KINETICS AND THERMODYNAMICS OF FLUCTUATION-INDUCED TRANSITIONS IN MULTISTABLE SYSTEMS

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I.   INTRODUCTION

Many physical systems obey, at the macroscopic level of description, evolution equations of the form[1]

$$\frac{d\bar{x}_i}{dt} = v_i(\{\bar{x}_j\}, \lambda) \tag{1}$$

Here $\{\bar{x}_i\}$, $i = 1, \cdots, n$ are state variables such as density, temperature, or concentration; $\{v_i\}$ represent the evolution laws, leading eventually an initial state $\{\bar{x}_i(0)\}$ toward an invariant part of phase space referred to as the attractor; and λ is a set of parameters expressing the coupling between the system and its environment.

In most situations of interest the v_i's are nonlinear functions of the $\{\bar{x}_j\}$'s. One of the principal signatures of such nonlinearities is the multiplicity of simultaneously available states that can be reached in the long time limit. On the other hand, at the level of description afforded by Eq. (1) a transition between these states, signaling a qualitative change of behavior of the underlying system, can only be realized by the action of an external preparation bringing the initial condition from the domain of attraction of the initially prevailing asymptotic state to that of the new one. If these two regimes are separated by a finite distance the corresponding initial perturbation needs to be quite massive, and hence hardly realizable under normal conditions.

Now systems composed of several subunits—as is typically the case of physical systems—are subjected to spontaneous deviations from the state predicted by a description like in Eq. (1) owing to microscopic-level processes such as thermal motion and interparticle collisions. Furthermore, they are as a rule embedded in a complex environment with which they continuously exchange matter, momentum and energy. To account for these universal sources of variability we augment Eqs. (1) by the addition of random forces $\{R_i(t)\}$. This leads to a set of stochastic evolution equations of the form [1–3]

$$\frac{dx_i}{dt} = v_i(\{x_j\}, \lambda) + R_i(t) \tag{2}$$

We refer to the descriptions afforded by Eqs. (2) and (1) as the mesoscopic and the mean-field description, respectively.

At the level of the observables, the action of $R_i(t)$ will be manifested in the form of fluctuations around the deterministic path as provided by Eq. (1). Our main objective in this chapter is to identify the principal features of these fluctuations starting from a set of assumptions on the nature of the random forces. A most important point for our purpose is that fluctuations provide a natural mechanism of transitions between states and much of the analysis will aim at determining the mean rates and other probabilistic properties of these transitions.

The general formulation is laid down in Section II. The case where the mean-field dynamics derives from a kinetic potential is considered in Section III, where the conditions of existence of such a potential and its connection with the thermodynamic potentials are also analyzed. We show that there exists a general class of phenomena for which this connection can be implemented and which includes a variety of nucleation phenomena associated to phase transitions, one of the principal themes of this volume. Section IV is devoted to the type of kinetic potentials compatible with two-step nucleation as observed, in particular, in protein solutions. State diagrams and phase space portraits are derived and different generic scenarios are identified. A discrete state model of transitions between states compatible with this information is derived in Section V, where the mean transition times are computed and compared with the result of full-scale stochastic simulations. It is shown that the presence of intermediate metastable states may be responsible of an enhancement in the transition rates. The repercussions of different transition scenarios on the dissipation generated by the system are studied in Section VI. The main conclusions are summarized in Section VII.

II.   FORMULATION

Our starting point is Eq. (2) under the additional assumption that the random forces R_i define a multivariate stationary Gaussian white noise process,

$$\langle R_i(t)R_j(t') \rangle = 2\epsilon D_{ij}\delta(t - t') \tag{3}$$

it being understood that D_{ij} form a positive definite matrix and are time independent (stationary process). ϵ is a small parameter related, depending on the case, to the thermal energy $k_\mathrm{B}T$ or to the inverse of the system size.

As is well known, under the above conditions the stochastic variables $\{x_i\}$ undergo a diffusion process in phase space, whose probability density P satisfies the Fokker–Planck equation [1–3]

$$\frac{\partial P}{\partial t} = -\sum_{i=1}^{n} \frac{\partial}{\partial x_i} v_i(\{x_j\})P + \epsilon \sum_{i,j=1}^{n} \frac{\partial}{\partial x_i} D_{ij} \frac{\partial P}{\partial x_j} \tag{4}$$

There is an abundant literature on both the stationary and time-dependent solutions of Eq. (4) in the case of a single variable, but the situation becomes markedly more involved in the presence of two or more variables. We summarize hereafter some results of special relevance for the purposes of the present chapter.

