J. Phys. Chem. A **2000,** *104,* 3159−3176

Statistical Ensemble Approach and Fluctuation−Dissipation Relations for Multivariable Chemical Systems Far from Equilibrium

Marcel Ovidiu Vlad[†,‡] and John Ross*[,†]

Department of Chemistry, Stanford University, Stanford, California 94305-5080, and Center of Mathematical Statistics, Casa Academiei Romane, Calea 13 Septembrie 13, 76100, Bucharest, Romania

Received: November 12, 1999; In Final Form: February 1, 2000

A statistical ensemble approach and an ensemble master equation are introduced for the study of concentration fluctuations in multivariable chemical systems far from equilibrium. The theory describes the stochastic properties of the numbers of replicas of the system characterized by different compositions. We give a general analytic solution of the ensemble master equation and investigate the relationships between the ensemble master equation and the one-system master equation. A condition of mesoscopic time reversal (mesoscopic reversibility) is introduced for a reference system; mesoscopic reversibility is less restrictive than microscopic reversibility. For systems with mesoscopic time reversal the general theory turns into a simple form and, in the thermodynamic limit, we derive an exact expression for the stochastic potential attached to the one-system master equation. We study the stochastic properties of the numbers of the reaction events both for system with or without mesoscopic time reversal. The condition of mesoscopic time reversal can be described by an extremum condition: if the contributions of different reactions to the total number of reaction events are constant, then the dispersions of the net numbers of the reaction events have minimum values for mesoscopic reversibility. A set of fluctuation−dissipation relations is derived for multivariable chemical systems, based on the use of the reaction extents as state variables of the system. We also consider systems that do not obey the condition of mesoscopic time reversal and measure the departure of a chemical process from mesoscopic reversibility in terms of a set a functions, which are proportional to the average values of the net numbers of the reaction events. In terms of these functions we derive a set of fluctuation−dissipation relations that establish a general relationship among the rates and the reaction affinities of the different reactions occurring in the system. A component of the dissipation function of the process is computed by using these fluctuation−dissipation relations.

1. Introduction

Fluctuation−dissipation relations play important roles in the development of statistical mechanical theories of nonequilibrium processes:[1] they bridge the gap between the microscopic (or mesoscopic) and macroscopic descriptions of physicochemical systems and make possible the evaluation of the rate coefficients for various transport processes from microscopic calculations.

Within the framework of a thermodynamic and stochastic theory of nonequilibrium processes[2−5] we have studied global fluctuation−dissipation relations for chemical systems far from equilibrium. Our first attempt dealt with one-variable chemical systems far from equilibrium described by a mesoscopic master equation.[6] For such systems we derived the following fluctuation−dissipation relation[6]

$$\tilde{\rho}(x,t) = 2D^{(2)}(x)\tanh\left[-\frac{1}{2k_BVT}\frac{\partial}{\partial x}\Phi(x)\right] = 2D^{(2)}(x)\tanh\left[-\frac{A(x)}{2k_BT}\right] \quad (1.1)$$

where x is the volume concentration of a chemical species X, $\tilde{\rho}(x,t)$ is the net rate of formation of the chemical species X, $D^{(2)}(x)$ is a probability diffusion coefficient, $\Phi(x)$ is a stochastic thermodynamic potential that determines the stochastic nonequilibrium stationary state of the system, $A(x)$ is a species-specific reaction affinity, V and T are the volume and the temperature of the system, and k_B is Boltzmann's constant. The stochastic potential, $\Phi(x)$, is related to the probability density $\tilde{P}_{st}(x)$ of fluctuations at a stochastic steady state by a relation similar to Boltzmann's relation for equilibrium thermodynamics

$$\tilde{P}_{st}(x) \sim \exp\left[-\frac{\Phi(x)}{k_BT}\right] \quad (1.2)$$

and the species-specific affinity is given by the derivative of the stochastic potential $\Phi(x)$ with respect to the total number $X = xV$ of particles of the X species

$$A(x) = \partial\Phi(x)/\partial X = V^{-1}\partial\Phi(x)/\partial x \quad (1.3)$$

The fluctuation−dissipation relation (1.1) has two different physical interpretations.[6] In the first place it is a relationship between the macroscopic properties of the system for any nonequilibrium state, expressed by the net reaction rate $\tilde{\rho}(x,t)$ of the species X and the mesoscopic (fluctuation) properties of the system, for a stochastic stationary state, expressed by the stochastic potential $\Phi(x)$. The second interpretation of the fluctuation−dissipation relation (1.1) is purely macroscopic: eq 1.1 is a force−flux relationship typical for nonequilibrium thermodynamics, where the net reaction rate $\tilde{\rho}(x,t)$ is a ther-

---

[†] Stanford University.

[‡] Casa Academiei Romane.

10.1021/jp994018b CCC: $19.00

modynamic flux and the species-specific affinity $A(x)$ is a thermodynamic force corresponding to a deterministic nonequilibrium steady state of the system. By using this second physical interpretation the fluctuation−dissipation relation (1.1) can be used for computing a component of the rate of dissipation of the process. We have

$$\frac{\mathrm{d}}{\mathrm{d}t}\Phi(x(t)) = 2VD^{(2)}(x)\, A(x) \tanh\left[-\frac{A(x)}{2k_\mathrm{B}T}\right] \tag{1.4}$$

Equation1.4 shows that far away from a steady state the contribution of the system to the dissipation function is proportional to the absolute value of the species-specific affinity,

$$\mathrm{d}\Phi[x(t)]/\mathrm{d}t \sim -2VD^{(2)}(x)|A(x)| \qquad \text{as} \qquad |A(x)| \to \infty \tag{1.5}$$

whereas close to a steady state, the dissipation function is proportional to the square of the species-specific affinity

$$\frac{\mathrm{d}}{\mathrm{d}t}\Phi(x(t)) = -\frac{V}{k_\mathrm{B}T} D^{(2)}(x)\, A^2(x) \qquad \text{as} \qquad |A(x)| \to 0 \tag{1.6}$$

We have attempted to extend the global fluctuation−dissipation relations to one-variable disordered systems, based on the use of characteristic functionals.[7] The resulting fluctuation−dissipation relations have been used for the study of the fluctuations of the reaction volume.[8]

Another class of systems for which we developed fluctuation−dissipation relations is a multivariable closed (but not isolated) chemical system with multiple reactions of the type[9]

$$\sum_i \nu_{iu}^{+} \mathrm{X}_i \rightleftarrows \sum_i \nu_{iu}^{-} \mathrm{X}_i \qquad u = 1, 2, ... \tag{1.7}$$

and for which, due to environmental variations, the rate coefficients are functions of time. For this type of system we have shown that, provided that some reasonable assumptions are fulfilled, the system evolves toward a stochastic normal regime for which the probability of fluctuations evolves toward a normal form independent of the initial conditions:[9]

$$\tilde{P}^*(\xi,t) \sim \exp[VJ^*(\xi,t)] \tag{1.8}$$

where $\xi = [\xi_u]_{u=1,2,...}$ is the vector of the reaction extents attached to the chemical processes (1.7) and $J^*(\xi,t)$ is a normal chemical action which plays the same role as the stochastic potential $\Phi(x)$ for one-variable systems. We have also derived a fluctuation−dissipation relation[9] similar to eq 1.1:

$$\Lambda = V\sum_u \left\{ 2D_u(\xi,t) \tanh\left(\frac{1}{2}\frac{\partial}{\partial \xi_u} J^*(\xi,t)\right) - \tilde{\rho}_u(\xi,t) \right\} \times \sinh\left(\frac{\partial}{\partial \xi_u} J^*(\xi,t)\right) \tag{1.9}$$

where $D_u(\xi,t)$ is a probability diffusion coefficient attached to the uth reaction 1.7, $\tilde{\rho}_u(\xi,t)$ is the net rate of the uth reaction 1.7, and

$$\Lambda = V\frac{\partial}{\partial t} J^*(\xi,t) \tag{1.10}$$

A component of the dissipation function of the process can be also computed from eq 1.9. We have[9]

$$-\frac{\mathrm{d}}{\mathrm{d}t}(VJ^*(\xi,t)) = V\sum_u \tilde{\rho}_u(\xi,t)\, J^*(\xi,t) + V\sum_u \sinh\left(\frac{\partial}{\partial \xi_u} J^*(\xi,t)\right) \times \left[\tilde{\rho}_u(\xi,t) - 2D_u(\xi,t)\tanh\left[\frac{1}{2}\frac{\partial}{\partial \xi_u} J^*(\xi,t)\right]\right] \tag{1.11}$$

For a single reaction the fluctuation−dissipation relation 1.9 reduces to

$$\tilde{\rho}(\xi,t) = 2D(\xi,t) \tanh\left(\frac{1}{2}\frac{\partial}{\partial \xi} J^*(\xi,t)\right) - \frac{\Lambda}{V \sinh\left(\frac{\partial}{\partial \xi} J^*(\xi,t)\right)} \tag{1.12}$$

If the normal stochastic regime is stationary, the normal chemical action $J^*(\xi,t) = J^*(\xi)$ and the probability diffusion coefficient $D(\xi,t) = D(\xi)$ are independent of time and the fluctuation−dissipation relation (1.12) reduces to a form similar to eq 1.1:

$$\tilde{\rho}(\xi) = 2D(\xi) \tanh\left(\frac{1}{2}\frac{\partial}{\partial \xi} J^*(\xi)\right) \tag{1.13}$$

Our previous attempt of deriving global fluctuation−dissipation relations for multivariable chemical systems has a serious limitation. Even though the systems of type (1.7) are described by many state variables, our theory leads to a single fluctuation−dissipation relation. Although this fluctuation−dissipation equation (eqs 1.9, 1.12, and 1.13) has a structure similar to the fluctuation−dissipation relation, (1.1), derived for one-variable systems, unlike eq 1.1 it cannot be interpreted as a force−flux relationship. To overcome these limitations of our multivariable theory, we shall investigate a general feature characteristic for multivariable systems, which is the lack of detailed balance. We shall show that for multivariable chemical systems it is possible to introduce a condition of mesoscopic time reversal (mesoscopic reversibility), which is less restrictive than the condition of microscopic reversibility.[10−12] The condition of mesoscopic reversibility leads to semidetailed (mesoscopic) balance, which is also less restrictive than the condition of detailed balance[10−12] derived in the literature for systems with microscopic reversibility. We shall develop a statistical ensemble approach for the study of concentration fluctuations in complex chemical systems. The systems studied do not generally obey the condition of mesoscopic reversibility; the condition of mesoscopic reversibility provides a useful reference state that serves as the starting point of our computations. On the basis of this idea, we shall introduce a set of functions that measure the departure of an arbitrary multivariable chemical system from mesoscopic reversibility. By using these functions as additional variables, we derive a set of fluctuation−dissipation relations that can be interpreted as a set of nonlinear flux−force relationship that may serve as a basis for developing a nonlinear thermodynamic approach for chemical systems far from equilibrium.

The structure of the paper is the following. In section 2 we give a general formulation of the problem and in section 3 we introduce a statistical ensemble description for the study of concentration fluctuations. In section 4 we introduce the condition of mesoscopic reversibility, show that it leads to the condition of semidetailed (mesoscopic) balance and study its main consequences. In section 5 we investigate the stochastic properties of the number of reaction events and study the main properties of the systems without detailed balance. In section 6 we derive the dissipation−fluctuation relations, and in section 7 we discuss their physical significance.

2. Formulation of the Problem

Chemical fluctuations in systems far from equilibrium are usually described in terms of a chemical master equation. Let us consider a homogeneous chemical system made up of S_1 stable substances A_j, $j = 1, 2, ..., S_1$, and S_2 active intermediates, X_j, $j = 1, ..., S_2$ which are involved in R elementary reactions

$$\sum_{j=1}^{S_1}\alpha_{ji}^{+}\mathrm{A}_j + \sum_{j=1}^{S_2}\beta_{ji}^{+}\mathrm{X}_j \underset{k_i^-}{\overset{k_i^+}{\rightleftharpoons}} \sum_{j=1}^{S_1}\alpha_{ji}^{-}\mathrm{A}_j + \sum_{j=1}^{S_2}\beta_{ji}^{-}\mathrm{X}_j \qquad i = 1, ..., R \tag{2.1}$$

where $\alpha_{ji}^{\pm}$ and $\beta_{ji}^{\pm}$ are stoichiometric coefficients and $k_i^{\pm}$ are the rates of the forward and backward steps, respectively. The rates of the chemical reactions (2.1) are assumed to obey the stochastic version of the mass-action law:[13]

$$r_i^{\pm} = Vk_i^{\pm}\left\{\prod_{j=1}^{S_1}\left[\frac{A_j(A_j-1)...(A_j-\alpha_{ji}^{\pm}+1)}{V^{\alpha_{ji}^{\pm}}}\right]\right\} \times \left\{\prod_{j=1}^{S_2}\left[\frac{X_j(X_j-1)...(X_j-\beta_{ji}^{\pm}+1)}{V^{\beta_{ji}^{\pm}}}\right]\right\} \tag{2.2}$$

where V is the volume of the system, $r_i^{\pm}$ and $k_i^{\pm}$ are the forward and backward rates and rate coefficients, respectively, and A_j and X_j are the numbers of molecular species A_j and X_j.

To prevent the approach of the system to chemical equilibrium, one assumes that the numbers of A_j are controlled by interaction with a system of reservoirs connected to the system by means of semipermeable walls. If the numbers of the A_j species are known, a simplified description of the system is possible. By removing from eq 2.1 the stable substances A_j, we get a set of reduced reactions:[14]

$$\sum_{j=1}^{S_2}\beta_{ji}^{+}\mathrm{X}_j \underset{k_i^-}{\overset{k_i^+}{\rightleftharpoons}} \sum_{j=1}^{S_2}\beta_{ji}^{-}\mathrm{X}_j \qquad i = 1, ..., R \tag{2.3}$$

The corresponding reaction rates are given by

$$r_i^{\pm} = V\kappa_i^{\pm}\left\{\prod_{j=1}^{S_2}\left[\frac{X_j(X_j-1)...(X_j-\beta_{ji}^{\pm}+1)}{V^{\beta_{ji}^{\pm}}}\right]\right\} \tag{2.4}$$

where the apparent rate coefficients

$$\kappa_i^{\pm} = k_i^{\pm}\left\{\prod_{j=1}^{S_1}\left[\frac{A_j(A_j-1)...(A_j-\alpha_{ji}^{\pm}+1)}{V^{\alpha_{ji}^{\pm}}}\right]\right\} \tag{2.5}$$

depend on A_j.

If we are interested only in the stoichiometry of the active intermediates, we can rewrite eqs 2.3 in the following form:[14]

$$\sum_{j=1}^{S_2} f_{ji}X_j \equiv 0 \qquad i = 1, ..., R, \quad f_{ji} = \beta_{ji}^{+} - \beta_{ji}^{-} \tag{2.6}$$

Although the reduced reactions are physically distinct, it is possible that two or more of them have the same stoichiometry for the active intermediates. A typical example is the well-known Schlögl model[15]

$$\mathrm{A}_1 + 2\mathrm{X}_1 \rightleftharpoons 3\mathrm{X}_1 \tag{2.7}$$

$$\mathrm{A}_2 \rightleftharpoons \mathrm{X}_1 \tag{2.8}$$

for which the stoichiometry of the X_1 intermediate is the same; that is, it is characterized by the same variation of the stoichiometric coefficients of X_1, $f_{11} = \beta_{11}^{+} - \beta_{11}^{-} = 3 - 2 = 1$ and $f_{12} = 1$:

$$\mathrm{X}_1 \equiv 0 \tag{2.9}$$

The reduced reactions with the same stoichiometry of the X_i intermediates can be lumped into a single reduced equation of the type (2.6). The corresponding forward and backward reaction rates are sums of the individual rates of the reactions lumped together

$$\rho_i^{\pm} = \sum_{\alpha} r_{i_\alpha}^{\pm} \qquad i = 1, ..., L \le R \tag{2.10}$$

where the rates $r_{i_\alpha}^{\pm}$ are given by eq 2.4.

