comparing this with that of (21) in a vicinity of $a \approx b$ provides possible values of $h_a(b, k)$ with the following universal bounds

$$\frac{2}{e} \leq h_a(b, k) \leq 1. \tag{23}$$

It is noteworthy that the left bound of $2/e \approx 0.74$ in (23) is being very close to the lowest value of 0.76 sighted in Fig. 3, which strengthens the validity of the approach. However, achieving a more coincidence between the numerical and estimated values is difficult, partially due to the effect of tailing the data, when varying the kinetic parameters near the very small $k \approx a$.

It is important to stress that the choice of a scaling exponent in the form (20) is not unique. Therefore, it is necessary to consider the alternative variants too. For example, it may be a situation where the backward parameter $b$ is not actually tuned, but rather running, while the input parameter $a$ instead tuned. Within the operational framework in Fig. 1, this means the use of an enthalpically driven scheme, where to achieve the high population of level 1 requires varying the energy difference $\Delta E$ between levels, while remaining the dimensionality of level 2 constant. Providing the corresponding analysis for the log odds $\ln[\overline{P}_1/(1 - \overline{P}_1)] = h_b(a, k) \ln[b/(a + k)]$ demonstrates that the respective scaling exponent $h_b(a, k)$ does not experience, in fact, any noticeable change being very close to unity at almost all tuned parameters $a$ and $k$ (data not shown). Consequently, if the running control parameter is driven almost enthalpically so that a principle of microscopic reversibility of the OS remains hold, then that OS retains its intrinsic stability and, hence, the initial non-cooperativity (or, equivalently, normalized maximum cooperativity) irrespective to which control parameters are tuned including those for the reversible input and irreversible output stages. Similarly, when energy level fluctuations inherent in the OS do not influence its microscopic reversibility like as in (15), then these fluctuations are lacking to impact its stability and non-cooperativity too. On the contrary, if a running control parameter is driven entropically so that to break the principle of microscopic reversibility of the OS, then that OS becomes "negatively" cooperative combining with the fractional degree bounded from

above and below by unity and a constant $2/e$, respectively, according to the universal relation (23).

## 4. Discussion and Conclusion

In this paper, a microscopic framework for describing the cooperativity of the nonequilibrium open system weakly interacting with the noisy equilibrium environment on the multiple time scales is presented. The cooperativity is characterized by the degree associated with the stability of the OS to quantify its sensitivity to the running and tuned controls. The approach is limited to treating the Liouville–Neumann quantum evolution equation (5) for the density matrix (7) of the total closed system (CS) (1) by the Nakajima–Zwanzig method which considers the CS as a sum of the OS plus the EE plus their interaction with projecting the overall evolution of the CS on state variables of the OS only. The Born–Markov approximation is used to reduce the integral differential master equation (8) for the density matrix of the OS (7) to the kinetic equations for its state populations (9). Providing a gain-loss balance (12) for equations with the probabilities of relaxation transitions between the energy levels (13) by averaging them over the fast fluctuations in the OS and the equilibrium vibrations in the EE is performed within a microscopic model [46–48]. In this model, Hamiltonian (2) of the OS is considered as a diagonal operator involving stochastic additions to eigenenergies; Hamiltonian (3) of the EE is regarded secular and represented by an infinite sum of harmonic oscillators; and the operator of interaction between the OS and the EE (4) weakly couples the corresponding transitions in the OS to the processes of creation or annihilation of one vibrational quantum (phonon) in the EE, respectively, conditioned by the energy conservation for the CS [49–51].

Setting the energy balance in the CS must mean that, when being in equilibrium, it holds stable in respect to all those disturbances of positions of its energy levels, which do not change the existed symmetry order. Since, for both the CS and its nonequilibrium counterpart, the OS, conserving a structure is equivalent to their stability, the latter will also be related to the cooperativity. Indeed, allowing it to be stable will imply the correlated (or cooperated) order in the OS. To characterize such a stability (or cooperativity), one can use a dimensionless degree for it in