A. Stationary Distribution

Let us write Eq. (4) in the form

$$\frac{\partial P}{\partial t} = -\sum_i \frac{\partial J_i}{\partial x_i} \tag{5a}$$

where the ith component J_i of the probability flux $\mathbf{J}$ is given by

$$J_i = v_i(\{x_j\})P - \epsilon \sum_j D_{ij} \frac{\partial P}{\partial x_j} \tag{5b}$$

For P to be stationary the divergence of $\mathbf{J}$ must vanish. Now, in a multivariate system subjected to nonequilibrium constraints this does not imply automatically the vanishing of $\mathbf{J}$ itself, since a circulating probability flow with nonzero curl may subsist, even if the state is globally stationary [4]. This entails that the stationary solution of (4) cannot be found analytically by a simple algorithm. Nevertheless, the presence of an ϵ factor in Eq. (4) suggests to seek approximate stationary solutions of the form [1–3]

$$P_s(\{x_j\}) = \exp[-\Phi(\{x_j\})/\epsilon] \tag{6}$$

Substituting into (4) and keeping dominant terms (in ϵ^{-1}) one obtains a Hamilton–Jacobi type equation satisfied by Φ [5, 6],

$$\sum_i v_i \frac{\partial \Phi}{\partial x_i} + \sum_{ij} D_{ij} \frac{\partial \Phi}{\partial x_i} \frac{\partial \Phi}{\partial x_j} = 0 \tag{7}$$

which can be solved approximately by expanding Φ in an appropriate basis.

There are two cases where the above difficulties do not arise: One variable systems; and closed physical systems, where P_s must coincide with one of the classical distributions given by equilibrium statistical mechanics. This latter type of systems is of special relevance in the problem of multistep nucleation and will be considered in detail in Section III.

An important point is that Φ possesses a local extremum along the solutions of the mean-field equations (1). On these grounds it has been suggested that it may be viewed as a generalized entropy-like function [7]. This analogy will be taken up again in Section III.

B. Exit from an Attraction Basin

Consider now the case where the system admits several simultaneously stable steady-state solutions $\bar{x}_{i,\alpha}$, $\alpha = 1, \cdots, M$ and let C_α be the corresponding attraction basins. Clearly, C_α partition the full phase space into nonoverlapping cells

separated by boundaries constituted by the stable manifolds of the unstable steady-state solutions of Eqs. (1) $\bar{x}_{i,\beta}$, $\beta = 1, \cdots, N$. Within each C_α the vector field $\{v_i\}$ will tend toward $\{\bar{x}_{i,\alpha}\}$. Still, under the effect of a noise defined on an unbounded support, as in Eq. (3), a trajectory emanating from a point inside cell C_α will sooner or later cross the boundaries of this cell and will find itself in the domain of attraction of another stable fixed point. Two natural questions arise then in this context.

  (i) Let **c** be a point on C_α. What is the distribution $\pi(\mathbf{x}, \mathbf{c})$ of points **c** by which the trajectory escapes from C_α starting from point $\mathbf{x} \in C_\alpha$?
  (ii) What is the mean exit time from C_α?

Just like for the stationary distribution, an exact analytic answer to these questions is not available in the most general case of a multivariate system subjected to nonequilibrium constraints. But in the limit $\epsilon \to 0$ some asymptotic estimates can again be obtained [2]. First, the distribution of exit points is given essentially by $\exp(-\Phi(\mathbf{c}/\epsilon))$, that is, by the stationary distribution [Eq. (6)]. And second, the mean exit time is given by the inverse of the lowest eigenvalue λ_1 of the Fokker–Planck operator, which in the case of multistable systems is exponentially small, $\lambda_1 \approx \exp(-K/\epsilon)$ where K is a finite positive number determined by the structure of velocity field **v** and by the diffusion matrix D.