The state of the system is described in terms of the composition vector of the active intermediates

$$\mathbf{N} = (X_1, ..., X_{S_2}) \tag{2.11}$$

From eq 2.10 we can evaluate the transition rate $W_{\mathbf{N}'\mathbf{N}}$ from the state $\mathbf{N}'$ to the state $\mathbf{N}$ by adding the contributions of the different reduced reactions with different stoichiometry:

$$W_{\mathbf{N}'\mathbf{N}} = \sum_{i,\pm}\rho_i^{\pm}(\mathbf{N} \pm \mathbf{f}_i)\delta_{\mathbf{N}'(\mathbf{N}\pm\mathbf{f}_i)} \tag{2.12}$$

where

$$\mathbf{f}_i = (f_{1i}, ..., f_{S_2 i}) \tag{2.13}$$

are row vectors made up of stoichiometric coefficients.

By assuming that the stochastic process describing the evolution of the chemical system considered is Markovian, we can derive a master equation:

$$\frac{\partial}{\partial t}G(\mathbf{N},t|\mathbf{N}',t') = \sum_{\mathbf{N}''\neq\mathbf{N}}[W_{\mathbf{N}''\mathbf{N}}G(\mathbf{N}'',t|\mathbf{N}',t') - W_{\mathbf{N}\mathbf{N}''}G(\mathbf{N},t|\mathbf{N}',t')] \tag{2.14}$$

with the initial condition

$$G(\mathbf{N}'',t=t'|\mathbf{N}',t') = \delta_{\mathbf{N}''\mathbf{N}'} \tag{2.15}$$

$G(\mathbf{N}'',t|\mathbf{N}',t')$ is the probability that at time t the state of the system is $\mathbf{N}''$, provided that at time t' the state of the system was $\mathbf{N}'$. The rates $W_{\mathbf{N}\mathbf{N}''}$ are generally time-dependent because of the possible time dependence of A_j.

As the evolution of the system is assumed to be Markovian, the conditional probability $G(\mathbf{N}'',t|\mathbf{N}',t')$ determines completely the random time evolution of the composition vector $\mathbf{N}$. In particular, the joint probability distributions $P_1(\mathbf{N}_1,t_1)$, $P_2(\mathbf{N}_1,t_1;\mathbf{N}_2,t_2)$, ..., are given by

$$P_1(\mathbf{N},t) = \sum_{\mathbf{N}'} G(\mathbf{N},t|\mathbf{N}',t')P_1(\mathbf{N}',t') \qquad (2.16)$$

$$P_2(\mathbf{N},t;\mathbf{N}',t') = G(\mathbf{N},t|\mathbf{N}',t')P_1(\mathbf{N}',t'), \quad \text{etc.} \qquad (2.17)$$

Solving the master equation (2.14) is very difficult. Although some approximate methods of analytic integration are available, their application is not easy. Sometimes even the finding of suitable numerical solutions is nontrivial. In the vicinity of equilibrium the principle of detailed balance allows the reduction of the integration of the master equation to a Hermitian eigenvalue problem. Applied to the reaction network (2.1) the principle of detailed balance[10−12] requires that at equilibrium the forward rate of each elementary reaction equals the corresponding backward rate

$$r_i^+ = r_i^- \qquad \text{for} \qquad A_l = A_l^{\text{eq}},\ X_l = X_l^{\text{eq}} \qquad i = 1, ..., R \quad (2.18)$$

where the rates $r_i^{\pm}$ are evaluated in terms of the equilibrium values of the numbers of molecules. The physical explanation of the occurrence of detailed balance at equilibrium is related to microscopic reversibility, i.e., to the fact that the classical or quantum Liouville equations attached to the chemical system (2.1) are invariant with respect to the change of the sign of the time variable.

In this paper we are concerned with systems far from equilibrium for which the condition of microscopic reversibility is generally invalid. However, it is useful to introduce a condition of time reversal for a stochastic nonequilibrium steady state. Although this condition of time reversal is generally not fulfilled, it simplifies the computations by providing a standard reference state. By introducing a set of variables, which measure the distance of a real system from a nonequilibrium stochastic reference state with time reversal, it is possible to define a set of fluctuation−dissipation relations for chemical systems far from equilibrium.

To derive a set of fluctuation−dissipation relations for complex chemical system described by eqs 2.3−2.6, we shall develop a statistical approach comprising the following steps:

1. the development of a statistical ensemble description for the study of chemical fluctuations
2. the introduction of a nonequilibrium standard reference state that fulfills the condition of time reversal
3. the investigation of the implications of the conditions of time reversal
4. the study of the statistics of the numbers of the reaction events occurring in the ensemble
5. the introduction of a set of functions that measure the distance between an arbitrary nonequilibrium state and a reference state obeying the condition of time reversal
6. the derivation of a set of fluctuation−dissipation relations and the study of their main properties

3. Dynamics of Reaction Events and Statistical Ensemble Description

We introduce a statistical ensemble description by considering a large number $\mathcal{M}_\Sigma$ of systems, each system being characterized by different composition vectors, $\mathbf{N}_1$, $\mathbf{N}_2$, ... Denoting by $\mathcal{M}_\mathbf{N}(t)$ the number of systems characterized by the composition vector $\mathbf{N}$ at time t, we have

$$\mathcal{M}_\Sigma = \sum_{\forall \mathbf{N}} \mathcal{M}_\mathbf{N}(t) = \text{constant} \qquad (3.1)$$

Although the total number $\mathcal{M}_\Sigma$ of systems is by definition constant, the numbers $\mathcal{M}_\mathbf{N}(t)$ are fluctuating quantities. For $\mathcal{M}_\Sigma \to \infty$ these fluctuations are negligible and we can approximate the one-time state probability density $P_1(\mathbf{N},t)$ by a relative frequency

$$P_1(\mathbf{N},t) \cong \mathcal{M}_\mathbf{N}(t)/\mathcal{M}_\Sigma \qquad \text{as} \qquad \mathcal{M}_\Sigma \to \infty \qquad (3.2)$$

For a finite number of statistical ensembles the sample fluctuations are finite and the one-time state probability is to be interpreted as an average value rather than an instantaneous relative frequency

$$\langle P_1(\mathbf{N},t)\rangle \cong \langle \mathcal{M}_\mathbf{N}(t)\rangle/\mathcal{M}_\Sigma \qquad \mathcal{M}_\Sigma \text{ finite} \qquad (3.3)$$

We can formulate the following problem: what is the probability of fluctuations of the vector

$$\mathcal{M} = (\mathcal{M}_{\mathbf{N}_1}, \mathcal{M}_{\mathbf{N}_2}, ...) \qquad (3.4)$$

of the numbers of different systems in the ensemble? By using a technique suggested by Ramakrishnan,[16] we can express the transition rates in the ensemble by the transition rates for a given system, defined by eq 2.12

$$\mathcal{W}(\mathcal{M} \to \mathcal{M}')\Delta t = \sum_{\mathbf{N},\mathbf{N}'\neq\mathbf{N}} \delta_{\mathcal{M}'(...,\mathcal{M}_\mathbf{N}+1,...,\ \mathcal{M}_{\mathbf{N}'}-1,...)}\mathcal{M}_\mathbf{N} W_{\mathbf{N}\mathbf{N}'}\Delta t \qquad (3.5)$$

Now we can introduce an ensemble probability distribution

$$\mathcal{G}(\mathcal{M},t|\mathcal{M}'t') \qquad \text{with} \qquad \sum_{\mathcal{M}} \mathcal{G}(\mathcal{M},t|\mathcal{M}'t') = 1 \quad (3.6)$$

which obeys the master equation

$$\frac{\partial}{\partial t}\mathcal{G}(\mathcal{M},t|\mathcal{M}'t') = \sum_{\mathcal{M}''} \mathcal{W}(\mathcal{M}''\to\mathcal{M})\,\mathcal{G}(\mathcal{M}'',t|\mathcal{M}'t') - \mathcal{G}(\mathcal{M},t|\mathcal{M}'t')\sum_{\mathcal{M}''}\mathcal{W}(\mathcal{M}\to\mathcal{M}'') \quad (3.7)$$

with the initial condition

$$\mathcal{G}(\mathcal{M},t=t'|\mathcal{M}',t') = \prod_{\mathbf{N}} \delta_{\mathcal{M}_\mathbf{N}\mathcal{M}'_\mathbf{N}} \qquad (3.8)$$

A detailed description of the ensemble statistics can be given in terms of the joint probabilities

$$\mathcal{B}_1(\mathcal{M},t) = \sum_{\mathcal{M}_0} \mathcal{G}(\mathcal{M},t|\mathcal{M}_0,t_0)\ \mathcal{B}_1(\mathcal{M}_0,t_0) \qquad (3.9)$$

$$\mathcal{B}_2(\mathcal{M}_2,t_2;\mathcal{M}_1,t_1) = \mathcal{G}(\mathcal{M}_2,t_2|\mathcal{M}_1,t_1)\ \mathcal{B}_1(\mathcal{M}_1,t_1), \quad \text{etc.} \qquad (3.10)$$

By introducing the generating function

$$\mathcal{L}(\mathbf{y}) = \sum_{\mathcal{M}} \mathcal{G}(\mathcal{M},t|\mathcal{M}',t')\prod_u (y_u)^{\mathcal{M}_{\mathbf{N}_u}} \qquad |y_u| \leq 1 \qquad (3.11)$$

we can reduce eq 3.7 to a first-order partial differential equation in $\mathcal{L}$. By solving this equation we come to

$$\mathcal{L}(\mathbf{y}) = \prod_{\forall \mathcal{M}'}\left\{\prod_{u'}\left[\sum_{\mathbf{N}_u} G(\mathbf{N}_u,t|\mathbf{N}'_{u'},t)y_u\right]^{\mathcal{M}'_{\mathbf{N}'_{u'}}}\right\} \qquad (3.12)$$

from which, we get the following expression for $\mathcal{G}(\mathcal{M},t|\mathcal{M}'t')$:

$$\mathcal{G}(\mathcal{M},t|\mathcal{M}'t') = \sum_{\forall m_{u\beta}\geq 0}\cdots\sum \prod_{\beta=1}^{\mathrm{O}}\left\{\mathcal{M}'_{\mathbf{N}'_{\beta}}!\prod_{u=1}^{\mathrm{O}}\left[\frac{(G(\mathbf{N}_u,t|\mathbf{N}'_{\beta},t'))^{m_{u\beta}}}{m_{u\beta}!}\right]\right\} \quad (3.13)$$

where O is the number of possible composition vectors and the sums over $m_{u\beta}$ obey two sets of constraints, which specify the final and initial values of the vector $\mathcal{M}$:

$$\mathcal{M}_{\mathbf{N}_u} = \sum_{\beta} m_{u\beta} \quad (3.14)$$

$$\mathcal{M}'_{\mathbf{N}'_{\beta}} = \sum_{u} m_{u\beta} \quad (3.15)$$

The dynamics of the reaction events can be described in a similar way. Denoting by $q_{\mathbf{NN}'}$ the number of reaction events of the type $\mathbf{N} \rightarrow \mathbf{N}'$ occurring in the ensemble in the time interval between t_0 and t, we can introduce the jump rates

$$\mathcal{W}^*(\mathcal{M},\mathbf{Q}\rightarrow\mathcal{M}',\mathbf{Q}')\Delta t = \sum_{\mathbf{N},\mathbf{N}'\neq\mathbf{N}} \delta_{\mathcal{M}'(\ldots,\mathcal{M}_{\mathbf{N}}+1,\ldots,\mathcal{M}_{\mathbf{N}'}-1,\ldots)}\,\delta_{(Q'_{\mathbf{NN}'}+1)Q_{\mathbf{NN}'}} \prod_{\mathbf{N};\mathbf{N}''\neq\mathbf{N}',\mathbf{N}} \{\delta_{Q'_{\mathbf{NN}''}Q_{\mathbf{NN}''}}\}\mathcal{M}_{\mathbf{N}}W_{\mathbf{NN}'}\Delta t \quad (3.16)$$

where

$$\mathbf{Q} = ||q_{\mathbf{N}_u\mathbf{N}_{u'}}|| \qquad u, u' = 1, \ldots, \mathrm{O} \quad (3.17)$$

The one-time joint probability of $\mathcal{M}$ and $\mathbf{Q}$, $\mathcal{B}^*_1(\mathcal{M},\mathbf{Q};t)$ obeys a master equation similar to eq 3.7

$$\frac{\partial}{\partial t}\mathcal{B}^*_1(\mathcal{M},\mathbf{Q};t) = \sum_{\mathcal{M}'',\mathbf{Q}''}[\mathcal{W}^*(\mathcal{M}'',\mathbf{Q}''\rightarrow\mathcal{M},\mathbf{Q})\mathcal{B}^*_1(\mathcal{M}'',\mathbf{Q}'';t) - \mathcal{W}^*(\mathcal{M},\mathbf{Q}\rightarrow\mathcal{M}'',\mathbf{Q}'')\,\mathcal{B}^*_1(\mathcal{M},\mathbf{Q};t)] \quad (3.18)$$

with the initial condition

$$\mathcal{B}^*_1(\mathcal{M},\mathbf{Q};t=t_0) = \delta_{\mathbf{Q0}}\mathcal{B}_1(\mathcal{M};t=t_0) \quad (3.19)$$

It is easy to show that the generating function of the joint probability $\mathcal{B}^*_1(\mathcal{M},\mathbf{Q};t)$,

$$\mathcal{L}^*(\mathbf{y},\mathbf{z}) = \sum_{\forall\mathcal{M},\mathbf{Q}} \mathcal{B}^*_1(\mathcal{M},\mathbf{Q};t)\prod_u (y_u)^{\mathcal{M}_{\mathbf{N}_u}}\prod_{u,u'}(z_{uu'})^{q_{\mathbf{N}_u\mathbf{N}_{u'}}} \qquad |y_u| \leq 1,\ |z_{uu'}| \leq 1 \quad (3.20)$$

is the solution of a partial differential equation, which can be solved analytically. After lengthy calculations we obtain (see ref 9 for a similar computation)

$$\mathcal{L}^*(\mathbf{y},\mathbf{z};t) = \sum_{\forall\mathcal{M}'}\mathcal{B}_1(\mathcal{M}',t_0)\left\{\prod_{u'}\left[\sum_{\mathbf{N}_u}G^*(\mathbf{z},\mathbf{N}_u,t|\mathbf{N}'_{u'},t_0)y_u\right]^{\mathcal{M}'_{\mathbf{N}'_{u'}}}\right\} \quad (3.21)$$

where the modified Green function $G^*(\mathbf{z},\mathbf{N}_u,t|\mathbf{N}'_{u'},t_0)$ obeys a master equation similar to eq 2.14

$$\frac{\partial}{\partial t}G^*(\mathbf{z},\mathbf{N}_u,t|\mathbf{N}'_{u'},t') = \sum_{\mathbf{N}_{u''}\neq\mathbf{N}_u}[z_{u''u}W_{\mathbf{N}_{u''}\mathbf{N}_u}G^*(\mathbf{z},\mathbf{N}_{u''},t|\mathbf{N}'_{u'},t') - W_{\mathbf{N}_u\mathbf{N}_{u''}}G^*(\mathbf{z},\mathbf{N}_u,t|\mathbf{N}'_{u'},t')] \quad (3.22)$$

with the initial condition

$$G^*(\mathbf{z},\mathbf{N}_u,t=t'|\mathbf{N}'_{u'},t') = \delta_{\mathbf{N}_u\mathbf{N}_{u'}} \quad (3.23)$$

Although in general we cannot derive an explicit analytical expression for the joint probability $\mathcal{B}^*_1(\mathcal{M},\mathbf{Q};t)$, the stochastic properties of the numbers of reaction events can be derived from eqs 3.21−3.23.

In conclusion, in this section we have developed a statistical ensemble approach for the study of concentration fluctuations in complex chemical systems. We have derived an ensemble master equation that describes the stochastic properties of the numbers of replicas of the system characterized by different composition vectors. We have derived an analytical solution of the ensemble master equations, which depends on the Green functions attached to the one-system master equation.

4. Mesoscopic Time Reversal

In statistical mechanics, the condition of microscopic time reversal[10−12] (microscopic reversibility) expresses the invariance of the microscopic equations of evolution with respect to the changing of the sign of the time variable. For systems without solenoidal fields, the application of the condition of time reversal leads to the conditions of detailed balance, which states that for each direct process, there is a reverse process and that at equilibrium the rate of each direct process equals the rate of the reverse process. For example, in the case of the reduced reactions (2.3) there are R conditions of detailed balance (eqs 2.18).