the interval, say, from zero to one being normalized to the maximum and number of the OS states. However, this fails in the infinite-level CS for the general complexity and in a few-level OS because of the inability to incorporate multiple time scales to the expressions derived for its stability (or cooperativity). In this situation, one paves another way, rather solving the problem of the lifetimes $\vartheta_i$ of metastable states $|i\rangle$ of the OS [59–61], which have, in their most highly populated periods, only the temporary existence. The populations $P_i(t)$ of metastable states present non-monotonic behaviors with peaks $\overline{P}_i = P_i(t_{\mathrm{peak}}^{(i)})$ at the times $t = t_{\mathrm{peak}}^{(i)}$ so that $\vartheta_i = \int_0^\infty P_i(t)dt$. Usually, it is difficult to provide the assigning of $P_i(t)$ for all times. In the stationary approximation for exponentially decaying $P_i(t) = \overline{P}_i e^{-kt}$ with $k \ll [t_{\mathrm{peak}}^{(i)}]^{-1}$ being the slowest Lyapunov exponent, one makes the estimate $\vartheta_i = \overline{P}_i/k$. Thus, instead of assessing the unknown integral quantities $\vartheta_i$, one can treat the measurable steady-state population amplitudes $\overline{P}_i$ as those fractional variables that are regarded featured with the degree of stability (or cooperativity) of the OS.

Considering the population peaks $\overline{P}_i$ in more details, one indicates three possibilities. The first is to refer to the elasticity coefficients $\eta_{ij} = \partial \overline{P}_i/\partial \overline{P}_j$. This signifies the reversible elastic interrelation of controllable changes – regardless running (induced) or tuned (spontaneous) – in the state variables $\overline{P}_i$ and $\overline{P}_{j\neq i}$. These very quantities often represent the signatures for both the stability [10,11] and the cooperativity [16], but within the narrow intervals constrained by the applicability of elasticity theory. The second possibility expands $\eta_{ij}$ to their logarithmic values $l_{ij} = \partial \ln \overline{P}_i/\partial \ln \overline{P}_j$ independent of the range of change of the $\overline{P}_i$ and $\overline{P}_{j\neq i}$. Since the latter obey the Boltzmann statistics with proportionality to the exponentials of the relative energies of metastable steady states, to involve the coefficients $l_{ij}$ becomes very close to using the concept of a strength of intermolecular interactions that stabilizes quite those states of the OS [25]. Finally, the third possibility is to model the relationships between some binary state variables $\overline{P}_1$ and $\overline{P}_2 = 1 - \overline{P}_1$, by using a linear logistic regression. This assumes that the log of the odds ratio $\overline{P}_1/\overline{P}_2$ is a linear function of the running control parameter, say $\ln a$, weighted with the coefficient $h_a(b,k)$ being dependent on two tuned parameters $b$ and $k$, plus a term indicating the instant of employing the onset of $a$. Physically, the odds ratio represents the direct way to quantify that how likely to be or not to be in state $|1\rangle$ of the two-state OS is associated with to be or not to be it in state $|2\rangle$. Therefore, the odds ratio presents a desired measure of the degree of cooperativity by in effect describing the strength of either the association or non-independence between normalized probabilities of the two energy levels reduced to the binary case. One can thus use the odds ratio as a sought quantity to feature those correlations of different states of the OS, which are responsible for its stability and the cooperativity. But in doing so, besides the singled out level 1 of the unstable state $|1\rangle$, all the remaining states $|i = 2, ..., M\rangle$ should be combined into one single level 2 such that the kinetics of transitions of the reduced two-level OS and the generic multilevel OS would be almost the same just on the transition time scale. This is what we did in Section 3 within a kinetic framework introduced in Section 2, cf. (1)–(6), (12)–(20).