III.   CLOSED SYSTEMS AND DETAILED BALANCE

We now limit ourselves to closed systems operating in the linear range of irreversible processes. On the one side, this implies the absence of systematic externally imposed nonequilibrium constraints, the only source of nonequilibrium being the initial deviation of $\{\bar{x}_i\}$ from the equilibrium values $\{\bar{x}_{i,\mathrm{e}}\}$. And on the other side, it implies that the fluxes **j** associated to the various irreversible processes present are connected to the associated thermodynamic forces by the relation [8, 9]

$$\mathbf{j} = L \cdot \mathbf{X} \tag{8}$$

where the matrix L of kinetic (Onsager) coefficients is assumed to be positive definite. The forces **X** are in turn related to the derivatives of a thermodynamic potential such as the free energy function F

$$\mathbf{X} = -\frac{\partial F}{\partial \mathbf{x}} \tag{9}$$

Furthermore, under an appropriate choice of variables the fluxes **j** can be identified to the time derivatives of the **x**'s, it being understood from now on that these

variables belong to the class of even variables under time reversal [2, 3]. Equation (2) takes now the form

$$\frac{d\mathbf{x}}{dt} = -L \cdot \frac{\partial F}{\partial \mathbf{x}} + \mathbf{R}(t) \tag{10}$$

expressing the evolution of the state variables as the overall result of thermodynamic driven processes accounted for by F and of kinetically driven ones accounted for by L and $\mathbf{R}$. Nonlinearity and in particular the multiplicity of steady states stems in this setting entirely from F, the states being thus related to different phases in which the system of interest can exist. As for L and $\mathbf{R}$ they account for the relaxation processes and for the fluctuations around each state as well as for transitions between the states. It has to be emphasized that in writing Eq. (10) we have lumped together the spatial degrees of freedom. In this view $\{x_i\}$ represent averaged quantities, such as for instance the mass fractions of the material in different states/phases at a given stage of the transformation.

The Fokker–Planck equation [Eq. (4)] associated to Eq. (10) reads

$$\frac{\partial P}{\partial t} = \sum_{i=1}^{n} \frac{\partial}{\partial x_i} \left(\sum_{j=1}^{n} L_{ij} \frac{\partial F}{\partial x_j} P + \epsilon \sum_{j=1}^{n} D_{ij} \frac{\partial P}{\partial x_j} \right) \tag{11}$$

To secure consistency with equilibrium statistical mechanics this equation must admit as stationary solution the equilibrium distribution

$$P_s = P_e \approx \exp(-F/\epsilon) \tag{12}$$

Inserting into Eq. (11) one sees that the diffusion matrix D and the kinetic matrix L must be proportional (a fluctuation–dissipation type relationship) and Eq. (11) simplifies further to

$$\frac{\partial P}{\partial t} = \sum_{i,j=1}^{n} \frac{\partial}{\partial x_i} L_{ij} \left(\frac{\partial F}{\partial x_j} P + \epsilon \frac{\partial P}{\partial x_j} \right) \tag{13}$$

Notice that this equation in conjunction with (12) implies a vanishing probability flux in the stationary (here equilibrium) state, $J_{i,e} = 0$ for all $\{x_j\}$'s within each of the attraction basins of the fixed points. This latter property implies by itself that the velocity field must be a linear combination of the derivatives of some potential function with respect to the state variables but is actually more general than detailed balance, in the sense that it may in principle be compatible with the presence of nonequilibrium constraints.

To extract from Eq. (13) information concerning the time-dependent properties we introduce a linear transformation of variables

$$\mathbf{x} = A \cdot \mathbf{z} \tag{14a}$$

$$\frac{\partial}{\partial \mathbf{x}} = \widetilde{A}^{-1} \cdot \frac{\partial}{\partial \mathbf{z}} \tag{14b}$$

$\widetilde{A}$ being the transposed of matrix A, and set

$$F(\mathbf{x}(\mathbf{z})) = U(\mathbf{z}) \tag{14c}$$

$$P(\mathbf{x}(\mathbf{z})) = \rho(\mathbf{z}) \tag{14d}$$

We assume from now on that the kinetic matrix L is state independent. By virtue of the fluctuation–dissipation theorem this applies to the correlation matrix D of the fluctuations as well (additive noise). Substituting into the equation we obtain, after some straightforward manipulations,

$$\frac{\partial \rho}{\partial t} = \left(\widetilde{A}^{-1} \cdot \frac{\partial}{\partial \mathbf{z}} \right) \cdot \left\{ L \cdot \left[\left(\widetilde{A}^{-1} \frac{\partial U}{\partial \mathbf{z}} \rho + \epsilon \widetilde{A}^{-1} \frac{\partial \rho}{\partial \mathbf{z}} \right) \right] \right\}$$

or, in more explicit form,

$$\frac{\partial \rho}{\partial t} = \sum_{jm} \left(A^{-1} L \widetilde{A}^{-1} \right)_{jm} \left(\frac{\partial}{\partial z_j} \frac{\partial U}{\partial z_m} \rho + \epsilon \frac{\partial^2 \rho}{\partial z_j \partial z_m} \right) \tag{15}$$