Within the framework of our model, the description of concentration fluctuations is not based on a microscopic description, but rather on a mesoscopic description, in terms of the ensemble master equation (3.7). If we impose that the ensemble master equation (3.7) is invariant with respect to the change of the sign of the time variable, we obtain a new condition of time reversal, which is less restrictive than microscopic reversibility. We suggest the name of "mesoscopic reversibility" for this new type of condition of time reversal. Unlike microscopic reversibility, the condition of mesoscopic reversibility is not introduced for equilibrium but for a stationary stochastic state that is generally far from equilibrium. For mesoscopic reversibility, the condition of time reversal is generally an assumption rather than a consequence of the underlying microscopic dynamics. The main reason for which we introduce the condition of mesoscopic reversibility is that it provides a useful reference state that may serve as the starting point of our calculations.

For a chemical system, mesoscopic reversibility is less restrictive than microscopic reversibility, in the sense that it imposes fewer constraints on the system. For example, for chemical systems described by the reduced reactions (2.3), microscopic reversibility leads to R conditions of detailed balance, eqs 2.18, one condition for each reduced reaction (2.3). Mesoscopic reversibility leads to a smaller number of restrictions, $L \leq R$, which requires the equality of the forward and backward rates (2.10) of the L lumped reactions, which can be derived from the R reduced reactions (2.3)

$$\rho_i^+ = \rho_i^- \qquad \text{i.e.} \qquad \sum_{\alpha} r^+_{i_\alpha} = \sum_{\alpha} r^-_{i_\alpha} \qquad i = 1, \ldots, L \leq R \quad (4.1)$$

In the following we refer to the conditions of type (4.1) as to semidetailed (mesoscopic) balance. The difference between detailed and semidetailed balance can be illustrated by considering the Schlögl model, eqs 2.7 and 2.8. For this model, detailed balance provides two conditions:

$$r_1^+ = r_1^-, r_2^+ = r_2^- \tag{4.2}$$

whereas semidetailed (mesoscopic) balance provides only one condition:

$$r_1^+ + r_2^+ = r_1^- + r_2^- \tag{4.3}$$

Concerning the possible existence of mesoscopic time reversal in real systems, we notice that all systems that obey microscopic reversibility also obey mesoscopic reversibility but the reverse statement is generally not true. One-variable nonequilibrium systems, such as the Schlögl model, obey the condition of mesoscopic reversibility for any nonequilibrium steady state, but microscopic reversibility is fulfilled only at chemical equilibrium. Multivariable chemical systems far from equilibrium obey mesoscopic reversibility only in special cases, which are nongeneric. Although for multivariable chemical systems far from equilibrium the occurrence of mesoscopic reversibility is rather rare, its study is useful, because it provides a reference state, which is the starting point of our calculations.

In this section we investigate the implications of mesoscopic reversibility for the statistical ensemble representation of a complex chemical process developed in section 3. We shall customize the methods used in the literature for the study of microscopic reversibility[10−12] for the statistical ensemble description of a multivariable chemical system far from equilibrium that obeys the condition of mesoscopic time reversal.

The general relationships presented in section 3 are valid even if the transition rates (i.e., the effective rate coefficients $\kappa_i^\pm$ or the concentrations of the stable intermediates A_j) are time-dependent. In most cases analyzed in the literature, however, one assumes that effective rate coefficients $\kappa_i^\pm$ are time-invariant and that the numbers of stable species are held constant. In this case a stationary probability distribution eventually emerges provided that all composition vectors are connected, that is, if for any two composition vectors $\mathbf{N}$ and $\mathbf{N}'$ there are at least two paths $\mathbf{N} \to \mathbf{N}_1 \to ... \to \mathbf{N}'$ and $\mathbf{N}' \to \mathbf{N}_1' \to ... \to \mathbf{N}$ for which the corresponding rates are different from zero. We have

$$P_1(\mathbf{N},t),\ G(\mathbf{N},t|\mathbf{N}',t') \to P_1^{\text{st}}(\mathbf{N}) \qquad \text{as} \qquad t \to \infty \tag{4.4}$$

$$P_2(\mathbf{N},t;\mathbf{N}';t') \to G(\mathbf{N},t - t'|\mathbf{N}';0)\ P_1^{\text{st}}(\mathbf{N}) \qquad \text{as} \quad t \to \infty, \text{etc.} \tag{4.5}$$

where $P_1^{\text{st}}(\mathbf{N})$ is independent of time and of the initial state of the system and $G(\mathbf{N},t-t'|\mathbf{N}';0)$ depends on $\mathbf{N},\mathbf{N}'$ and on the time difference $t - t'$. Such stationary probability distributions exist even if the corresponding system of deterministic equations does not have stationary solutions, for example, in the case of a stable limit cycle. In the literature there are many proofs of eqs 4.4 and 4.5 based on the Perron−Frobenius theorem, on the use of H-functions,[17] etc. These proofs rely on the fact that the total number O of composition vectors, although possibly very large, is however finite.

From eqs 3.9, 3.l0, and 3.13 we notice that the asymptotic property expressed by eqs 4.4 and4.5 leads to a similar property for the ensemble probability distributions

$$B_1(M,t),\ G(M,t|M',t') \to B_1^{\text{st}}(M) \qquad \text{as} \qquad t \to \infty \tag{4.6}$$

$$B_2(M,t;M',t') \to G(M,t - t'|M',0) B_1^{\text{st}}(M) \qquad \text{as} \quad t \to \infty, \text{etc.} \tag{4.7}$$

where

$$B_1^{\text{st}}(M) = \frac{M_\Sigma!}{M_{\mathbf{N}_1}!...M_{\mathbf{N}_\text{O}}!} \prod_{u=1}^{\text{O}} [P_1^{\text{st}}(\mathbf{N}_u)]^{M_{\mathbf{N}_u}} \tag{4.8}$$

and the ensemble Green function $G(M,t-t'|M',0)$ is given by eq 3.13 applied for the particular case where the canonical Green function $G(\mathbf{N},t|\mathbf{N}',t')$ is time-invariant:

$$G(\mathbf{N},t|\mathbf{N}',t') = G(\mathbf{N},t-t'|\mathbf{N}',0) \tag{4.9}$$

These equations may be used to evaluate the stochastic properties of the numbers $M_{\mathbf{N}_1}$, ..., $M_{\mathbf{N}_\text{O}}$ of systems characterized by different composition vectors in the stationary regime. In particular we get the following expressions for the moments of first and second order

$$\langle M_{\mathbf{N}_u}(t)\rangle^{\text{st}} = M_\Sigma P_1^{\text{st}}(\mathbf{N}_u) \tag{4.10}$$

$$\langle \Delta M_{\mathbf{N}_u}(t)\ \Delta M_{\mathbf{N}_{u'}}(t')\rangle^{\text{st}} = M_\Sigma P_1^{\text{st}}(\mathbf{N}_{u'})[G(\mathbf{N}_u,t-t'|\mathbf{N}_{u'},0) - P_1^{\text{st}}(\mathbf{N}_u)] \tag{4.11}$$

Now we introduce the condition of mesoscopic reversibility by requiring that

$$\langle \Delta M_{\mathbf{N}_u}(t)\ \Delta M_{\mathbf{N}_{u'}}(t')\rangle^{\text{st}} = \langle \Delta M_{\mathbf{N}_{u'}}(t)\ \Delta M_{\mathbf{N}_u}(t')\rangle^{\text{st}} \qquad \text{for all } \mathbf{N}_u, \mathbf{N}_{u'} \tag{4.12}$$

Equations 4.11 and 4.12 are simultaneously fulfilled only if

$$G(\mathbf{N},t - t'|\mathbf{N}';0)\ P_1^{\text{st}}(\mathbf{N}') = G(\mathbf{N}',t - t'|\mathbf{N};0)\ P_1^{\text{st}}(\mathbf{N}) \tag{4.13}$$

To investigate the significance of the condition of mesoscopic reversibility (4.13), we shall try to express it in terms of the transition rates $W_{\mathbf{NN}'}$. For simplicity we attach to each vector $\mathbf{N}$ a label u and use matrix notation. We have

$$\mathbf{N} \to u, \quad \mathbf{N}' \to u'; \quad P(\mathbf{N},t) \to P_u(t); \quad G(\mathbf{N},t|\mathbf{N}',t') \to G_{u'u}(t-t') \tag{4.14}$$

The time reversal condition (4.13) may be rewritten as

$$\boldsymbol{\sigma}\mathbf{G} = \mathbf{G}^+\boldsymbol{\sigma} \tag{4.15}$$

where

$$\mathbf{G} = ||G_{uu'}|| \qquad \boldsymbol{\sigma} = ||\delta_{uu'}P_\text{u}^{\text{st}}|| \tag{4.16}$$

On the other hand, the master equation (2.14) becomes

$$\text{d}\mathbf{G}(t)/\text{d}t = \mathbf{G}(t)(\mathbf{W} - \mathbf{\Omega}) \qquad \text{with} \qquad \mathbf{G}(t{=}0) = \mathbf{I} \tag{4.17}$$

where

$$\mathbf{W} = ||W_{uu'}|| \qquad W_{uu} = 0 \tag{4.18}$$

and

$$\mathbf{\Omega} = \left|\left|\delta_{uu'}\sum_{u''} W_{uu''}\right|\right| \tag{4.19}$$

The formal solution of eq 4.17 is

$$\mathbf{G}(t) = \exp\{t(\mathbf{W} - \boldsymbol{\Omega})\} \tag{4.20}$$

By taking the time derivative of eq 4.15 at the point $t = 0$ and using eq 4.20, we come to

$$\boldsymbol{\sigma}(\mathbf{W} - \boldsymbol{\Omega}) = (\mathbf{W}^{+} - \boldsymbol{\Omega})\boldsymbol{\sigma} \tag{4.21}$$

The diagonal terms on both sides of eq 4.21 are equal to zero; the off-diagonal terms lead to

$$W_{\mathbf{N}'\mathbf{N}} P_1^{\mathrm{st}}(\mathbf{N}') = W_{\mathbf{N}\mathbf{N}'} P_1^{\mathrm{st}}(\mathbf{N}) \tag{4.22}$$

Equation 4.22 or its matrix version (4.21) is equivalent to the time-reversal condition (4.12)−(4.13). To prove that we evaluate the general term in the expansion

$$\boldsymbol{\sigma}\mathbf{G} = \sum_{m=0}^{\infty} \frac{t^m}{m!} \boldsymbol{\sigma}(\mathbf{W} - \boldsymbol{\Omega})^m \tag{4.23}$$

By using eq 4.21 repeatedly we come to

$$\boldsymbol{\sigma}(\mathbf{W} - \boldsymbol{\Omega})^m = (\mathbf{W} - \boldsymbol{\Omega})^{+}\boldsymbol{\sigma}(\mathbf{W} - \boldsymbol{\Omega})^{m-1} = ... = [(\mathbf{W} - \boldsymbol{\Omega})^{+}]^m\, \boldsymbol{\sigma} = (\mathbf{W}^{+} - \boldsymbol{\Omega})^m\, \boldsymbol{\sigma} \tag{4.24}$$

By combining eqs 4.23 and 4.24, we recover eq 4.15.

Equation 4.15 has an important consequence: there is a similarity transformation of $\mathbf{W} - \boldsymbol{\Omega}$ that leads to a symmetric matrix

$$\boldsymbol{\sigma}^{1/2}(\mathbf{W} - \boldsymbol{\Omega})\sigma^{-1/2} = [\boldsymbol{\sigma}^{1/2}(\mathbf{W} - \boldsymbol{\Omega})\boldsymbol{\sigma}^{-1/2}]^{+} \tag{4.25}$$

and thus the eigenvalues of $\mathbf{W} - \boldsymbol{\Omega}$ are all real and the determination of the Green function G reduces, at least in principle, to an expansion in eigenfunctions.[10−12]

Now we introduce the thermodynamic limit

$$X_i,\ V \to \infty \qquad \text{with} \qquad \forall x_i = X_i/V \text{ constant} \tag{4.26}$$

We define a scaled probability distribution

$$P_1(\mathbf{N},t)\Delta\mathbf{N} = \tilde{P}(\mathbf{x},t)\,\mathrm{d}\mathbf{x} \qquad \text{with} \qquad \Delta\mathbf{N} = [1] \tag{4.27}$$

and use a method due to Kubo, Matsuo, and Kitahara (KMK[18]). In the thermodynamic limit we can write the master equation for $\tilde{P}(\mathbf{x},t)$ in a form similar to a Schrödinger equation

$$\frac{\partial}{\partial t}\tilde{P}(\mathbf{x},t) = -\mathrm{H}(\mathbf{x},V^{-1}\nabla_{\mathbf{x}})\tilde{P}(\mathbf{x},t) \tag{4.28}$$

where the Hamiltonian operator $\mathrm{H}(\mathbf{x},V^{-1}\nabla_{\mathbf{x}})$ is given by

$$\mathrm{H}(\mathbf{x},V^{-1}\nabla_{\mathbf{x}}...) = \sum_{b=1;\pm}^{b=L}\left\{1 - \exp\left[\mp V^{-1}\sum_j f_{jb}\frac{\partial}{\partial x_j}\right]\right\}\tilde{\rho}_b^{\pm}(\mathbf{x}) \tag{4.29}$$

The quantities $\tilde{\rho}_b^{\pm}(\mathbf{x})$ are the scaled forms of the reaction rates (2.10) in the thermodynamic limit

$$\rho_b^{\pm} \sim V\tilde{\rho}_b^{\pm}(\mathbf{x}) = V\sum_{\alpha}\tilde{r}_{b\alpha}^{\pm}(\mathbf{x}) \qquad \text{as} \qquad V \to \infty \tag{4.30}$$

with

$$\tilde{r}_{b\alpha}^{\pm}(\mathbf{x}) = \tilde{\kappa}_b^{\pm}\prod_{j=1}^{S_2}(x_j)^{\beta_{jb}^{\pm}} \tag{4.31}$$

and

$$\tilde{\kappa}_b^{\pm} = k_b^{\pm}\prod_{j=1}^{S_1}(A_j/V)^{\alpha_{jb}} \tag{4.32}$$

We look for a stationary solution

$$\tilde{P}^{\mathrm{st}}(\mathbf{x}) \sim \exp\{VJ(\mathbf{x})\} \qquad \text{as} \qquad V \to \infty \tag{4.33}$$

where the stationary action $J(\mathbf{x})$ is volume-independent

$$J(\mathbf{x}) \sim V^0 \tag{4.34}$$

We insert eq 4.33 into eq 4.28 and keep the dominant terms in V. We come to a stationary Hamilton−Jacobi equation in $J(\mathbf{x})$

$$\mathrm{H}(\mathbf{x},\nabla_{\mathbf{x}}J(\mathbf{x})) = 0 \tag{4.35}$$

In the thermodynamic limit the condition of mesoscopic reversibility (4.22) can be written in a form similar to eq 4.35. We note that to each pair of transitions $\mathbf{N} \to \mathbf{N}'$ and $\mathbf{N}' \to \mathbf{N}$ there corresponds a single reduced reaction (2.6). By using eqs 2.12, 4.33, and 4.34, the conditions (4.22) of mesoscopic reversibility become

$$\mathrm{H}_b(\mathbf{x},\nabla_{\mathbf{x}}J(\mathbf{x})) = 0 \qquad b = 1,2,...,L \tag{4.36}$$

where

$$\mathrm{H}_b(\mathbf{x},V^{-1}\nabla_{\mathbf{x}}...) = \sum_{\pm}\left\{1 - \exp\left[\mp V^{-1}\sum_j f_{jb}\frac{\partial}{\partial x_j}\right]\right\}\tilde{\rho}_b^{\pm}(\mathbf{x}) \tag{4.37}$$

is the contribution of the bth reduced reaction (2.6) to the Hamiltonian (4.36). We have

$$\mathrm{H}(\mathbf{x},V^{-1}\nabla_{\mathbf{x}}...) = \sum_{b=1}^{b=L}\mathrm{H}_b(\mathbf{x},V^{-1}\nabla_{\mathbf{x}}...) \tag{4.38}$$

Thus, the mesoscopic reversibility implies that not only the total Hamiltonian of the system expressed in terms of the chemical action is equal to zero for a stationary solution, but also each individual contribution of the reduced reaction to the Hamiltonian must be equal to zero.