Let us discuss some consequences following from a quantitative approach used here to describe the degree of cooperativity of the OS among other more qualitative approaches. First is an implication of the hypothesis about the correspondence between the stability and the cooperativity. The direct implementation of this idea blunders into difficulties with describing the complex dynamics of a few-level OS in the presence of fluctuations and reducing it to the far simpler two-level kinetics on the multiple time scales. To overcome these difficulties, we employ a model of the nonequilibrium OS weakly interacting with the EE and exhibiting energy level fluctuations (1)–(4) within the microscopic approach [46–51]. An advantage of this approach is the possibility to operate with the unified expression (13) for the averaged probability $W_{ij}$ of transitions between the energy levels of different dimensionalities $d_i$ (17) in the frame of the kinetic equations for level populations $P_i(t)$ as relevant state variables for different cases (12) and (16). Having $W_{ij}$ (13) and knowing a relation between the reduced intensities $\gamma_{ij}$ of fluctuations and the natural frequencies $|\Omega_{ij}|$ of oscillations of the levels, one is able to rigorously find $W_{ij}$ for two limiting cases of largely extended $|\Omega_{ij}| \gg k_{\mathrm{B}}T/\hbar \gg \gamma_{ij}$ and nearly degenerate $|\Omega_{ij}| \ll \gamma_{ij} \approx k_{\mathrm{B}}T/\hbar$ energy levels (14),(15). Thus, one can correctly differenti-

ate between the enthalpic and entropic factors of the two-level OS, which guarantees either its stability or the instability (so being responsible either for unit or fractional cooperativity) in the correspondence to the quantum and classical limits above, respectively, cf. (18)–(22).

The second consequence concerns with the bounds for the degree of cooperativity of the two-level OS (23). A question arises: Can such degree $h$ be larger than 1 and lower than $2/e$? In the context of maximal stability of the OS, it would only be a convention to take the maximum degree of cooperativity equal to unity. However, there are many realistic OSs, where $h < 0.7$ and even $h \approx 0.2$–$0.3$ [62, 63]. But, in the latter case, at least three-body phenomena come into play leading to the anticooperative effects with very low $h$ [64, 65]. On the other hand, the Michaelis–Menten reaction, known to correspond just to the irreversible kinetics of the two-level OS, is well-recognized as a straightforwardly implemented mass-action law showing any realization of cooperative behavior [56, 66]. Relation (23) demonstrates the emergence of cooperativity quite for the Michaelis–Menten case. In this regard, bounds (23) established for the fractional degree of cooperativity could even be considered as universal in a sense of the very fact of the presence of an irreversible kinetic stage in the two-level OS (cf. Figs. 1, *b* and 3). Note that the damped two-level OS might also have an analogy with the one-level limit for a two-state vertex model of the multipartite networks [67].

The third consequence deals with the dependence of the degree of cooperativity on the context, in which it is determined. In the context-dependent analysis, one links the strengths of the non-additive thermodynamic interactions with their most likely contributions to the kinetics of the OS [25]. In contrast, we provide here a context-dependence with linking $h_a(b, k)$ to the controlled parameters by suggesting the additivity of the total free energy when grouping degenerate states $|i = 2, ..., M\rangle$ to a single level 2 of dimensionality $d = M - 1$, cf. (12), (13), (16), and (17). We observe that this effect reveals itself if only to drive the input kinetic parameter $a$ (or, equivalently, the dimensionality $d$) as running, while the backward $b$ and output $k$ parameters are tuned (see Fig. 3), and otherwise is not sighted. Therefore, in terms of the context-dependence, the "negative" or fractional degree of cooperativity of the OS can-

not be enthalpically driven, but rather entropically driven. This corresponds to the stable OSs as only those, which obey the principle of microscopic reversibility with respect to enthalpically driven transitions between the energy levels, but do not possess entropically driven changes in the number of levels. Obviously, the latter will lead to the fractional cooperativity of the OSs and, hence, to the loss of their stability.

Finally, the fourth consequence regards the plausible applications of the approach presented to quantify the cooperativity of the OS viewed here as of a physical-chemical-biological molecular structure to the wider class of the social-economic-informational-game agencies or organizations. It is common to represent an agency as a long-standing well-managed system [68] that constantly changes in time due to a coupling to the environment to provide an exchange of energy (force efforts) and matter (material or non-material agents) with it. Thus, an agency is very close to a few-level nonequilibrium OS. For it, one directly relates the cooperativity to the stability by referring a control over the latter to the some degree factor, in favor of which the levels and the number of states of the OS are being able (or managed) to collectively correlate (or cooperatively interact) with one another so that to provide an uttermost stable structure. Hence, there is a one-to-one correspondence between the lowering of a degree of cooperativity of the OS and the damping of a control over its stability. Moreover, when properly normalized, there are universal bounds for this degree $h$ (23); under downside of which $h < 2/e \approx 0.74$, the OS breaks down as a stable structure. However, this is the case only if the cooperativity will be entropically driven with the input control parameter $a$ is running. The backward and output parameters are tuned as small $b \to 0$, while nonzero $k > 0$ (Figs. 1, *b* and 3). To return the controllability, it is sufficient to regularize either these instabilities by making the backward control positive $b > 0$ or cutting off the output control $k \to 0$ (Fig. 3). The latter corresponds to the cancellation of an irreversible kinetic stage in Fig. 1, *b*, which provides, by definition, the OS with a well-controlled reversibility.