Equation (15) features the matrix

$$\Lambda = A^{-1} L \widetilde{A}^{-1} \tag{16}$$

linked to L by a congruent transformation. As well known under such a transformation a symmetric matrix can be diagonalized and actually, upon a further linear scaling, be reduced to the unit matrix. This requirement determines fully the transformation matrix A and upon substituting into Eq. (15), one obtains [10]

$$\frac{\partial \rho}{\partial t} = \sum_{j=1}^{n} \frac{\partial}{\partial z_j} \left(\frac{\partial U}{\partial z_j} \rho + \epsilon \frac{\partial \rho}{\partial z_j} \right) \tag{17}$$

where t is a rescaled time. This is the standard form of the Fokker–Planck equation of a system whose deterministic part of the evolution is driven by a *kinetic potential* U and which is subjected to additive fluctuations of identical variance. A system of this kind undergoes a process of isotropic diffusion in phase space described by

the Langevin equation [cf. also Eq. (10)]

$$\frac{dz_i}{dt} = -\frac{\partial U}{\partial z_i} + r_i(t) \tag{18a}$$

where the random forces satisfy the properties

$$\langle r_i(t) \rangle = 0, \qquad \langle r_i(t) r_j(t') \rangle = 2\epsilon \delta_{ij}^{\mathrm{kr}} \delta(t - t') \tag{18b}$$

As a corollary the invariant (equilibrium) probability density is given by

$$\rho_s(\mathbf{z}) = \rho_e \approx \exp(-U(\mathbf{z})/\epsilon) \tag{18c}$$

Equations (18) establish the possibility to cast the evolution equations of a multivariate system, under the assumptions of detailed balance and of additive noise, in a form deriving from a kinetic potential generating both the dynamical evolution and the invariant probability of the relevant variables z_i. These properties of the kinetic potential U are to be contrasted from those of quantity Φ introduced in Section II, for a system subjected to nonequilibrium constraints and not satisfying the detailed balance property. The extent to which they subsist if the matrices L and D are state dependent will be discussed briefly in the subsequent sections.

It should be pointed out that the conjunction of fluctuations and nonlinearities implies that the evolution of the mean values generated by Eq. (17),

$$\frac{\langle dz_i \rangle}{dt} = -\left\langle \frac{\partial U}{\partial z_i} \right\rangle$$

is not closed with respect to $\langle z_i \rangle$, but involves higher moments of the probability density as well. It is only when the mean-field approximation can be justified that these latter equations reduce to a closed set of deterministic evolution laws,

$$\frac{d\bar{z}_i}{dt} = -\frac{\partial U}{\partial \bar{z}_i} \tag{19}$$

Otherwise, one needs to resort to the full Eq. (18a).

Let $\{\bar{z}_{i,\alpha}\}$ be the steady-state solutions to which the solutions $\{\bar{x}_{i,\alpha}\}$ introduced in Section II transform through Eq. (14a). It follows from (19) that they are extrema of the kinetic potential U and, by virtue of Eqs. (12) and (14c), of the free energy and thus of the invariant probability itself as well. Linearizing around these states, setting $\bar{z}_i = \bar{z}_{i,\alpha} + \delta z_{i,\alpha}$ yields

$$\frac{d\delta z_{i,\alpha}}{dt} = -\sum_j \left(\frac{\partial^2 U}{\partial \bar{z}_i \partial \bar{z}_j} \right)_\alpha \delta z_{j,\alpha}$$

$$\equiv -\sum_j H_{ij} \delta z_{j,\alpha} \tag{20}$$

where $H = \{H_{ij}\}$ is the Hessian matrix of U. If all eigenvalues of H are positive the reference state $\{\bar{z}_{i,\alpha}\}$ is asymptotically stable and, at the same time, a minimum of both U and F. If at least one eigenvalue of H is negative the reference state is unstable. Typically it corresponds to a saddle of the potential surface U as a function of $\bar{z}_i$ and, exceptionally, (if all eigenvalues are negative) to a maximum.