Equation 4.36 are quadratic equations in the functions

$$C_b = \exp\left(\sum_u f_{ub}\frac{\partial J(\mathbf{x})}{\partial x_u}\right) \tag{4.39}$$

By solving these equations in C_b and keeping the physically significant solutions, we get a set of first-order partial differential equations in $J(\mathbf{x})$

$$\sum_u f_{ub}\frac{\partial J(\mathbf{x})}{\partial x_u} = \ln\left[\frac{\tilde{\rho}_b^{+}}{\tilde{\rho}_b^{-}}\right] \qquad b = 1, ..., L \tag{4.40}$$

The equations (4.40) are redundant: we have many equations for only one unknown function. This fact shows clearly that the mesoscopic reversibility is not generally valid: it holds only if among the different reaction rates $\tilde{r}_b^{\pm}$ there are some relationships so that the different solutions of eqs 4.40 are equivalent to each other.

Each of the eqs 4.40 can be solved analytically. They are first-order partial differential equations and for this type of equations the general solution is related to the solution of the system of characteristic equations

$$\frac{\mathrm{d}x_1}{f_{1b}} = ... = \frac{\mathrm{d}x_{S_2}}{f_{S_2b}} = \frac{\mathrm{d}J}{\ln[\tilde{\rho}_b^+/\tilde{\rho}_b^-]} \qquad i = 1, ..., S_2; \quad b = 1, ..., L \tag{4.41}$$

The solution of each of the L equations (4.40) can be represented implicitly as an arbitrary function of the integrals of motion of the system of characteristic equations (4.41). Considering a set of characteristic equations (4.41) for a given b, we note that the first $S_2 - 1$ equations

$$\mathrm{d}x_1/f_{1b} = ... = \mathrm{d}x_{S_2}/f_{S_2b} \tag{4.42}$$

define a straight line in the concentration space. Introducing a coordinate ξ_b along this straight line, we have

$$\mathrm{d}\xi_b = \mathrm{d}x_1/f_{1b} = ... = \mathrm{d}x_{S_2}/f_{S_2b} \tag{4.43}$$

ξ_b is the intensive reaction extent attached to the bth reduced reaction. Considering the effect of all reactions, we notice that the concentration vector $\mathbf{x}(t)$ will not move along a straight line, but in an L-dimensional subspace of the concentration space. We have

$$x_u = x_u(0) + \sum_b f_{ub}\xi_b \tag{4.44}$$

Now the necessary and sufficient conditions for the validity of mesoscopic reversibility are clear. Equations 4.40, which are equivalent to the mesoscopic reversibility, provide a set of expressions for the partial derivatives of chemical action with respect to the reaction extents. In order that these partial derivatives are generated by the same expression of the chemical action $J = J(\mathbf{x}) = J(\mathbf{x}(\xi))$, it is necessary and sufficient that

$$\frac{\partial}{\partial \xi_{b_2}}\left\{\ln\left[\frac{\tilde{\rho}_{b_1}^+(\xi)}{\tilde{\rho}_{b_1}^-(\xi)}\right]\right\} = \frac{\partial}{\partial \xi_{b_1}}\left\{\ln\left[\frac{\tilde{\rho}_{b_2}^+(\xi)}{\tilde{\rho}_{b_2}^-(\xi)}\right]\right\} \qquad b_1, b_2 = 1, ..., L \tag{4.45}$$

These conditions ensure that the expressions (4.40) are the derivatives of a potential; they are an alternative form of the condition of mesoscopic reversibility. Indeed, starting from equations 4.45 and 4.33, we can recover eq 4.28 and then eq 4.22. If the conditions (4.45) are fulfilled, then the evaluation of the chemical action reduces to a path integration. The path can be arbitrary; however, the simplest choice is

$$(\xi_1(0), ..., \xi_L(0)) \rightarrow (\xi_1, ..., \xi_L(0)) \rightarrow (\xi_1, \xi_2, ..., \xi_L(0)) \rightarrow ... \rightarrow (\xi_1, ..., \xi_L) \tag{4.46}$$

By using the path (4.46) we get

$$J(\xi) = J(\xi(0)) + \int_{\xi_1(0)}^{\xi_1} \ln\left[\frac{\tilde{\rho}_{b_2}^+(\xi_1,\xi_2(0),...,\xi_L(0))}{\tilde{\rho}_{b_2}^-(\xi_1,\xi_2(0),...,\xi_L(0))}\right] \mathrm{d}\xi_1 + ... + \int_{\xi_L(0)}^{\xi_L} \ln\left[\frac{\tilde{\rho}_{b_2}^+(\xi_1,\xi_2,...,\xi_L)}{\tilde{\rho}_{b_2}^-(\xi_1,\xi_2,...,\xi_L)}\right] \mathrm{d}\xi_L \tag{4.47}$$

It follows that for a system with mesoscopic reversibility the state probability can be evaluated analytically in the thermodynamic limit. In terms of the reaction extents, we have

$$\tilde{P}^{\mathrm{st}}(\xi) = B \exp[VJ(\xi)] \qquad \text{as} \qquad V \rightarrow \infty \tag{4.48}$$

where B is a normalization factor

$$B = \{\int \exp[VJ(\xi)]\, \mathrm{d}\xi\}^{-1} \tag{4.49}$$

In terms of concentrations, we have

$$\tilde{P}^{\mathrm{st}}(\mathbf{x}) = \int_\xi \prod_u \delta(x_u - x_u(0) - \sum_b f_{ub}\xi_b)\tilde{P}^{\mathrm{st}}(\xi)\, \mathrm{d}\xi = \int_\xi \prod_u \delta(x_u - x_u(0) - \sum_b f_{ub}\xi_b) \exp[VJ(\xi)]\, \mathrm{d}\xi \Big/ \int_\xi \exp[VJ(\xi)]\, \mathrm{d}\xi \tag{4.50}$$

These equations allow us to clarify the relations between the condition of mesoscopic reversibility used in this article and semidetailed (mesoscopic) balance. The macroscopic steady states correspond to the maximum values of P_1^{st}, that is, to the maximum values of the chemical action J. The stationarity condition for J

$$\mathrm{d}J = \sum_b (\partial J/\partial \xi_b)\, \mathrm{d}\xi_b = 0 \tag{4.51}$$

implies that

$$\tilde{\rho}_b^+ = \tilde{\rho}_b^- \qquad b = 1, ..., L \tag{4.52}$$

This condition is less restrictive than the condition of detailed balance (eq 2.18), which requires that all forward and backward individual processes making up a lumped reduced reaction are equal to each other, respectively.

For a given steady state $\mathbf{x}_\mathrm{s}$ (or ξ_s) the difference $\Delta J = J(\xi) - J(\xi_\mathrm{s})$ is a Lyapunov function of the macroscopic evolution equations

$$\mathrm{d}\xi_b/\mathrm{d}t = \tilde{\rho}_b^+ - \tilde{\rho}_b^- \qquad b = 1, ..., L \tag{4.53}$$

for the domain of attraction of ξ_s. The proof of this property is straightforward. For a stable steady state ξ_s, the state probability and the chemical action have a local maximum and therefore

$$\Delta J < 0 \quad \text{for} \quad \xi \neq \xi_\mathrm{s}; \qquad \Delta J = 0 \quad \text{for} \quad \xi = \xi_\mathrm{s} \tag{4.54}$$

On the other hand by using eqs 4.45 and 4.53, we have

$$\Delta\dot{J} = \sum_b (\tilde{\rho}_b^+ - \tilde{\rho}_b^-) \ln(\tilde{\rho}_b^+/\tilde{\rho}_b^-) \tag{4.55}$$

from which we get

$$\Delta\dot{J} > 0 \quad \text{for} \quad \xi \neq \xi_s; \qquad \Delta\dot{J} = 0 \quad \text{for} \quad \xi = \xi_\mathrm{s} \tag{4.56}$$

The formulation (4.45) of mesoscopic reversibility has an advantage: unlike the alternative formulations (4.36) or (4.22), it can be easily checked. Given a particular model we should express the rates $\tilde{\rho}_b^\pm$ in terms of the reaction extents ξ_b and verify whether the partial derivatives (4.45) are equal to each other. By expressing the conditions (4.45) in terms of concentrations we come to

$$\sum_u f_{b_1u}\frac{\partial}{\partial x_u}\ln\left[\frac{\tilde{\rho}_{b_2}^+}{\tilde{\rho}_{b_2}^-}\right] = \sum_u f_{b_2u}\frac{\partial}{\partial x_u}\ln\left[\frac{\tilde{\rho}_{b_1}^+}{\tilde{\rho}_{b_1}^-}\right] \tag{4.57}$$

By recalling the definition of the lumped rates $\tilde{\rho}_b^{\pm}$ (4.30) we notice that eq 4.57 is automatically fulfilled at least in two cases.

1. For each distinct reduced reaction (2.6) the corresponding reaction rates $\tilde{\rho}_b^{\pm}$ depend only on one concentration of the active intermediates, denoted by x_{u_b}

$$\tilde{\rho}_b^{\pm} = \tilde{\rho}_b^{\pm}(x_{u_b}) \tag{4.58}$$

and is independent of the other concentrations $x_{u_{b'}}$, $b' \neq b$, which enter the expressions of other reduced reactions. A special case corresponds to the condition $S_2 = L$ and $u_b \neq u_{b'}$ for $b \neq b'$. This situation is fulfilled when the elementary processes corresponding to a lumped reduced reaction with a given label b involve only the intermediate x_{u_b}. In this case in eq 4.57 both sums are equal to zero. As the number L of reaction extents is the same as the number S_2 of reaction intermediates, the passage from reaction extents to concentrations and vice versa is very easy. By applying eq 4.47 we get

$$J(\mathbf{x}) = J(\mathbf{x}(0)) + \sum_b \int_{x_{u_b}(0)}^{x_{u_b}} \ln\left[\frac{\tilde{\rho}_b^{+}(x_{u_b})}{\tilde{\rho}_b^{-}(x_{u_b})}\right] \mathrm{d}x_{u_b} \tag{4.59}$$

In particular, for $L = 1$ eq 4.59 reduces to an equation derived by Ross, Hunt, and Hunt for one-variable open chemical systems.

2. A lumped reduced reaction 2.6 is made up either of a unique autocatalytic reaction or of multiple noncatalytic reactions with the same stoichiometric coefficients $\beta_{ub}^{\pm}$ of the active intermediates and with possible different stoichiometric coefficients $\alpha_{ub_q}^{\pm}$ for the stable substances. In this case the ratios of lumped rates can be written in the form

$$\tilde{\rho}_b^{+}/\tilde{\rho}_b^{-} = \mathrm{W}_b \prod_u (x_u)^{f_{ub}} \tag{4.60}$$

where

$$\mathrm{W}_b = \kappa_b^{+}/\kappa_b^{-} \tag{4.61}$$

for autocatalytic processes and

$$\mathrm{W}_b = \left(\sum_a \kappa_{b_a}^{+}\right) \Big/ \left(\sum_a \kappa_{b_a}^{-}\right) \tag{4.62}$$

for nonautocatalytic processes. By inserting eq 4.60 into eq 4.57 we get

$$\sum_u f_{ub_1} f_{ub_2}/x_u = \sum_u f_{ub_2} f_{ub_1}/x_u \tag{4.63}$$

which is an identity. The line integral (4.47) can be evaluated analytically. After some calculations we get

$$\begin{aligned} J(\xi) = J(\xi(0)) + {} & \\ \sum_u \left(x_u(0) + \sum_b f_{ub}\xi_b\right) & \left[\ln\left(1 + \sum_b ((f_{ub}\xi_b)/x_u(0))\right)\right] + \\ & \sum_b \xi_b \left\{\ln\left[\mathrm{W}_b \prod_u (x_u(0)) f^{ub}\right]\right\} \end{aligned} \tag{4.64}$$

Here we use the convention that the initial integration point is the reference concentration vector $\mathbf{x}(0)$ with respect to which the reaction extents are evaluated. This convention corresponds to

$$\xi(0) = \mathbf{0} \tag{4.65}$$

In particular, if $\mathbf{x}(0) = \mathbf{x}_s$, where $\mathbf{x}_s$ is the composition vector corresponding to a steady state, we have

$$\mathrm{W}_b \prod_u ((x_s)_u)^{f_{ub}} = 1 \tag{4.66}$$

and we get the following expression for the Lyapunov function $\Delta J(\xi)$

$$\begin{aligned} \Delta J(\xi) = \sum_u \left(x_u(0) + \sum_b f_{ub}\xi_b\right) \times & \\ \left[\ln\left(1 + \sum_b ((f_{ub}\xi_b)/x_u(0))\right) - 1\right] & \end{aligned} \tag{4.67}$$

The main results obtained in this section are the following. We have used the statistical ensemble approach for investigating the implications of the condition of mesoscopic time reversal. We have shown that the time reversal condition leads to a condition of semidetailed balance for the probability fluxes, which connect two different states of the statistical ensemble. We have made a connection between these semidetailed balance conditions and the eikonal approximation of the solutions of the one-system master equations in the thermodynamic limit. We obtained an analytical solution for the stochastic stationary solution of the one-system master equation for systems with semidetailed balance in the thermodynamic limit. Further implications of mesoscopic reversibility, related to the statistics of reaction events, are investigated in the following section.

5. Statistics of Reaction Events

In this section we discuss the ensemble statistics in terms of the number of reaction events.[19] The purpose of our analysis is to investigate the differences between systems with or without mesoscopic reversibility and to use these results for the development of a set of multivariable master equations. We have shown in section 3 that the dynamics of the reaction events is described by a modified Green function $G^*(\mathbf{z},\mathbf{N}_u,t|\mathbf{N}'_{u'},t_0)$, which is the solution of eqs 3.22 and 3.23. In matrix notation eqs 3.22 and 3.23 become

$$\mathrm{d}\mathbf{G}^*/\mathrm{d}t = \mathbf{G}^*(\mathbf{W} - \mathbf{\Omega}) + \mathbf{G}^*\mathbf{E} \tag{5.1}$$

with the initial condition

$$\mathbf{G}^*(0) = \mathbf{I} \tag{5.2}$$

where

$$\mathrm{G}^* = ||G^*_{bb'}|| \qquad \mathbf{E} = ||W_{bb'}(z_{bb'} - 1)|| \qquad E_{bb} = 0 \tag{5.3}$$

It is easy to check that the solution of eq 5.1 with the initial condition (5.2) is also the unique solution of the integral equation

$$\mathbf{G}^*(t) = \mathbf{G}(t) + \int_0^t \mathbf{G}^*(t')\,\mathbf{E}\mathbf{G}(t-t')\,\mathrm{d}t' \tag{5.4}$$

The exact perturbative solution of eq 5.4 is

$$\mathbf{G}^*(t) = \mathbf{G}(t) + \sum_{q=1}^{\infty} \underbrace{\{[\mathbf{G}(t)\mathbf{E}] \otimes \cdots \otimes [\mathbf{G}(t)\mathbf{E}]\}}_{q \text{ times}} \otimes \mathbf{G}(t) \tag{5.5}$$

where $\otimes$ denotes the temporal convolution product. The series (5.5) has an important property; the qth term contains the matrix $\mathbf{E}$ q times and thus it is a homogeneous function of qth order in $z_{bb'} - 1$. It follows that this term determines completely the derivatives of qth order of $\mathbf{G}^*(t)$ with respect to the variables

$z_{bb'}$ in the point $z_{bb'} - 1$. By evaluating these derivatives, we can compute, at least in principle (cf. eqs 3.20 and 3.21), the values of all the moments of the reaction events. In particular, we get the following expressions for the moments of first and second order of the number of reaction events in stationary conditions:

$$\langle q_{bm}(t)\rangle = tM_{\Sigma}P_1^{\mathrm{st}}(b)W_{bm} \tag{5.6}$$

$$\begin{aligned}\langle \Delta q_{b_1m_1}(t)\Delta q_{b_2m_2}(t)\rangle = {} & tM_{\Sigma}P_1^{\mathrm{st}}(b_1)W_{b_1m_1}(\delta_{b_1b_2}\delta_{m_1m_2} - tP_1^{\mathrm{st}}(b_2)W_{b_2m_2}) + \\ & M_{\Sigma}W_{b_1m_1}W_{b_2m_2}\int_0^t (t-t')[P_1^{\mathrm{st}}(b_1)\, G_{m_1b_2}(t') + \\ & P_1^{\mathrm{st}}(b_2)\, G_{m_2b_1}(t')]\, \mathrm{d}t'\end{aligned} \tag{5.7}$$