In summary, the non-stationary kinetics of a few-state nonequilibrium open system (OS) weakly interacting with a noisy equilibrium environment (EE) depends on the energy-level spectrum of the OS, as

well as on the interaction parameters, noise intensity, and temperature of the EE. All factors above in turn impact the degrees $h$ of both the cooperativity and the stability of the OS. To answer the question about how to relate these quantities, one appeals to the reduced scheme of the damped two-level OS (Fig. 1). In this case, one starts from the pair of fluctuating energy levels of different dimensionalities, for which one chooses the initial condition of population of the first level and sets the two rates of reversible transitions between the levels and the one rate of irreversible decay of the second level. Then, to operate with this pair, one uses four independent parameters united in the quadruples, either $\Omega, \Phi, d, k$ or $\Omega, a, b, k$ (16), (17). Here, $\Omega$ is the frequency of oscillations between largely extended energy levels of the OS put fast relative to a thermal vibrational frequency $\omega_T = k_B T / \hbar \approx 4 \times 10^{13} s^{-1}$ of the EE, $\Phi$ is the far slower rate limit for reversible kinetics of relaxation transitions, $d$ is the relative level dimensionality (logarithmic entropy), $a$ is the reversible input rate, $b$ is the reversible backward rate, and $k$ is the irreversible output rate. Finally, to involve a controlled guide in the cooperativity (or stability) of the OS, one considers two scenarios for it to display a dependence on the context of their use. In the first scenario, one fixes $\Omega$ and $\Phi$ so that $\Phi \ll \omega_T \ll \Omega$, which is equivalent to fix $b$, then runs $a$ given $k$, and finally plots the degree of cooperativity $h_a(b, k)$ as a function of the tuned $b$ and $k$ (20). The corresponding 3D graph is depicted in Fig. 3. Obviously, if $k = 0$, then the OS is stable and non-cooperative; while, at $k > 0$, it becomes both unstable and fractionally cooperative. Therefore, controlling $k$ is the necessary condition impacting the emergence and/or the disappearance of the fractional cooperativity in the OS. But the degree of cooperativity depends on tuning $b$ too. Moreover, down to the limit $b \to 0$, $h_a(b, k)$ (20) attains its lower bound $h_a(0, k) = 2/e$ (23) sighted in Fig. 3. At this bound, the OS turns out to be critically unstable such that to return its normal stability requires to make both zero $k = 0$ and nonzero $b > 0$. Thus, to realize the scenario above stipulates, in fact, the use of quite radical means for stabilizing the OS that would otherwise be unstable. Conversely, in the second scenario, if running $b$, while tuning both $a$ and $k$, one observes no noticeable change in the corresponding degree of cooperativity $h_b(a, k)$ comparing to unity (data not shown). This directly points to the non-cooperative

case respectively implying that when to run $b$ and else to tune $a$, the OS remains stable irrespective of tuning $k$. Thus, for that scenario, the irreversibility, if being present in the OS, does not destroy its controllability, keeping the OS almost stable without any need to restore it.