Under the conditions of existence of a kinetic potential considered in the present section the exit problem formulated in Section IIB simplifies considerably. Specifically, it can be shown that in the limit, again, of small ϵ the transition between stable states $\{\bar{x}_{i,\alpha}\}$ and $\{\bar{x}_{i,\alpha'}\}$ will follow a path across the saddle point $\{\bar{x}_{i,\beta}\}$ lying on the manifold separating the corresponding attraction basins. Furthermore, in the same limit the mean exit time depends principally on the following elements [11]:

(i) The value of the *potential barrier* ΔU, that is, the difference of values of U on the unstable (transition) state and the stable state. Since U has a local minimum on the stable state, ΔU is necessarily a positive quantity. Furthermore, by virtue of Eq. (14c) ΔU is equal in magnitude to the free energy barrier separating the states concerned by the transition.

(ii) The Hessian determinant, that is, the product of the eigenvalues of the Hessian matrix $\{H_{ij}\}$, evaluated at the minimum of the potential on the stable state.

(iii) The curvature of U on the unstable state in the direction across the saddle point.

In contrast to ΔU which as pointed out in (i) is determined from the thermodynamics, the two latter quantities depend on kinetic effects and are thus different from those associated to the free energy. Explicit expressions will be provided in Section IV for generic potentials U involving two variables.

We close this section by an application of the above outlined formalism to first-order phase transitions mediated by intermediate metastable phases [12–15]. As alluded already in the Introduction and discussed extensively in the chapters by Vekilov, Dinsmore et al., and Lutsko in this volume transitions of this kind are known to occur in a variety of materials, from protein solutions to aerosols to plasma crystals. Of special relevance is protein crystallization, where the weakness and short-range character of the attractive part of the interactions favors the existence of a long-living metastable phase in the form of a high concentration liquid. This phase tends to enhance significantly, under certain conditions, the rate of nucleation of crystals. Here we focus on the kinetic aspects of the process and, in particular, on the role of the kinetic potential U and its relationship with the free energy F. For this purpose nucleation is formulated as the dynamics of two coupled order parameters x_1 and x_2 related respectively to density—or concentration—and structure (crystallinity), evolving in an effective force field provided by the first

part of Eq. (10) and subjected to thermal fluctuations in the form of Gaussian white noise,

$$\frac{dx_1}{dt} = -L_1 \frac{\partial F}{\partial x_1} - L \frac{\partial F}{\partial x_2} + R_1(t)$$

$$\frac{dx_2}{dt} = -L \frac{\partial F}{\partial x_1} - L_2 \frac{\partial F}{\partial x_2} + R_2(t) \tag{21}$$

where the matrix L of the kinetic coefficients has been taken to be symmetrical by virtue of Onsager's reciprocity relations. We stress that in the absence of the intermediate phase Eq. (21) collapse into a single equation for a unique order parameter, which can be cast straightforwardly in a variational form.

Switching to the Fokker–Planck description and assuming that the fluctuation–dissipation theorem is valid we seek for a congruent transformation (14) diagonalizing L with a matrix A of the form $A_{ii} = a_i$, $A_{ij} = A_{ji} = a$. Upon carrying out the algebra one obtains

$$a_1 = \frac{L_1 \pm \sqrt{L_1 L_2 - L^2}}{L} a$$

$$a_2 = \frac{L_2 \pm \sqrt{L_1 L_2 - L^2}}{L} a \tag{22a}$$

and the Fokker–Planck equation in the z_1, z_2 variables

$$\frac{\partial \rho}{\partial t} = \frac{\sqrt{L_1 L_2 - L^2} L^2}{a^2 (L_1 + L_2 + 2\sqrt{L_1 L_2 - L^2})} \left\{ \frac{\partial}{\partial z_1} \frac{\partial U}{\partial z_1} \rho + \frac{\partial}{\partial z_2} \frac{\partial U}{\partial z_2} \rho + \epsilon \left(\frac{\partial^2 \rho}{\partial z_1^2} + \frac{\partial^2 \rho}{\partial z_2^2} \right) \right\} \tag{22b}$$

Notice that the argument in the square root is positive, owing to the positive definiteness of the matrix L. This relation can be further reduced to the form of Eq. (17) by rescaling the variables z_1, z_2 or, more straightforwardly, the time,

$$t = \tau \frac{a^2 (L_1 + L_2 + 2\sqrt{L_1 L_2 - L^2})}{L^2 \sqrt{L_1 L_2 - L^2}} \tag{22c}$$

yielding

$$\frac{\partial \rho}{\partial \tau} = \frac{\partial}{\partial z_1} \frac{\partial U}{\partial z_1} \rho + \frac{\partial}{\partial z_2} \frac{\partial U}{\partial z_2} \rho + \epsilon \left(\frac{\partial^2 \rho}{\partial z_1^2} + \frac{\partial^2 \rho}{\partial z_2^2} \right) \tag{23}$$