We consider a given reduced reaction (2.6) and two composition vectors $\mathbf{N}_b$ and $\mathbf{N}_m = \mathbf{N}_b + \mathbf{f}_b$ and evaluate with the help of eqs 5.7 the correlations between the forward and backward reaction events

$$\begin{aligned}\langle (\Delta q_{bm}(t))^2\rangle = {} & tM_{\Sigma}P_1^{\mathrm{st}}(b)W_{bm}(1 - tP_1^{\mathrm{st}}(b)W_{bm}) + \\ & 2M_{\Sigma}(W_{bm})^2 \int_0^t (t-t')P_1^{\mathrm{st}}(b)\, G_{mb}(t')\, \mathrm{d}t'\end{aligned} \tag{5.8}$$

$$\begin{aligned}\langle \Delta q_{bm}(t)\, \Delta q_{mb}(t)\rangle = {} & -t^2M_{\Sigma}P_1^{\mathrm{st}}(b)W_{bm}P_1^{\mathrm{st}}(m)W_{mb} + \\ & M_{\Sigma}W_{bm}W_{mb}\int_0^t (t-t')[P_1^{\mathrm{st}}(b)\, G_{mb}(t') + P_1^{\mathrm{st}}(m)\, G_{bm}(t')]\, \mathrm{d}t'\end{aligned} \tag{5.9}$$

$$\begin{aligned}\langle (\Delta q_{mb}(t))^2\rangle = {} & tM_{\Sigma}P_1^{\mathrm{st}}(m)W_{mb}(1 - tP_1^{\mathrm{st}}(m)W_{mb}) + \\ & 2M_{\Sigma}(W_{mb})^2\int_0^t (t-t')P_1^{\mathrm{st}}(m)\, G_{bm}(t')\, \mathrm{d}t'\end{aligned} \tag{5.10}$$

If mesoscopic reversibility does not exist, then the dispersions of the forward and backward reaction events are generally different. Mesoscopic reversibility leads to the equality between the two dispersions. This fact suggests that the mesoscopic reversibility is characterized by an extremum condition. A simplified analysis of this effect is possible by evaluating the number of reaction events occurring in a time interval Δt that is smaller than the chemical relaxation time of the system, τ_{ch}:

$$\Delta t \ll \tau_{\mathrm{ch}} \tag{5.11}$$

but large enough so that the total number of reaction events is a large number

$$\langle q\rangle = \sum_b\sum_{m\neq b}\langle q_{bm}\rangle = \Delta tM_{\Sigma}\sum_b\sum_{m\neq b}P_1^{\mathrm{st}}(b)W_{\mathrm{bm}} \gg 1 \tag{5.12}$$

The total number of replicas (systems) in the ensemble is assumed to be much bigger than the total number of reaction events

$$M_{\Sigma} \gg \langle q\rangle \gg 1 \tag{5.13}$$

The restrictions (5.11)−(5.13) are consistent with each other. The sum $\sum_b\sum_{m\neq b}P_1^{\mathrm{st}}(b)W_{bm}$ in eq 5.12 is smaller than the reciprocal value of the chemical relaxation time, $1/\tau_{\mathrm{ch}}$, and thus from eqs 5.11 and 5.12 it follows that

$$\langle q\rangle/M_{\Sigma} < \Delta t/\tau_{\mathrm{ch}} \ll 1 \tag{5.14}$$

which is equivalent to eq 4.13. If these conditions are fulfilled, then the modified Green function $G^*(\mathbf{z},\mathbf{N}_u,t|\mathbf{N}'_{u'},t_0)$ can be approximated by

$$\mathbf{G}^* = \exp[\Delta t(\mathbf{W} - \mathbf{\Omega} + \mathbf{E})] \approx \mathbf{I} + \Delta t(\mathbf{W} - \mathbf{\Omega} + \mathbf{E}) \tag{5.15}$$

For a stationary ensemble described by the distribution $B_1^{\mathrm{st}}(M)$ (eq 4.8), the generating function of the probability distribution of reaction events, $L^*(\mathbf{y} = (1),\mathbf{z}{:}t)$, may be evaluated as follows

$$\begin{aligned}L^*(\mathbf{y} = (1),\mathbf{z}{:}t) = {} & \sum_{M(0)} B_1^{\mathrm{st}}(M(0))\prod_m\Big[1 - \mathbf{\Omega}_m\Delta t + \sum_b z_{mb}W_{mb}\Delta t\Big]^{M_m(0)} = \\ & \Big\{1 - \sum_m P_1^{\mathrm{st}}(m)\mathbf{\Omega}_m\Delta t + \sum_b\sum_{m\neq b} z_{mb}P_1^{\mathrm{st}}(m)W_{mb}\Delta t\Big\}^{M_{\Sigma}}\end{aligned} \tag{5.16}$$

Now we introduce the net numbers of the reaction events from an initial state b to a final state m

$$g_{bm} = q_{bm} - q_{mb} \tag{5.17}$$

For a process $\mathbf{N}_b \rightarrow \mathbf{N}_m$ with $\mathbf{N}_m = \mathbf{N}_b + \mathbf{f}_b$, corresponding to a given reduced reaction 2.6, g_{bm} is the difference between the forward and backward reaction events occurring in the time interval Δt. The variables g_{bm} are somewhat similar to the extensive reaction extents $V\xi_b$. The difference between these two functions is that $V\xi_b$ are overall variables attached to the reactions (2.6), whereas g_{bm} are mesoscopic variables attached to the same reactions and to the two sets of initial and final composition vectors $\mathbf{N}_b$ and $\mathbf{N}_m = \mathbf{N}_b + \mathbf{f}_b$.

We analyze the behavior of the stochastic variables g_{bm} in both continuous and discrete time. In continuous time the generating function of the probability distribution of g_{bm}

$$\Xi(\mathbf{g},\Delta t) \qquad \text{with} \qquad \sum_{\mathbf{g}}\Xi(\mathbf{g},\Delta t) = 1 \tag{5.18}$$

can be derived from eq 5.16 by means of the substitution $z_{mb} = (z_{bm})^{-1}$. After lengthy calculations we get the following expression for $\Xi(\mathbf{g},\Delta t)$:

$$\begin{aligned}\Xi(\mathbf{g},\Delta t) = {} & \sum_{\forall q_{mb}} \frac{M_{\Sigma}!}{\Big(M_{\Sigma} - \sum_m\sum_{b\neq m} q_{mb}\Big)!}\Big(1 - \sum_m P_1^{\mathrm{st}}(m)\mathbf{\Omega}_m\Delta t\Big)^{M_{\Sigma}-\sum_m\sum_{b\neq m}q_{ml}} \times \\ & \prod_m\prod_{b\neq m}\Bigg[\frac{(W_{mb}P_1^{\mathrm{st}}(m)\Delta t)^{q_{mb}}}{q_{mb}!}\Bigg]\prod_m\prod_{b>m}[\delta_{g_{mb}(q_{mb}-q_{bm})}]\end{aligned} \tag{5.19}$$

The cumulants of first and second order corresponding to the probability distribution (5.19) are given by

$$\langle g_{mb}(\Delta t)) = \Delta tM_{\Sigma}[P_1^{\mathrm{st}}(m)W_{mb} - P_1^{\mathrm{st}}(b)W_{bm}] \tag{5.20}$$

$$\begin{aligned}\langle g_{m_1b_1}(\Delta t)\, g_{m_2b_2}(\Delta t)\rangle = {} & \Delta tM_{\Sigma}[(P_1^{\mathrm{st}}(m_1)W_{m_1b_1} + P_1^{\mathrm{st}}(b_1)W_{b_1m_1})(\delta_{m_1m_2}\delta_{b_1b_2} - \\ & \delta_{b_1m_2}\delta_{m_1b_2})] + (\Delta t)^2M_{\Sigma}(M_{\Sigma} - 1)(P_1^{\mathrm{st}}(m_1)W_{m_1b_1} - \\ & P_1^{\mathrm{st}}(b_1)W_{b_1m_1})(P_1^{\mathrm{st}}(m_2)W_{m_2b_2} - P_1^{\mathrm{st}}(b_2)W_{b_2m_2})\end{aligned} \tag{5.21}$$

We can also analyze the evolution of the random variables g_{bm} by using the total number of reaction events

$$q = \sum_m\sum_{b\neq m} q_{mb}$$

as a discrete time variable. The generating function of the probability distribution of the discrete time variable q may be obtained from eq 5.16 by means of the substitution $\forall z_{ml} \rightarrow z$. After some calculations we come to a binomial distribution for this probability:

$$\sum_{\forall M} \sum_{\forall \mathbf{q}, q=\text{constant}} B_1(M, \mathbf{q}; \Delta t) = \frac{M_\Sigma!}{(M_\Sigma - q)!q!} \left(\sum_m P_1^{\text{st}}(m) \boldsymbol{\Omega}_m \Delta t \right)^q \left(1 - \sum_m P_1^{\text{st}}(m) \boldsymbol{\Omega}_m \Delta t \right)^{M_\Sigma - q} \tag{5.22}$$

We introduce the probability distribution

$$\Psi(\mathbf{g}; q) \qquad \text{with} \qquad \sum_{\mathbf{g}} \Psi(\mathbf{g}; q) = 1 \tag{5.23}$$

that after the occurrence of q reaction events the random variables g_{bm} have given values. We come to

$$\Psi(\mathbf{g}; q) = \Xi(\mathbf{g}; \Delta t) \Big/ \sum_{\forall M} \sum_{\forall \mathbf{q}, q=\text{constant}} B_1(M, \mathbf{q}; \Delta t) \tag{5.24}$$

By combining eqs 5.19, 5.22, and 5.24, we have

$$\Psi(\mathbf{g}; q) = \sum_{\forall \mathbf{q}} q! \prod_b \prod_{m \neq b} \left[\frac{(\eta_{bm})^{q_{bm}}}{q_{bm}!} \right] \prod_m \prod_{b>m} [\delta_{g_{bm}(q_{bm} - q_{mb})}] \tag{5.25}$$

where

$$\eta_{\text{bm}} = P_1^{\text{st}}(b) W_{\text{bm}} \Big/ \left(\sum_b P_1^{\text{st}}(b) W_{\text{bm}} \right) \tag{5.26}$$

is the probability that a reaction event $\mathbf{N}_b \rightarrow \mathbf{N}_m$ takes place. The cumulants of first and second order of $\mathbf{g}$ are given by two relationships similar to eqs 5.20 and 5.21:

$$\langle g_{mb}(q) \rangle = q[\eta_{mb} - \eta_{bm}] \tag{5.27}$$

$$\langle g_{m_1 b_1}(q) g_{m_2 b_2}(q) \rangle = q[(\eta_{m_1 b_1} + \eta_{b_1 m_1})(\delta_{m_1 m_2} \delta_{b_1 b_2} - \delta_{b_1 m_2} \delta_{m_1 b_2})] + q(q-1)(\eta_{m_1 b_1} - \eta_{b_1 m_1})(\eta_{m_2 b_2} - \eta_{b_2 m_2}) \tag{5.28}$$

The condition of mesoscopic reversibility (4.18) can be expressed in terms of η_{bm} by means of the relation

$$\eta_{bm} = \eta_{mb} \tag{5.29}$$

From eqs 5.20 and 5.21 and 5.27 and 5.28 it follows that at mesoscopic reversibility the average values of g_{bm} are equal to zero. If the total contribution of a process $\mathbf{N}_b \rightleftarrows \mathbf{N}_m$ to the total number of reaction events is constant, that is, if

$$P_1^{\text{st}}(b) W_{bm} + P_1^{\text{st}}(m) W_{mb} = \text{constant} \tag{5.30}$$

which is equivalent to

$$\eta_{bm} + \eta_{mb} = \text{constant} \tag{5.31}$$

then for mesoscopic reversibility the dispersions of the variables g_{bm} have minimum values

$$\langle (\Delta g_{bm}(\Delta t))^2 \rangle = \text{minimum for } P_1^{\text{st}}(b) W_{bm} = P_1^{\text{st}}(m) W_{mb} \tag{5.32}$$

$$\langle (\Delta g_{bm}(q))^2 \rangle = \text{minimum for } \eta_{bm} = \eta_{mb} \tag{5.33}$$

Equations 5.32 and 5.33 may be considered as "variational principles" that characterize the mesoscopic reversibility. The corresponding minimum values of the dispersions are equal to

$$\langle (\Delta g_{bm}(\Delta t))^2 \rangle_{\min} = 2 \Delta t M_\Sigma P_1^{\text{st}}(b) W_{bm} \tag{5.34}$$

$$\langle (\Delta g_{bm}(\Delta t))^2 \rangle_{\min} = 2 q \eta_{bm} \tag{5.35}$$

The cross-correlation functions can be analyzed in a similar way. From eqs. 5.21 and 5.28 it follows that two distinct random variables, $g_{b_1 m_1}$ and $g_{b_2 m_2}$, with $b_1 \neq b_2$, $m_1 \neq m_2$ or $b_1 \neq m_2$, $b_2 \neq m_1$ are generally correlated. At mesoscopic reversibility, however, they become uncorrelated

$$\langle \Delta g_{b_1 m_1}(q) \, \Delta g_{b_2 m_2}(q) \rangle = \langle \Delta g_{b_1 m_1}(\Delta t) \, \Delta g_{b_2 m_2}(\Delta t) \rangle = 0 \qquad \text{for} \quad b_1 \neq b_2,\ m_1 \neq m_2 \text{ or } b_1 \neq m_2,\ b_2 \neq m_1 \qquad \text{and} \quad \forall P_1^{\text{st}}(b) W_{bm} = P_1^{\text{st}}(m) W_{mb} \tag{5.36}$$

Equation 5.36 suggests that at mesoscopic reversibility it might be possible that the two distinct variables $g_{b_1 m_1}$ and $g_{b_2 m_2}$ are not only uncorrelated but also independent. By using the continuous time description, we can prove that this is indeed the case in the limit on an infinity of replicas, $M \rightarrow \infty$. At mesoscopic reversibility the generating function of the probability $\Xi(\mathbf{g}; t)$ is given by

$$\left\{ 1 + \sum_m \sum_{b>m} \Delta t P_1^{\text{st}}(m) [z_{mb} + (z_{mb})^{-1} - 2] \right\}^{M_\Sigma} \rightarrow \exp \left\{ M_\Sigma \sum_m \sum_{b>m} \Delta t P_1^{\text{st}}(m) [z_{mb} + (z_{mb})^{-1} - 2] \right\} \qquad \text{as} \quad M_\Sigma \rightarrow \infty \tag{5.37}$$

which corresponds to a product of independent modified Bessel probability distributions

$$\Xi((\mathbf{g}; t)) = \prod_{m, b>m} \{ \exp[-2 \Delta t M_\Sigma P_1^{\text{st}}(m) W_{mb}] \times I_{g_{mb}}(2 \Delta t M_\Sigma P_1^{\text{st}}(m) W_{mb}) \} \tag{5.38}$$

where

$$I_\nu(x) = \sum_{m=0}^{\infty} (x/2)^{2m+\nu} \Big/ [m! \Gamma(m + \nu + 1)] \tag{5.39}$$

is the modified Bessel function of νth order. Each term in the product (5.38) is a probability distribution corresponding to a given random variable g_{mb}.

The main results of this section are the following. We have derived an ensemble master equation for the numbers of the reaction events and have shown that the solution of this master equation can be expressed in terms of the modified Green function of the ensemble master equation for the numbers of statistical ensembles. An infinite order perturbation theory has been developed that makes possible the exact evaluation of the moments of the numbers of reaction events. We have shown that the condition of semidetailed balance is characterized by an extremum condition for the fluctuations of the net numbers of reaction events: at semidetailed balance the dispersions of the net numbers have minimum values.