1. J. Gates, *The Ownership Solution* (Penguin, London, 1998).
2. J. Rothschild and J. Allen-Whitt, *The Cooperative Workplace* (Cambridge Univ. Press, Cambridge, 1986).
3. H. Hotelling, Economic J. **39**, 41 (1929).
4. C. Bohr, Zentralblatt Physiol. **23**, 688 (1904).
5. A.J. Clark, *The Mode of Action of Drugs on Cells* (Edward Arnold, London, 1933)
6. J.B.S. Haldane, *Enzymes* (MIT Press, Cambridge, MA, 1965).
7. F.C. Frank, Proc. Roy. Soc. A **215**, 43 (1952).
8. A.W. Adamson, J. Am. Chem. Soc. **76**, 1578 (1954).
9. F.H. Stillinger and T.A. Weber, Phys. Rev. A **28**, 2408 (1983).
10. K.A. Connors, *Binding Constants: The Measurements of Molecular Complex Stability* (Wiley, New York, 1987).
11. P. Hobza and R. Zahradnik, *Intermolecular Complexes* (Elsevier, Amsterdam, 1988).
12. J.-M. Lehn, *Supramolecular Chemistry: Concepts and Perspectives* (Wiley-VCH, Weinheim, 1995).
13. J.C. Dyre, Rev. Mod. Phys. **78**, 953 (2006).
14. A.V. Hill, J. Physiol. **40**, 389 (1910).
15. R. Heinrich and T.A. Rapoport, Acta Biol. Med. Ger. **31**, 479 (1973).
16. J. H. Hofmeyr and A. Cornish-Bowden, Eur. J. Biochem. **200**, 223 (1991).
17. R. Heinrich and S. Schuster, *The Regulation of Cellular Systems* (Chapman and Hall, New York, 1996).
18. G.S. Adair, J. Biol. Chem. **63**, 529 (1925).
19. L. Pauling, Proc. Nat. Acad. Sci. USA **21**, 186 (1935).
20. J. Monod, J. Wyman and J.-P. Changeux, J. Mol. Biol. **12**, 88 (1965).
21. D.E. Koshland, Jr., G. Nemethy, and D. Filmer, Biochemistry **5**, 365 (1966).
22. W.G. Bardsley and R.E. Childs, Biochem. J. **149**, 313 (1975).
23. J. Ricard and A. Cornish-Bowden, Eur. J. Biochem. **166**, 255 (1987).
24. A.L. Horovitz and A.R. Fersht, J. Mol. Biol. **214**, 613 (1990).

25. T. Shem-Ad and O. Yifrach, J. Gen. Physiol. **141**, 507 (2013).

26. A. Cornish-Bowden, FEBS J. **281**, 621 (2014).

27. Q. Cui and M. Karplus, Protein Sci. **17**, 1295 (2008).

28. G.R. Fleming and M. Ratner, Phys. Today **July**, 28 (2008).

29. H.E. Stanley, Rev. Mod. Phys. **71**, S358 (1999).

30. K. Lindenberg and B.J. West, *The Nonequilibrium Statistical Mechanics of Open and Closed Systems* (Wiley-VCH, New York, 1990).