In the context of the two-step nucleation the free energy F possesses three minima. Now, from Eq. (14) one has

$$\frac{\partial F}{\partial x_i} = \sum_{k=1}^{2} \widetilde{A}_{ik}^{-1} \frac{\partial U}{\partial z_k}$$

$$\frac{\partial^2 F}{\partial x_i \partial x_j} = \sum_{k,\ell=1}^{2} \widetilde{A}_{ik}^{-1} A_{\ell j}^{-1} \frac{\partial^2 U}{\partial z_k \partial z_\ell} \tag{24}$$

The first of these relations implies that the extrema of F transform into extrema of U, since the matrix A is nonsingular. The second relation implies that the Hessians of U and F (in their respective variables) are related by the congruent transformation used to reduce L to the unit matrix which, by construction, preserves positivity. The nature of the extrema of F is thus not affected in the evolution in terms of the transformed variables. In short, the nucleation of crystals of the solid phase is reflected by fluctuation-induced transitions removing the system, initially located in a minimum of U associated to the fluid phase, toward a minimum associated to the solid phase.

An interesting question from the standpoint of irreversible thermodynamics is whether the processes associated to the density and crystallinity (structure) fields can be thermodynamically coupled, as implied in Eq. (21) by the presence of the off-diagonal element L of the Onsager matrix. Now density is a true scalar whereas structure is accounted for by a tensor. At first sight, in an isotropic medium, this would rule out a thermodynamic coupling on the grounds of the Curie symmetry principle [8, 9]. On the other hand, a tensor T can be split in the following way

$$T = \frac{1}{3} I \, tr \, T + T^{(a)} + T^{(s)} \tag{25}$$

where I is the unit tensor, $tr \, T$ the trace of T that is a scalar, $T^{(a)}$ its antisymmetric part that can alternatively be viewed as an axial ("pseudo") vector, and $T^{(s)}$ its symmetric traceless part that can be alternatively be viewed as a polar ("true") vector. Clearly, then, the density field x_1 can legitimately be coupled to the first part of the decomposition in Eq. (25) or, alternatively, to any other structure related quantity x_2 of scalar nature such as the first coefficient of a Fourier series expansion of the solid-phase density. The terms in L at the level of Eq. (21) stand, precisely, for this type of coupling. Notice that even in the absence of a nondiagonal term L in this equation x_1 and x_2 would still be coupled kinetically, through the x_1, x_2 dependence of the potential.

IV.   GENERIC POTENTIALS AND THEIR UNFOLDINGS

In this section, we develop some generic models of transitions between states compatible with different types of nucleation scenarios observed in nanosize materials

such as protein solutions, under the conditions of existence of a kinetic potential put forward in the preceding section. The latter is viewed as a Landau type polynomial [16, 17] that depends nonlinearly on appropriate linear combinations of the original variables—the order parameters—the main question being to determine for each given scenario the minimal number of relevant order parameters and the minimal relevant nonlinearities displayed in this potential providing a qualitative explanation of the process of interest.

Now the above described program is reminiscent of the philosophy underlying bifurcation theory [18, 19] or more appropriately catastrophe theory [20–22], which deals more specifically with the classification of the different behaviors of dynamical systems deriving from a potential. Applications of catastrophe theory to phase transitions have been the subject of several investigations [23–25], but to our knowledge they have so far been concerned with the structure of the phase diagrams of a material as some key parameters are varied. Here we also focus on dynamical aspects, including the kinetics of the transitions between different states. The particular class of phenomena that we address are transitions between a reference state, denoted by 1, to a final state, denoted by 3 it being understood that under certain conditions another state 2 may also exist such that transitions from 1 to 2 and from 2 to 3 are possible. In the literature of multistep nucleation [12–15], 1 can be a dilute protein solution phase, 3 a crystalline phase with high protein concentration, and 2 a dense protein solution phase, but in actual fact the approach is generic: it extends beyond this example and covers a wide class of materials, including colloidal systems. All states 1, 2, 3 are supposed to be locally stable and thus to correspond to minima of the kinetic potential U. We place ourselves in conditions where 3 is much more stable than 1 and 2, entailing that $U(3)$ is significantly less than $U(1)$ and $U(2)$. The relative stability of states 1 and 2 can change. Of special interest will be situations where state 2 represents a metastable phase.