6. Fluctuation−Dissipation Relations for Multivariable Systems

To derive the fluctuation−dissipation relations for multivariable chemical systems we resume the study of the eikonal approximation for the chemical master equation, by using the reaction extents as state variables. We rewrite the Schrödinger form of the master equation, eq 4.23, in terms of the reaction extents $\xi_1, ..., \xi_L$ of the lumped reactions, resulting in

$$\frac{\partial}{\partial t}\tilde{P}(\xi,t) = -\mathrm{H}_{\xi}(\xi,V^{-1}\nabla_{\xi})\,\tilde{P}(\xi,t) \tag{6.1}$$

where the chemical Hamiltonian operator $\mathrm{H}_{\xi}(\xi,V^{-1}\nabla_{\xi})$ is made up of the contributions $\mathrm{H}_{\xi}^{(u)}(\xi,V^{-1}\nabla_{\xi})$, $u = 1, 2, ..., L$ of the different lumped reactions

$$\mathrm{H}_{\xi}(\xi,V^{-1}\nabla_{\xi}) = \sum_{u=1}^{L}\mathrm{H}_{\xi}^{(u)}(\xi,V^{-1}\nabla_{\xi}) \tag{6.2}$$

with

$$\mathrm{H}_{\xi}^{(u)}(\xi,V^{-1}\nabla_{\xi})... = \left\{1 - \exp\left[-\frac{1}{V}\frac{\partial}{\partial\xi_u}\right]\right\}[\tilde{\rho}_u^{+}(\xi,t)...] + \left\{1 - \exp\left[+\frac{1}{V}\frac{\partial}{\partial\xi_u}\right]\right\}[\tilde{\rho}_u^{-}(\xi,t)...] \tag{6.3}$$

and

$$\tilde{\rho}_u^{\pm}(\xi,t) = \sum_{\alpha}\tilde{r}_{u\alpha}^{\pm}\left(\mathbf{x}(0) + \left[\sum_b f_{\upsilon b}\xi_b\right]\right) \tag{6.4}$$

We rewrite the master equation (6.1) in the form of a hydrodynamic continuity equation of a probability fluid:

$$\frac{\partial}{\partial t}\tilde{P}(\xi,t) + \nabla_{\xi}\,\mathcal{I}\,(\xi,t) = 0 \tag{6.5}$$

where the L-dimensional vector $\mathcal{I}\,(\xi,t) = [\,\mathcal{I}_u(\xi,t)]_{u=1,...,L}$ is a probability current. By comparing eqs 6.1 and 6.5 it follows that the components $\mathcal{I}_u(\xi,t)$, $u = 1, ..., L$ of the probability current $\mathcal{I}\,(\xi,t)$ can be evaluated from the differential equations

$$\frac{\partial}{\partial\xi_u}\mathcal{I}_u(\xi,t) = \left\{1 - \exp\left[-\frac{1}{V}\frac{\partial}{\partial\xi_u}\right]\right\}[\tilde{\rho}_u^{+}(\xi,t)\,\tilde{P}(\xi,t)] + \left\{1 - \exp\left[+\frac{1}{V}\frac{\partial}{\partial\xi_u}\right]\right\}[\tilde{\rho}_u^{-}(\xi,t)\,\tilde{P}(\xi,t)] = \sum_{m=1}^{\infty}\frac{(-1)^{m-1}}{V^m}\frac{\partial^m}{\partial(\xi_u)^m}\{D_u^{(m)}(\xi,t)\,\tilde{P}(\xi,t)\} \tag{6.6}$$

where

$$D_u^{(m)}(\xi,t) = \frac{1}{m!}[\tilde{\rho}_u^{+}(\xi,t) + (-1)^m\tilde{\rho}_u^{-}(\xi,t)] \qquad u = 1, ..., L \tag{6.7}$$

are generalized probability diffusion coefficients of different orders $m = 1, 2, ...$ attached to different lumped reactions, $u = 1, ..., L$. In particular, for $m = 1$, these probability diffusion coefficients are equal to the net rates $\tilde{\rho}_u(\xi,t)$ of the lumped reactions, $u = 1, ..., L$:

$$\tilde{\rho}_u(\xi,t) = \tilde{\rho}_u^{+}(\xi,t) - \tilde{\rho}_u^{-}(\xi,t) = D_u^{(1)}(\xi,t) \tag{6.8}$$

By integrating Eqs.(6.6) we come to

$$\mathcal{I}_u(\xi,t) = \mathrm{constant}_u + \sum_{m=1}^{\infty}\frac{(-1)^{m-1}}{V^m}\frac{\partial^{m-1}}{\partial(\xi_u)^{m-1}}\{D_u(\xi,t)\,\tilde{P}(\xi,t)\} \tag{6.9}$$

that is, the components $\mathcal{I}_u(\xi,t)$, $u = 1, ..., L$ of the probability current $\mathcal{I}\,(\xi,t)$ can be evaluated up to a set of integration constants, constant$_u$, $u = 1, ..., L$. To avoid the ambiguities generated by undetermined integration constants, it is more advantageous to use the derivatives of the components of the probability current $\mathcal{I}\,(\xi,t)$ with respect to the reaction extents ξ_u, $u = 1, ..., L$ of the lumped reactions

$$\chi_u^{*}(\xi,t) = \frac{\partial}{\partial\xi_u}\mathcal{I}_u(\xi,t) \qquad u = 1, ..., L \tag{6.10}$$

To evaluate the functions $\chi_u^{*}(\xi,t)$, $u = 1, ..., L$, we use the eikonal approximation applied to the state probability $\tilde{P}(\xi,t)$ expressed in terms of the reaction extents of the lumped reactions. We look for a solution similar to (4.33)

$$\tilde{P}(\xi,t) \sim \exp\{VJ(\xi,t)\} \qquad \text{as} \qquad V \to \infty \tag{6.11}$$

where the chemical action $J(\xi,t)$ is generally time-dependent. By inserting eq 6.11 into the master eq 6.1 and keeping the dominant terms in the thermodynamic limit $V \to \infty$, we come to a Hamilton−Jacobi equation for the chemical action $J(\xi,t)$:

$$\frac{\partial}{\partial t}J(\xi,t) + \sum_{u=1}^{L}\left\{\tilde{\rho}_u^{+}(\xi,t)\left\{1 - \exp\left[-\frac{\partial}{\partial\xi_u}J(\xi,t)\right]\right\} + \tilde{\rho}_u^{-}(\xi,t)\left\{1 - \exp\left[\frac{\partial}{\partial\xi_u}J(\xi,t)\right]\right\}\right\} = 0 \tag{6.12}$$

Similarly, by combining eqs 6.6, 6.10, and 6.11, we get the following asymptotic expressions for the functions $\chi_u^{*}(\xi,t)$, valid in the thermodynamic limit $V \to \infty$:

$$\chi_u^{*}(\xi,t) = \frac{\partial}{\partial\xi_u}\mathcal{I}_u(\xi,t) = V\,\tilde{P}(\xi,t)\left\{\tilde{\rho}_u^{+}(\xi,t)\left\{1 - \exp\left[-\frac{\partial}{\partial\xi_u}J(\xi,t)\right]\right\} + \tilde{\rho}_u^{-}(\xi,t)\left\{1 - \exp\left[+\frac{\partial}{\partial\xi_u}J(\xi,t)\right]\right\}\right\} \qquad \text{as} \qquad V \to \infty \tag{6.13}$$

The functions $\chi_u^{*}(\xi,t)$ play an important role in the further development of the theory. In the following section we shall show that $\chi_u^{*}(\xi,t)$ is a measure of how far away is the uth lumped reaction from the mesoscopic reversibility and that these functions are closely connected to the net average numbers of the reaction events, $\langle g_{\mathrm{mb}}(\Delta t)\rangle$, given by eq 5.20. In particular, for mesosopic reversibility, all functions $\chi_u^{*}(\xi,t)$, $u = 1, 2, ...$ are equal to zero:

$$\chi_u^{*}(\xi,t) = 0,\ u = 1, 2, ... \qquad \text{for mesoscopic reversibility} \tag{6.14}$$

To derive the fluctuation−dissipation relations, we try to express the net reaction rates $\tilde{\rho}_u(\xi,t)$ of the lumped reactions in terms of the probability diffusion coefficients of second order,

$$D_u^{(2)}(\xi,t) = \frac{1}{2}[\tilde{\rho}_u^{+}(\xi,t) + \tilde{\rho}_u^{-}(\xi,t)] \tag{6.15}$$

and of the chemical action $J(\xi,t)$. By eliminating $\tilde{\rho}_u^{+}(\xi,t)$ and $\tilde{\rho}_u^{-}(\xi,t)$ from eqs 6.8, 6.12, and 6.14 after some calculations we come to

$$\tilde{\rho}_u(\xi,t) = 2D_u^{(2)}(\xi,t)\tanh\left[\frac{1}{2}\frac{\partial}{\partial\xi_u}J(\xi,t)\right] + \frac{\chi_u^*(\xi,t)}{V\,\tilde{P}(\xi,t)\sinh\left[\frac{\partial}{\partial\xi_u}J(\xi,t)\right]} \tag{6.16}$$

For a rather general class of chemical systems the state probability densities $\tilde{P}(\mathbf{x},t)$ and $\tilde{P}(\xi,t)$ tend toward normal forms $\tilde{P}^*(\mathbf{x},t)$ and $\tilde{P}^*(\xi,t)$, independent of the initial conditions. To each of these normal probability density corresponds a normal chemical action, $J^*(\mathbf{x},t)$ and $J^*(\xi,t)$, respectively. We have

$$\tilde{P}^*(\xi,t) \sim \exp[VJ^*(\xi,t)] \qquad \text{and} \qquad \tilde{P}^*(\mathbf{x},t) \sim \exp[VJ^*(\mathbf{x},t)] \tag{6.17}$$

Various conditions for the emergence of the normal solutions of the chemical master equations have been given in the literature. In this article we do not give details concerning these conditions. We only mention that there are two different types of normal solutions:

1. Stationary normal stochastic solutions, for which the normal probability densities $\tilde{P}^*(\mathbf{x},t)$ and $\tilde{P}^*(\xi,t)$, and the corresponding chemical actions $J^*(\mathbf{x},t)$ and $J^*(\xi,t)$, are independent of time. We emphasize that a stationary normal probability density may correspond to a time-dependent attractor of the deterministic kinetic equations. A well-known example is a chemical system for which the deterministic kinetic equations have an attractor, which is a stable limit cycle. For such a chemical system the normal probability densities are stationary and have the shape of a volcano, and the rim of the volcano corresponds to the deterministic limit cycle.
2. Variable normal stochastic solutions, for which the normal probability densities $\tilde{P}^*(\mathbf{x},t)$ and $\tilde{P}^*(\xi,t)$ and the corresponding chemical actions $J^*(\mathbf{x},t)$ and $J^*(\xi,t)$, are dependent on time. An example is a closed chemical system with time-dependent rate coefficients.[9]

We apply eq 6.16 to the particular case where the state probability and the chemical action correspond to a stochastic normal regime $\tilde{P}(\xi,t) = \tilde{P}^*(\xi,t)$ and $J(\xi,t) = J^*(\xi,t)$. We come to a general set of fluctuation–dissipation relations, which establish a connection among the net reaction rates, $\tilde{\rho}_u(\xi,t)$, the second-order probability diffusion coefficients, $D_u^{(2)}(\xi,t)$, of the different lumped reactions, the normal chemical action, $J^*(\xi,t)$, the normal probability density, $\tilde{P}^*(\xi,t)$, and the measures, $\chi_u^*(\xi,t)$, of the departure of the different lumped chemical reactions from mesoscopic reversibility.

$$\tilde{\rho}_u(\xi,t) = 2D_u^{(2)}(\xi,t)\tanh\left[\frac{1}{2}\frac{\partial}{\partial\xi_u}J^*(\xi,t)\right] + \frac{\chi_u^*(\xi,t)}{V\,\tilde{P}^*(\xi,t)\sinh\left[\frac{\partial}{\partial\xi_u}J^*(\xi,t)\right]} \tag{6.18}$$

By using the functions $\chi_u^*(\xi,t)$ as additional variables, we have managed to derive a set of many fluctuation–dissipation relations for multivariable chemical systems far from equilibrium. As expected, the fluctuation–dissipation relations (6.18) are compatible with the single fluctuation–dissipation relation (1.9) derived in ref 9 (eq 1.9 can be easily derived from eq 6.18). By combining the continuity equation for the probability fluid, eq 6.5, with the definition (6.10) of the functions $\chi_u^*(\xi,t)$ and with the scaling condition (6.17) for the normal probability density $\tilde{P}^*(\xi,t)$, we get the following identity:

$$V\tilde{P}^*(\xi,t)\Lambda(\xi,t) + \sum_u \chi_u^*(\xi,t) = 0 \tag{6.19}$$

where

$$\Lambda(\xi,t) = \frac{\partial}{\partial t}J^*(\xi,t) \tag{6.20}$$

By solving eq 6.18 with respect to $\chi_u^*(\xi,t)$ and inserting the resulting equations into eq 6.19 we come to eq 1.9.

The fluctuation–dissipation relations make it possible to compute a component of the dissipation function of the process. In terms of the normal form of the chemical action, a component of the dissipation function is given by

$$\Theta(t) = -\frac{\mathrm{d}}{\mathrm{d}t}(VJ^*(\xi,t)) \tag{6.21}$$

We introduce the affinity of the uth lumped reaction

$$\mathcal{A}_u(\xi,t) = -\frac{\partial}{\partial\xi_u}J^*(\xi,t) \tag{6.22}$$

and evaluate the time derivative of the normal chemical action, $J^*(\xi,t)$. We have

$$\Theta(t) = -\frac{\partial}{\partial t}(VJ^*(\xi,t)) - \sum_u\left(\frac{\partial\xi_u}{\partial t}\right)\frac{\partial}{\partial\xi_u}(VJ^*(\xi,t)) \tag{6.23}$$

Now we take into account that

$$\tilde{\rho}_u(\xi,t) = \partial\xi_u/\partial t \tag{6.24}$$

and use the fluctuation–dissipation relations (6.18). After some calculations we come to

$$\Theta(t) = -V\sum_u 2D_u^{(2)}(\xi,t)\mathcal{A}_u(\xi,t)\tanh\left[\frac{1}{2}\mathcal{A}_u(\xi,t)\right] + \frac{1}{\tilde{P}^*(\xi,t)}\sum_u \chi_u^*(\xi,t)\left\{1 + \frac{\mathcal{A}_u(\xi,t)}{\sinh[-\mathcal{A}_u(\xi,t)]}\right\} \tag{6.25}$$

We notice that the component of the dissipation function can be expressed as the sum of two different subcomponents:

$$\Theta(t) = \Theta_1(t) + \Theta_2(t) \tag{6.26}$$

where

$$\Theta_1(t) = -V\sum_u 2D_u^{(2)}(\xi,t)\mathcal{A}_u(\xi,t)\tanh\left[\frac{1}{2}\mathcal{A}_u(\xi,t)\right] \tag{6.27}$$

is a main contribution that is different from zero both for systems with or without detailed balance. The second subcomponent of the dissipation function

$$\Theta_2(t) = \frac{1}{\tilde{P}^*(\xi,t)} \sum_u \chi_u^*(\xi,t) \left\{ 1 + \frac{\mathsf{A}_u(\xi,t)}{\sinh[-\mathsf{A}_u(\xi,t)]} \right\} \tag{6.28}$$

is different from zero only for systems without detailed balance. The asymptotic behavior of these two subcomponents for small or large affinities is given by

$$\Theta_1(t) = -V \sum_u 2D_u^{(2)}(\xi,t)[\mathsf{A}_u(\xi,t)]^2 \qquad \text{as all } |\mathsf{A}_u(\xi,t)| \to 0 \tag{6.29}$$

$$\Theta_1(t) \cong -V \sum_u 2D_u^{(2)}(\xi,t)|\mathsf{A}_u(\xi,t)| \qquad \text{as all } |\mathsf{A}_u(\xi,t)| \to \infty \tag{6.30}$$

$$\Theta_2(t) \cong \frac{1}{6\tilde{P}^*(\xi,t)} \sum_u \chi_u^*(\xi,t)|\mathsf{A}_u(\xi,t)|^2 \qquad \text{as all } |\mathsf{A}_u(\xi,t)| \to 0 \tag{6.31}$$

$$\Theta_2(t) \cong \frac{1}{\tilde{P}^*(\xi,t)} \sum_u \chi_u^*(\xi,t) = V\Lambda(\xi,t) \qquad \text{as all } |\mathsf{A}_u(\xi,t)| \to \infty \tag{6.32}$$

In the linear thermodynamic regime, as all $|\mathsf{A}_u(\xi,t)| \to 0$, both subcomponents of the dissipation are quadratic functions of the reaction affinities. In the other extreme of very large reaction affinities, as all $|\mathsf{A}_u(\xi,t)| \to \infty$, both components display a saturation effect: the main contribution $\Theta_1(t)$ is a linear function of the absolute values of the reaction affinities, whereas the secondary contribution $\Theta_2(t)$, due to the violation of the detailed balance, does not depend directly on the reaction affinities.