31. A. Rivas and S.F. Huelga, *Open Quantum Systems: An Introduction* (Springer, Heidelberg, 2012).

32. C.H. Fleming and B.L. Hu, Ann. Phys. **327**, 1238 (2012).

33. M.A. Miller, J.P.K. Doe, and D.J. Wales, Phys. Rev. E **60**, 3701 (1999).

34. Y. Levy, J. Jortner, and R.S. Berry, Phys. Chem. Chem. Phys. **4**, 5052 (2002).

35. J. Cao and R.J. Silbey, J. Phys. Chem. A **113**, 13825 (2009).

36. Y.R. Chemla, J.R. Moffitt, and C. Bustamante, J. Phys. Chem. B **112**, 6025 (2008).

37. A.I. Burshtein, Adv. Phys. Chem. **2009**, 214219 (2009).

38. G. Lindblad, *Nonequilibrium Entropy and Irreversibility* (Reidel, Dordrecht, 1983).

39. E.C.G. Sudarshan, Phys. Rev. A **46**, 37 (1992).

40. N.N. Bogoliubov, *Lectures on Quantum Statistics* (Gordon and Breach, New York, 1967), Vol. 1.

41. N.N. Bogoliubov, *Lectures on Quantum Statistics* (Gordon and Breach, New York, 1970), Vol. 2.

42. S. Nakajima, Progr. Theor. Phys. **20**, 948 (1958).

43. R. Zwanzig, J. Chem. Phys. **33**, 1338 (1960).

44. E.G. Petrov, Eur. Phys. J. Special Topics **216**, 205 (2013).

45. I. Goychuk and P. Hanggi, Adv. Phys. **54**, 525 (2005).

46. E.G. Petrov and V.I. Teslenko, Theor. Math. Phys. **84**, 986 (1991).

47. E.G. Petrov, V.I. Teslenko, and I.A. Goychuk, Phys. Rev. E **49**, 3894 (1994).

48. E.G. Petrov, I.A. Goychuk, and V. May, Physica A **233**, 560 (1996).

49. V.I. Teslenko, E.G. Petrov, A. Verkhatsky, and O.A. Krishtal, Phys. Rev. Lett. **104**, 178105 (2010).

50. E.G. Petrov and V.I. Teslenko, Chem. Phys. **375**, 243 (2010).

51. V.I. Teslenko and O.L. Kapitanchuk, Int. J. Mod. Phys. B **27**, 1350169 (2013).

52. E. Langmann and G. Lindblad, J. Stat. Phys. **134**, 749 (2009).

53. A. Nitzan, *Chemical Dynamics in Condensed Phases* (Oxford Univ. Press, Oxford, 2006).

54. R.D. Coalson, D.G. Evans, and A. Nitzan, J. Chem. Phys. **101**, 436 (1994).

55. J. Jortner, J. Chem. Phys. **64**, 4860 (1976).

56. J. Gunawardena, Mol. Biol. Cell **23**, 517 (2012).

57. B. Efron and R. Tibshirani, Science **253**, 390 (1991).

58. K. Banerjee, B. Das, and G. Gangopadhyay, J. Chem. Phys. **136**, 154502 (2012).

59. S.S. Plotkin, J. Wang, and P.G. Wolynes, J. Phys. I **7**, 395 (1997).

60. V.N. Smelyanskiy, M.I. Dykman, H. Rabitz, and B.E. Vugmeister, Phys. Rev. Lett. **79**, 3113 (1997).

61. A. Fiasconaro, B. Spagnolo, and S. Boccaletti, Phys. Rev E **72**, 061110 (2005).

62. G.G. Hammes, Proc. Natl. Acad. Sci. USA **79**, 6881 (1982).

63. D. Alvarado, D.E. Klein, and M.A. Lemmon, Cell **142**, 568 (2010).

64. C. Czaplewski, A. Liwo, D.R. Ripoll, and H.A. Scheraga, J. Phys. Chem. B **109**, 8108 (2005).

65. L. Wang, R.A. Freisner, and B.J. Berne, Faraday Discuss. **146**, 247 (2010).

66. A. Cornish-Bowden, *Fundamentals of Enzyme Kinetics* (Wiley-VCH, Weinheim, 2012).

67. H. Hooyberghs, B. Van Schaeybroeck, and J.O. Indekeu, Physica A **389**, 2920 (2010).

68. D. Wren and A.G. Bedeian, *The Evolution of the Management Thought* (Wiley, New York, 2009).

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ДРОБОВА КООПЕРАТИВНІСТЬ
СИСТЕМИ З КІЛЬКОМА СТАНАМИ
В ОТОЧУЮЧОМУ СЕРЕДОВИЩІ

Р е з ю м е

Кооперативність репрезентує тип недостатньо добре визначених величин, які знаходять застосування в різних галузях фізики, хімії, біології, інформатики, тощо. В цій роботі ми визначаємо кооперативність з фізичної точки зору, пов'язуючи її з наявністю стабільності для системи з кількома станами по відношенню до необоротності. Спочатку ми редукуємо розвинення у часі такої системи до еволюції її двох ефективно флуктуюючих енергетичних рівнів різної розмірності за початкового заселення одного рівня, деяких відмінних ймовірностей мікроскопічно зворотних переходів між двома рівнями, та деякою ймовірністю необоротного розпаду іншого рівня. Потім проводимо для редукованої системи усереднення за енергіями флуктуацій рівнів, що дозволяє для швидкостей міжрівневих переходів точно врахувати вплив зовнішніх чинників, що контролюють положення рівнів та їх розмірність. Нарешті, ми демонструємо появу в цій системі дробової кооперативності, нормований ступінь якої знаходиться в межах від $2/e$ до одиниці за умови, що перехід через його нижню границю сягає нестабільної системи, відновлення стабільності котрої потребує уповільнення в ній швидкості необоротного розпаду або пришвидшення її оборотних переходів у зворотному напрямку.