The simplest "reference" situation is when state 2 does not exist. The transition between 1 and 3, a first-order phase transition, can then be understood qualitatively in terms of a Landau polynomial of 4th degree involving a single order parameter z related, for example, to the protein concentration,

$$U_4(z) = \frac{z^4}{4} + \lambda \frac{z^2}{2} + uz \qquad (26)$$

This type of nonlinearity along with the two control parameters λ and u are sufficient to account for all different behaviors. Criticalities separating these behaviors are associated with the cusp catastrophe [21], one of the seven known elementary catastrophes. The transition per se from 1 to 3 occurs through an intermediate unstable state (13), lying between 1 and 2.

Let us now place ourselves under conditions that state 2 also exists. Different situations can be envisaged.

A. Transitions from 1 to 3 Occur Necessarily Through State 2

This scenario is in turn compatible with the presence of both a single or two order parameters.

(i) In the first case the minimal Landau polynomial compatible with the existence of three local minima is of 6th degree [21].

$$U_6(z) = \frac{z^6}{6} + w\frac{z^4}{4} + c\frac{z^3}{3} + \lambda\frac{z^2}{2} + uz \qquad (27)$$

It involves the four control parameters w, c, λ, and u [21] and generates at criticality the butterfly catastrophe [21]. The transition from 1 to 3 involves two steps [26]. One from 1 to 2 via an intermediate unstable state (12); and one from 2 to 3 via an intermediate unstable state (23).

(ii) In the second more realistic case, in addition to order parameter z_1 related to, for example, concentration in the example of protein crystallization one also accounts for a second order parameter z_2 associated to the structure of the solid phase. We require that the associate potential switches, as the control parameters are varied, from a two-well geometry (minima at states 1 and 3) to a three-well one (minima at states 1, 2, and 3). This transition scenario is typical of the parabolic umbilic catastrophe [21] and its universal features can be captured by the potential involving four control parameters [21]

$$U(z_1, z_2) = \frac{z_1^2 z_2}{2} + \frac{z_2^4}{4} + \lambda\frac{z_1^2}{2} + \mu\frac{z_2^2}{2} + uz_1 + vz_2 \qquad (28)$$

In spite of the presence of the additional variable z_2 the transition from 1 to 3 still occurs necessarily via state 2 [27] and involves two intermediate unstable states, (12) and (23) behaving as saddle points in the two-dimensional phase space spanned by z_1 and z_2.

B. Transitions from 1 to 3 Need Not Occur Through State 2

In this more flexible scenario, which is compatible with the experimental data on crystallization of protein solutions or of colloidal systems, we are led to require that all three states 1, 2, and 3 must be able to communicate with each other directly. In a two-dimensional phase space this entails three stable nodes whose attraction basins are separated by the stable manifolds of three saddle points. If only these six fixed points were present this would lead to a forbidden configuration in the form of a closed loop delimited by the unstable manifolds of the three saddles. One thus needs to stipulate the existence of a seventh fixed point, which for topological reasons must be an unstable node and thus a maximum of the kinetic potential.

To accommodate this configuration it is necessary to go beyond the potentials associated to the seven elementary catastrophes, the minimal solution satisfying the necessary genericity properties being the unfolding of the double cusp catastrophe [28, 29], which we write here in the form

$$U(z_1, z_2) = \frac{z_1^4 + z_2^4}{4} + k\frac{z_1^2 z_2^2}{2} + a\frac{z_1^3}{3} + b\frac{z_1^2 z_2}{2}$$

$$+ \lambda\frac{z_1^2}{2} + \mu\frac{z_2^2}{2} + cz_1 z_2 + uz_1 + vz_2 \qquad (29)$$

with $k > -2$ and $k \neq 2$. This potential involves eight control parameters. It reduces along $z_1 = 0$ and along $z_2 = 0$ to a potential of the form (26) associated to the classical cusp catastrophe—whence the "double cusp catastrophe" denomination. In what follows we will be interested in the dynamical behaviors and the bifurcations generated by the partial unfolding in which we set $k = b = 0$.