7. Physical Significance of Dissipation−Fluctuation Relations

For simplicity in this section we limit ourselves to the particular case where the rates of the lumped reactions do not depend directly on time.

$$\tilde{\rho}_u^{\pm}(\xi;t) = \tilde{\rho}_u^{\pm}(\xi) \tag{7.1}$$

We assume that these rates can depend only indirectly on time, since the vector of the reaction extents is generally time-dependent, $\xi = \xi(t)$.

We start out by discussing the physical meaning of two sets of functions in the fluctuation−dissipation relations, the functions $\chi_u(\xi,t)$ and the probability diffusion coefficients of second order, $D_u^{(2)}(\xi,t)$. To clarify the physical meaning of the functions $\chi_u(\xi,t)$, we rewrite the master equation (6.1) and the continuity equation (6.5) in the following forms:

$$\frac{\partial}{\partial t}\tilde{P}(\xi,t) = \sum_u \{\tilde{\rho}_u^{+}(\xi + \vartheta_u)\, \tilde{P}(\xi + \vartheta_u,t) + \tilde{\rho}_u^{-}(\xi - \vartheta_u)\, \tilde{P}(\xi - \vartheta_u,t)\} - \sum_u [\tilde{\rho}_u^{+}(\xi) + \tilde{\rho}_u^{-}(\xi)]\tilde{P}(\xi,t) \tag{7.2}$$

and

$$\frac{\partial}{\partial t}\tilde{P}(\xi,t) + \sum_u \chi_u(\xi,t) = 0 \tag{7.3}$$

where

$$\vartheta_u = [\delta_{u\nu}/V]_{\nu=1,...,\mathrm{L}} \qquad u = 1, ..., L \tag{7.4}$$

By comparing eqs 7.2 and 7.3, we notice that

$$\chi_u(\xi,t) = [\tilde{\rho}_u^{+}(\xi) + \tilde{\rho}_u^{-}(\xi)]\tilde{P}(\xi,t) - \tilde{\rho}_u^{+}(\xi + \vartheta_u)\, \tilde{P}(\xi + \vartheta_u,t) - \tilde{\rho}_u^{-}(\xi - \vartheta_u)\, \tilde{P}(\xi - \vartheta_u,t) \tag{7.5}$$

By using the label notation for the master equation developed in section 3, we can rewrite eq 7.5 in the following form

$$\chi_u(\xi,t) = \sum_{m'(u)} [W_{m(\xi)m'(u)} P_1(m(\xi);t) - W_{m'(u)m(\xi)}\, P_1(m'(u);t)] \tag{7.6}$$

where $m(\xi)$ is the label attached to the state characterized by the reaction extent vector ξ and $m'(u)$ are the labels attached to the states that can be reached from the state $m(\xi)$, when one step of the uth lumped reaction occurs, that is, the labels $m'(u)$ correspond to the states characterized by the extent vectors $\xi + \vartheta_u$ and $\xi - \vartheta_u$, respectively.

For a system with time-independent rate coefficients, the normal probability distribution $P_1{}^*(m(\xi);t)$, and the transition rates $W_{m(\xi)m'(u)}$, $W_{m'(u)m(\xi)}$ are stationary and thus the functions $\chi_u^*(\xi)$ are also stationary

$$\chi_u^*(\xi) = \sum_{m'(u)} [W_{m(\xi)m'(u)} P_1^{\mathrm{st}}(m(\xi)) - W_{m'(u)m(\xi)}\, P_1^{\mathrm{st}}(m'(u))] \tag{7.7}$$

By comparing eqs 5.20 and 7.7, we notice that

$$\chi_u^*(\xi) = \lim_{\Delta t \to 0} \frac{1}{\Delta t M_\Sigma} \sum_{m'(u)} \langle g_{m(\xi)m'(u)}(\Delta t)\rangle \tag{7.8}$$

Now the physical interpretation of the functions $\chi_u^*(\xi)$ is straightforward. $\chi_u^*(\xi)$ is the ratio between the rate of variation of the average net number of reaction events from the state $m(\xi)$ to the states $m'(u)$, compatible with the occurrence of one step of the lumped reaction u, and the number M_Σ of statistical ensembles. Since the average values of the net numbers of reaction events vanish for mesoscopic reversibility, it follows that $\chi_u^*(\xi)$ can be considered as a normal function that is a measure of how far away the lumped reaction u is from mesoscopic reversibility.

Concerning the probability diffusion coefficients of second order, $D_u^{(2)}(\xi,t)$, we can consider a physical interpretation similar to the one introduced in our former study of one-variable fluctuation−dissipation relations.[6] In this case too, we limit ourselves to the particular case for which the lumped reaction rates $\tilde{\rho}_u(\xi,t)$ depend only on the reaction extents and do not depend directly on time, $\tilde{\rho}_u(\xi,t) = \tilde{\rho}_u(\xi)$. Under these circumstances the probability diffusion coefficients of second order, $D_u^{(2)}(\xi,t)$, depend only on the extent vector:

$$D_u^{(2)}(\xi,t) = D_u^{(2)}(\xi) = \frac{1}{2}[\tilde{\rho}_u^{+}(\xi) + \tilde{\rho}_u^{-}(\xi)] \tag{7.9}$$

In the following[6] we try to make a connection between $D_u^{(2)}(\xi,t)$ and the statistics of the total numbers of reaction events, ϵ_1, ..., ϵ_L of the different lumped reactions, occurring in a time interval of length t, in a single system. We emphasize that these numbers of reaction events are different from the number of reaction events studied in the preceding sections, which refer to an ensemble of systems.

For one system we introduce the joint probability density of the vector ξ of the reaction extents and the vector $\epsilon = (\epsilon_1, ..., \epsilon_L)$ of the total numbers of reaction events, corrsponding to a stochastic steady-state characterized by a one-system probability density $\tilde{P}^{st}(\xi)$:

$$\mathrm{A}(\xi,\epsilon;t) \qquad \text{with} \qquad \sum_{\epsilon} \int (\mathrm{A}(\xi,\epsilon;t))\, d\xi = 1 \tag{7.10}$$

and the corresponding conditional probability density density of the vector $\epsilon = (\epsilon_1, ..., \epsilon_L)$

$$\mathcal{U}(\epsilon|\xi;t) = \mathrm{A}(\xi,\epsilon;t)/\tilde{P}^{st}(\xi) \qquad \text{with} \qquad \sum_{\epsilon} \mathcal{U}(\epsilon|\xi;t) = 1 \tag{7.11}$$

The probability density $\mathrm{A}(\xi,\epsilon;t)$ obeys the master equation

$$V^{-1}\frac{\partial}{\partial t}\mathrm{A}(\xi,\epsilon;t) = -\sum_u [\tilde{\rho}_u^+(\xi_u) + \tilde{\rho}_u^-(\xi)]\mathrm{A}(\xi,\epsilon;t) + \sum_u (1 - \delta_{\epsilon_u 0})[\tilde{\rho}_u^+(\xi + \vartheta_u)\mathrm{A}(\xi + \vartheta_u, \epsilon - \vartheta_u;t) + \tilde{\rho}_u^-(\xi - \vartheta_u)\mathrm{A}(\xi - \vartheta_u, \epsilon - \vartheta_u;t)\,] \tag{7.12}$$

We insert eq 7.11 into eq 7.12, take into account that $\tilde{P}^{st}(\xi)$ is the solution of

$$\sum_u [\tilde{\rho}_u^+(\xi_u) + \tilde{\rho}_u^-(\xi)]\tilde{P}^{st}(\xi) = \sum_u [\tilde{\rho}_u^+(\xi + \vartheta_u)\, \tilde{P}^{st}(\xi + \vartheta_u) + \tilde{\rho}_u^-(\xi - \vartheta_u)\, \tilde{P}^{st}(\xi - \vartheta_u)] \tag{7.13}$$

and notice that in the thermodynamic limit we have

$$\mathcal{U}(\epsilon|\xi \pm \vartheta_u;t) \cong \mathcal{U}(\epsilon|\xi;t) \tag{7.14}$$

From eqs 7.12−7.14 we come to

$$\frac{\partial}{\partial t}\mathcal{U}(\epsilon|\xi;t) = \sum_u (1 - \delta_{\epsilon_u 0}) 2VD_u^{(2)}(\xi)\mathcal{U}(\epsilon - \vartheta_u|\xi;t) - \mathcal{U}(\epsilon|\xi;t)\sum_u 2VD_u^{(2)}(\xi) \tag{7.15}$$

By solving eq 7.15 with the initial condition

$$\mathcal{U}(\epsilon|\xi;0) = \prod_u \delta_{\epsilon_u 0} \tag{7.16}$$

we obtain a multivariate Poissonian distribution

$$\mathcal{U}(\epsilon|\xi;0) = \prod_u \left\{ \frac{[2VD_u^{(2)}(\xi)t]^{\epsilon_u}}{\epsilon_u!} \exp[-2VD_u^{(2)}(\xi)t] \right\} \tag{7.17}$$

The physical interpretation of this result is simple. In the thermodynamic limit for a stochastic steady state the reaction system behaves as a chemical clock that measures the time in a uniform way: the numbers of reaction events $\epsilon = (\epsilon_1, ..., \epsilon_L)$ behave as count events that obey Poissonian statistics. The cumulants $c_u^{(m)}(t)$ of the numbers of reaction events are all equal to the parameters $\lambda_u(t) = 2VD_u^{(2)}(\xi)t$ of the multivariate Poissonian distribution (7.17)

$$c_u^{(m)}(t) = 2VD_u^{(2)}(\xi)t \qquad u = 1, ..., L, \quad m = 1, 2, ... \tag{7.18}$$

In particular

$$\langle \epsilon_u(t) \rangle = \langle [\Delta\epsilon_u(t)]^2 \rangle = 2VD_u^{(2)}(\xi)t \tag{7.19}$$

Equations 7.19 are similar to the well-known Einstein equation for the mean square displacement of a Brownian particle confined in a one-dimensional system, $\langle \Delta X^2(t) \rangle = 2Dt$. From this similarity between eqs 7.19 and the Einstein equation for the dispersion of a Brownian particle, it follows that $D_u^{(2)}(\xi)$ are probability diffusion coefficients in the space of reaction extents: $D_u^{(2)}(\xi)$ is a measure of the strength of fluctuations of the number ϵ_u of reaction events of type u. This interpretation is a generalization of the original interpretation of the probability diffusion coefficient for the particular case of first-order reactions at equilibrium.[19]

Now we can proceed to give a physical interpretation of the fluctuation−dissipation relations as a whole. We rewrite the fluctuation−dissipation relations (6.18) for the particular case of time-independent rate coefficients.

$$\tilde{\rho}_u(\xi) = 2D_u^{(2)}(\xi) \tanh\left[\frac{1}{2}\frac{\partial}{\partial \xi_u}J^{st}(\xi)\right] + \frac{\chi_u^*(\xi)}{V\tilde{P}^{st}(\xi) \sinh\left[\frac{\partial}{\partial \xi_u}J^{st}(\xi)\right]} \tag{7.20}$$

or

$$\tilde{\rho}_u(\xi) = 2D_u^{(2)}(\xi) \tanh\left[-\frac{1}{2}\mathcal{A}_u(\xi)\right] + \frac{\chi_u^*(\xi)}{VN \exp[VJ^{st}(\xi)] \sinh[-\mathcal{A}_u(\xi)]} \tag{7.21}$$

where we have assumed the existence of a stationary stochastic solution of the eikonal type:

$$\tilde{P}^{st}(\xi) = N \exp[VJ^{st}(\xi)] \qquad \text{with} \qquad N = \{\int \exp[VJ^{st}(\xi)]d\xi\}^{-1} \tag{7.22}$$

and $\mathcal{A}_u(\xi)$, $u = 1, ..., L$ are the reaction affinities attached to the different lumped reactions, defined by eqs 6.22.

From the kinetic and thermodynamic point of view the fluctuation−dissipation relations 7.20 and 7.21 establish a connection between the net rates $\tilde{\rho}_u(\xi)$, $u = 1, ..., L$, attached to the different lumped reactions and the corresponding reaction affinities $\mathcal{A}_u(\xi)$, $u = 1, ..., L$. They may be compared to the classical rate−affinity relationship of elementary reactions:[20]

$$\tilde{r} = \tilde{r}^+[1 - \exp(-A/k_BT)] = \tilde{r}^-[\exp(A/k_BT) - 1] \tag{7.23}$$

where $\tilde{r}$ is the net reaction rate, $\tilde{r}^\pm$ are the forward and backward reaction rates, and A is the reaction affinity. Between our fluctuation−dissipation relations (7.20) and (7.21) and the classical rate affinity relations (7.23) there is an important difference. Equationss 7.23 are asymmetric with respect to the forward and backward rates. This is why there are two equations (7.23), one depending on the forward rate $\tilde{r}^+$ and the second depending on the backward rate $\tilde{r}^-$, respectively. On the contrary, in our fluctuation−dissipation relations (7.20) and (7.21) the individual forward and backward rates of the lumped reactions, $\tilde{\rho}_u^+(\xi)$ and $\tilde{\rho}_u^-(\xi)$, enter in the form of symmetric combinations, expressed by the probability diffusion coefficients, $D_u^{(2)}(\xi) = {}^1\!/_2[\,\tilde{\rho}_u^+(\xi) + \tilde{\rho}_u^-(\xi)]$, $u = 1, ..., L$. Therefore, from the kinetic and thermodynamic points of view, the fluctuation–dissipation relations (7.20) and (7.21) are symmetric with respect to the forward and backward rates of the lumped reactions.

The stochastic interpretation of the fluctuation–dissipation relations is simple: they express the connection of fluctuation dynamics, described in terms of the chemical action and probability diffusion coefficients and the dynamics of chemical dissipation, expressed in terms of the net reaction rates of the lumped reactions. The symmetric role played by the forward and backward rates is also important in connection with the stochastic interpretation of our fluctuation–dissipation relations. Our approach is consistent with the Klimontovich representation of a master equation,[21] which is based on the symmetry properties of the transition rates. To apply Klimontovich's representation, we rewrite the master eq 7.2 in the standard form:

$$\frac{\partial}{\partial t}\tilde{P}(\xi,t) = \sum_{u=1}^{L}\int \tilde{P}(\xi',t)\, W_u(\xi'\rightarrow\xi)\, \mathrm{d}\xi' - \tilde{P}(\xi,t)\sum_{u=1}^{L}\int W_u(\xi\rightarrow\xi')\, \mathrm{d}\xi' \quad (7.24)$$

where

$$W_u(\xi\rightarrow\xi') = \tilde{\rho}_u^{+}(\xi)\, \delta(\xi' - \xi - \vartheta_u) + \tilde{\rho}_u^{-}(\xi)\, \delta(\xi' - \xi + \vartheta_u) \quad (7.25)$$

and express the transition rate $W_u(\xi\rightarrow\xi')$ as the sum of two additive contributions, a symmetric one, $W_u^{(s)}(\xi,\xi')$, and an antisymmetric one, $W_u^{(a)}(\xi,\xi')$, respectively:

$$W_u(\xi\rightarrow\xi') = W_u^{(s)}(\xi,\xi') + W_u^{(a)}(\xi',\xi) \quad (7.26)$$

where the component $W_u^{(s)}(\xi,\xi')$ is symmetric

$$W_u^{(s)}(\xi,\xi') = W_u^{(s)}(\xi',\xi) \quad (7.27)$$

and the component $W_u^{(a)}(\xi',\xi)$ is antisymmetric

$$W_u^{(a)}(\xi,\xi') = -W_u^{(a)}(\xi',\xi) \quad (7.28)$$

We have

$$W_u^{(s)}(\xi,\xi') = \frac{1}{2}[W_u(\xi\rightarrow\xi') + W_u(\xi'\rightarrow\xi)] \quad (7.29)$$

$$W_u^{(a)}(\xi,\xi') = \frac{1}{2}[W_u(\xi\rightarrow\xi') - W_u(\xi'\rightarrow\xi)] \quad (7.30)$$

According to Klimontovich,[21] the antisymmetric components of the transition rates express the dynamics of dissipation, whereas the symmetric components are related to fluctuations. In the following we shall try to compute the contributions of the dissipative (antisymmetric) and fluctuational (symmetric) components of the transition rates to the fluctuation–dissipation relations.

The master equation (7.24) can be rewritten in the following form:

$$\frac{\partial}{\partial t}\tilde{P}(\xi,t) = \sum_{u=1}^{L}\int W_u^{(s)}(\xi,\xi')[\tilde{P}(\xi',t) - \tilde{P}(\xi,t)]\, \mathrm{d}\xi' - \sum_{u=1}^{L}\int W_u^{(a)}(\xi,\xi')[\tilde{P}(\xi',t) + \tilde{P}(\xi,t)]\, \mathrm{d}\xi' \quad (7.31)$$

By comparing eqs 7.3 and 7.31, one can express the functions $\chi_u(\xi,t)$ as the sum of the contributions generated by the symmetric and antisymmetric components of the transition rates, $\chi_u^{(s)}(\xi,t)$ and $\chi_u^{(a)}(\xi,t)$, respectively:

$$\chi_u(\xi,t) = \chi_u^{(s)}(\xi,t) + \chi_u^{(a)}(\xi,t) \quad (7.32)$$

where

$$\chi_u^{(s)}(\xi,t) = \int W_u^{(s)}(\xi,\xi')[\tilde{P}(\xi,t) - \tilde{P}(\xi',t)]\, \mathrm{d}\xi' \quad (7.33)$$

$$\chi_u^{(a)}(\xi,t) = \int W_u^{(a)}(\xi,\xi')[\tilde{P}(\xi',t) + \tilde{P}(\xi,t)]\, \mathrm{d}\xi' \quad (7.34)$$

In the particular case of a stochastic stationary state, characterized by the state probability density $\tilde{P}^{\mathrm{st}}(\xi) = N \exp[V\mathcal{J}^{\mathrm{st}}(\xi)]$, the components $\chi_u^{(s)}(\xi,t)$ and $\chi_u^{(a)}(\xi,t)$ can be computed explicitly. By combining eqs 7.4, 7.22, 7.25, 7.29, 7.30, 7.33, and 7.34 and keeping the dominant terms in the size of the system, we obtain

$$\chi_u^{(s)}(\xi) = -VD_u^{(2)}(\xi)\left[\exp\left(\frac{1}{V}\frac{\partial}{\partial\xi_u}\right) + \exp\left(-\frac{1}{V}\frac{\partial}{\partial\xi_u}\right) - 2\right]\tilde{P}^{\mathrm{st}}(\xi) = -4VD_u^{(2)}(\xi)\tilde{P}^{\mathrm{st}}(\xi)\sinh^2\left[\frac{1}{2}\frac{\partial}{\partial\xi_u}\mathcal{J}^{\mathrm{st}}(\xi)\right] \quad (7.35)$$

$$\chi_u^{(a)}(\xi) = \frac{1}{2}\tilde{\rho}_u(\xi)\left[\exp\left(\frac{1}{V}\frac{\partial}{\partial\xi_u}\right) - \exp\left(-\frac{1}{V}\frac{\partial}{\partial\xi_u}\right)\right]\tilde{P}^{\mathrm{st}}(\xi) = V\tilde{\rho}_u(\xi)\tilde{P}^{\mathrm{st}}(\xi)\sinh\left[\frac{\partial}{\partial\xi_u}\mathcal{J}^{\mathrm{st}}(\xi)\right] \quad (7.36)$$

The fluctuation–dissipation relations can be recovered by inserting the expressions (7.35) and (7.36), for $\chi_u^{(s)}(\xi,t)$ and $\chi_u^{(a)}(\xi,t)$, into eq 7.32, applied for a stochastic stationary state. We have

$$\chi_u(\xi) = \chi_u^{(s)}(\xi) + \chi_u^{(a)}(\xi) = -4VD_u^{(2)}(\xi)\, \tilde{P}^{\mathrm{st}}(\xi)\sinh^2\left[\frac{1}{2}\frac{\partial}{\partial\xi_u}\mathcal{J}^{\mathrm{st}}(\xi)\right] + V\tilde{\rho}_u(\xi)\, \tilde{P}^{\mathrm{st}}(\xi)\sinh\left[\frac{\partial}{\partial\xi_u}\mathcal{J}^{\mathrm{st}}(\xi)\right] \quad (7.37)$$

It is easy to check that eq 7.37 is an alternative form of the fluctuation–dissipation relations (7.20). The fluctuation–dissipation relations (7.37) outline the contributions of the fluctuation (symmetric) and dissipation (antisymmetric) components of the functions $\chi_u(\xi)$. Equation 7.37 also shows that for systems with mesoscopic reversibility, for which $\chi_u(\xi) = 0$, the fluctuation and dissipation components compensate each other: they have the same absolute values but different signs.

Our fluctuation–dissipation relations are global; for example, for a system with multiple deterministic stable attractors, e.g., multiple stable stationary states, there is only one set of fluctuation–dissipation relations for all states. Other fluctuation–dissipation relations developed in the literature are local;[22,23] that is, for each stable attractor there is another set of fluctuation–dissipation relations. We conclude this section by examining the relationships between our global theory and the local fluctuation–dissipation relations developed in the literature. For simplicity we limit ourselves to the study of small fluctuations in the neighborhood of a deterministic steady state for a system with multiple stationary steady states.

We consider a deterministic steady state characterized by the state vector $\xi = \xi^{st}$ and consider small fluctuations around this state. We expand the chemical action around the maximum value $J^{st}(\xi^{st})$ and keep the first nonvanishing terms, resulting in

$$J^{st}(\xi) \cong J^{st}(\xi^{st}) + \frac{1}{2}\sum_{u_1=1}^{L}\sum_{u_2=1}^{L} \mathrm{M}_{u_1u_2}(\xi_{u_1} - \xi_{u_1}^{st})(\xi_{u_2} - \xi_{u_2}^{st}) \quad (7.38)$$

where

$$\mathrm{M}_{u_1u_2} = -\frac{\partial^2}{\partial\xi_{u_1}^{st}\ \xi_{u_2}^{st}} J^{st}(\xi^{st}) \quad (7.39)$$

The normalized probability distribution corresponding to the quadratic chemical action of the type (7.38) is a Gaussian

$$\tilde{P}^{st}(\xi) = [(2\pi V)^L \det|\mathrm{M}|]^{-1/2} \exp\left[-\frac{1}{2}V(\xi - \xi^{st})^{+}\,\mathrm{M}(\xi - \xi^{st})\right] \quad (7.40)$$

and the covariance matrix

$$\boldsymbol{\sigma} = [\langle(\xi_{u_1} - \xi_{u_1}^{st})(\xi_{u_2} - \xi_{u_2}^{st})\rangle]$$

of the reaction extents of the lumped reactions is equal to

$$\boldsymbol{\sigma} = (V\mathrm{M})^{-1} \quad (7.41)$$

For deriving a set of local fluctuation−dissipation relations we make use of the condition (6.19) applied for a stochastic stationary state

$$\sum_u \chi_u^*(\xi) = 0 \quad (7.42)$$

By combining eqs 7.7 and 7.42, we obtain

$$\sum_u \left\{2D_u(\xi)\tanh\left(\frac{1}{2}\frac{\partial}{\partial\xi_u}J^{st}(\xi)\right) - \tilde{\rho}_u(\xi)\right\}\sinh\left(\frac{\partial}{\partial\xi_u}J^{st}(\xi)\right) = 0 \quad (7.43)$$

We expand in eq 7.43 all ξ-dependent functions around $\xi - \xi^{st}$ and keep the dominant terms in $\delta\xi_u = \xi_u - \xi_u^{st}$ as $\xi \rightarrow \xi^{st}$. We come to

$$\sum_{u'=1}^{L}[\lambda_{u_1u'}(\mathrm{M}^{-1})_{u'u_2} + \lambda_{u_2u'}(\mathrm{M}^{-1})_{u'u_1}] = 2D_{u_1}^{(2)}(\xi^{st})\delta_{u_1u_2} \quad (7.44)$$

where

$$\lambda_{u_1u_2} = \frac{\partial}{\partial\xi_{u_2}^{st}}\tilde{\rho}_{u_1}(\xi^{st},t) \quad (7.45)$$

By combining eqs 7.41 and 7.45, we obtain the fluctuation−dissipation relations derived by Keizer:[23]

$$V\sum_{u'=1}^{L}[\lambda_{u_1u'}(\boldsymbol{\sigma})_{u'u_2} + \lambda_{u_2u'}(\boldsymbol{\sigma})_{u'u_1}] = 2D_{u_1}^{(2)}(\xi^{st})\delta_{u_1u_2} \quad (7.46)$$

In conclusion, in this section we have discussed the physical meaning of the main functions from our fluctuation−dissipation relations as well as the meaning of the relations themselves. We have shown that the functions $\chi_u^*(\xi)$ are norm functions that measure the distance of the different lumped reactions from the state of mesoscopic reversibility. We have shown that the probability diffusion coefficients of second order, $D_u^{(2)}(\xi)$, are measures of the strength of fluctuations of the total numbers of reaction events attached to the different lumped reactions. The fluctuation−dissipation relations have two different physical interpretations. They are generalized force−flux relationships that may serve as the basis for a thermodynamic theory of nonequilibrium processes and at the same time they express the balance between the fluctuation and dissipation in a nonequilibrium system. By using an approach suggested by Klimontovich, we have computed the contributions of fluctuation and dissipation and have shown that for mesoscopic reversibility they compensate each other. Although our fluctuation−dissipation relations are global, they are compatible with the local fluctuation−dissipation relations derived in the literature. In particular, in the case of small fluctuations in the neighborhood of a stable steady state, our relations can be used for deriving the local fluctuation−dissipation relations introduced by Keizer.

8. Conclusions

In this paper we have introduced a statistical ensemble approach for multivariable chemical systems far from equilibrium, which makes it possible to investigate the stochastic properties of the numbers of reaction events. We have considered a reference system for which a condition of mesoscopic time reversal (mesoscopic reversibility) holds and introduced a set of norm functions, which measure the distance of an arbitrary chemical system from a reference state with mesoscopic reversibility. These norm functions have been used for deriving a set of fluctuation-disssipation relations for complex chemical processes far from equilibrium. The main results of our theory have been summarized at the end of each section of the article and we are not going to repeat them here. Instead, we give an outline of the meaning of our results.

We must emphasize that our fluctuation−dissipation relations are equivalent to the one-system master equation for chemical fluctuations and to the Hamilton−Jacobi equation derived from it in the thermodynamic limit. The main advantage of our approach is that it makes it possible to look at the information contained in the master equation from a new point of view and thus it reveals some features of nonlinear chemical systems that are hidden in the mathematical formalism. An interesting feature revealed by our approach is the saturation effect for the dependence between the fluxes (reaction rates) and thermodynamic forces (reaction affinities), due to the presence of the hyperbolic tangent in the fluctuation−dissipation relations. Our theory shows that the reference systems with mesoscopic reversibility have some interesting properties. At mesoscopic reversibility for each lumped reaction the contribution of fluctuations is exactly compensated by the contribution of dissipation processes and the dispersions of the net numbers of reaction events have minimum values.

An important feature of fluctuation−dissipation relations is that they may serve as a basis for the development of a nonequilibrium thermodynamic theory for chemical systems far from equilibrium.

Acknowledgment. This research has been supported in part by the National Science Foundation and the Department of Energy, Basic Energy Sciences Engineering Program. The authors thank Profs. Th. Nonnenmacher and F. W. Schneider for useful discussions.

References and Notes

(1) Fox, R. F. *Phys. Rep.* **1978**, *48*, 179. Stratonovich, R. L. *Nonlinear Nonequilibrium Thermodynamics I*; Springer: Berlin, 1992.

(2) Ross, J.; Hunt, K. C. L.; Hunt, P. M. *J. Chem. Phys.* **1988**, *88*, 2179; **1992**, *96*, 618.

(3) Ross, J.; Harding, R. H.; Wolff, A. N.; Chu, X. *J. Chem. Phys.* **1991**, *95*, 5206. Ross, J.; Chu, X.; Hjelmfeldt, A.; Velarde, M. *J. Phys. Chem*. **1993**, *97*, 4708.

(4) Peng, Bo.; Hunt, K. L. C.; Hunt, P. M.; Suàrez, A.; Ross, J. J. *Chem. Phys.* **1995**, *102*, 4548.

(5) Suàrez, A.; Ross, J.; Peng, Bo.; Hunt, K. L. C.; Hunt, P. M. *J. Chem Phys.* **1995**, *102*, 4563. Suàrez, A.; Ross, J. *J. Phys. Chem.* **1995**, *99*, 14854; Vance, W.; Ross, J. *J. Chem. Phys*. **1996**, *105*, 479.

(6) Vlad, M. O.; Ross, J. *J. Chem. Phys.* **1994**, *100*, 7268, 7279, 7295.

(7) Vlad, M. O.; Ross, J.; Mackey, M. C. *J. Math. Phys.* **1995**, *37*, 803.

(8) Vlad, M. O.; Ross, J.; Plonka, *A. Chem. Phys.* **1999**, *243*, 273.

(9) Vlad, M. O.; Ross, J. *J. Phys. Chem. B* **1997**, *101*, 8756.

(10) Onsager, L.; Machlup, S. *Phys. Rev.* **1953**, *91*, 1505. Machlup, S.; Onsager, L. *Phys. Rev.* **1953**, *91*, 1512.

(11) Hashitsume, H. *Prog. Theor. Phys.* **1952**, *8*, 461; **1956**, *15*, 369.

(12) Van Kampen, N. G. *Stochastic Processes in Physics and Chemistry*, 2nd Ed.; Elsevier: Amsterdam, 1992.

(13) McQuarrie, D. *J. Chem. Phys.* **1963**, *38*, 433. McQuarrie, D.; Keizer, J. In *Theoretical Chemistry: Advances and Perspectives*; Academic Press: New York, 1981; Vol. 6A, pp 165−203. Oppenheim, I.; Shuler, K.; Weiss, G. H. *Stochastic Processes in Chemical Physics: The Master Equation*; MIT Press: Cambridge, MA, 1977. Kurz, T. *J. Appl. Prob.* **1971**, *8*, 344. Van Den Broeck, C.; Malek-Mansour, M.; Hortshemke, W. *Physica* **1977**, *A89*, 339. Glansdorff, P.; Prigogine, I. *Thermodynamic Theory of Structure, Stability and Fluctuations*; Wiley: New York, 1971. Nicolis, G.; Prgogine, I. *Self-Organization in Nonequilibrium Systems*; Wiley: New York, 1977.

(14) Feinberg, M.; Horn, F. J. M. *Arch. Rat. Mech. Anal.* **1977**, *66*, 83. Horn, F. *Ibid.* **1973**, *49*, 172; *Proc. R. Soc. London, Ser. A* **1973**, *334*, 313, 331.

(15) Schlögl, F. *Phys. Rep.* **1980**, *62*, 267.

(16) Ramakrishnan, A. in *Handbuch der Physik*; Flügge, S., Ed.; Springer: Berlin, 1959; pp 525−651.

(17) Schnakenberg, J. *Rev. Mod. Phys.* **1976**, *48*, 571. Shear, D. B. *J. Chem. Phys.* **1968**, *48*, 4144.

(18) Kubo, R.; Matsuo, K.; Kitahara, K. *J. Stat. Phys.* **1973**, *9*, 51. Kitahara, K. *Adv. Chem. Phys.* **1975**, *29*, 85.

(19) Solc, M. *Z. Phys. Chem. Neue Folge* **1974**, *92*, 1; *Collect. Czech. Chem. Commun.* **1974**, *39*, 197; **1981**, *46*, 1217.

(20) De Groot, S. R.; Mazur, P. *Nonequilibrium Thermodynamics*; Dover: New York, 1989.

(21) Klimontovich, Y. L. *Physica A* **1990**, *163*, 515; **1992**, *182*, 121.

(22) Graham, R. In *Fluctuations, Instabilities and Phase Transitions*; Riste, T., Ed.; Plenum: New York, 1969. Graham, R.; Tél, T. *J. Stat. Phys.* **1984**, *35*, 729; *Phys. Rev. A* **1985**, *31*, 1109.

(23) Keizer, J. *J. Chem. Phys.* **1975**, *63*, 5037; **1976**, *64*, 1679; **1976**, *64*, 4466; **1978**, *69*, 2609; **1985**, *82*, 2751; *Phys. Rev.* **1984**, *A30*, 1115. *Statistical Thermodynamics of Nonequilibrium Processes*, Springer: New York, 1987.