The mean-field evolution equations of the two order parameters generated by the potential in Eq. (29) are [cf. Eq. (19)]

$$\frac{d\bar{z}_1}{dt} = -\bar{z}_1^3 - a\bar{z}_1^2 - \lambda\bar{z}_1 - c\bar{z}_2 - u$$

$$\frac{d\bar{z}_2}{dt} = -\bar{z}_2^3 - \mu\bar{z}_2 - c\bar{z}_1 - v \qquad (30)$$

In the limit where the coefficient c is zero these equations are uncoupled. Their steady-state solutions are thus solutions of two independent cubic equations. Depending on the sign of the corresponding discriminant each of these can have one to three real solutions, the transition between these different regimes being conditioned by the cusp catastrophe. Globally therefore, barring nongeneric situations where two real solutions merge into a single one (discriminant of one of the cubics vanishes) the full system can have for given parameter values one, three, or nine real solutions.

Consider now the case of c being nonzero. Equation (30) become then coupled and their steady state solutions z_{1s}, z_{2s} satisfy the relations

$$z_{2s} = -\frac{1}{c}\left(z_{1s}^3 + az_{1s}^2 + \lambda z_{1s} + u\right) \qquad (31a)$$

$$-\frac{1}{c^3}\left(z_{1s}^3 + az_{1s}^2 + \lambda z_{1s} + u\right)^3$$

$$-\frac{\mu}{c}\left(z_{1s}^3 + az_{1s}^2 + \lambda z_{1s} + u\right) + cz_{1s} + v = 0 \qquad (31b)$$

The stability of these solutions is determined by the eigenvalues ω of the Jacobian matrix of (30), which satisfy the characteristic equation

$$\omega^2 + \left\{ 3 \left(z_{1s}^2 + z_{2s}^2 \right) + 2az_{1s} + \lambda + \mu \right\} w$$
$$+ \left(3z_{1s}^2 + 2az_{1s} + \lambda \right) \left(3z_{2s}^2 + \mu \right) - c^2 = 0 \qquad (32)$$

We notice that Eq. (31b) is of ninth degree. It can thus have up to nine real solutions continuing those of the uncoupled case, as long as c is sufficiently small. The situation will change as c is gradually increased. Since there cannot be more than nine solutions, one expects that the number of solutions will decrease. Furthermore, degenerate situations where two real solutions were merging for $c = 0$ should now give rise to two structurally stable solutions following the splitting of the degeneracy caused by the "perturbation" terms $c\bar{z}_2$ and $c\bar{z}_1$.

Figure 1 depicts the bifurcation diagram of solution z_{1s} [Eq. (31b)] versus parameter c keeping a, λ, μ, u, and v fixed such that in the limit $c = 0$ one has nine real solutions. As can be seen, increasing c leads successively from four simultaneously stable solutions (among a total of nine solutions) to three simultaneously stable solutions (among a total of seven solutions) and finally to two simultaneously stable solutions (among a total of three solutions). This is in full agreement
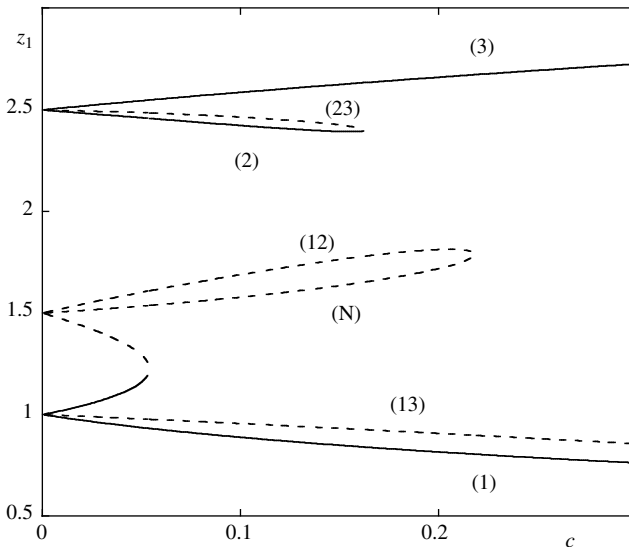
Figure 1. Bifurcation diagram of solution z_{1s} of Eq. (31b) versus parameter c for $a = -5$, $\lambda = 7.75$, $\mu = -7/4$, $u = -3.75$, and $v = 1/2$. Full and dashed lines denote stable and unstable states, respectively. (1) Reference stable state; (3) final stable state; (2) intermediate stable state; (12), (13), (23) intermediate unstable saddle-type states; (N) unstable node.
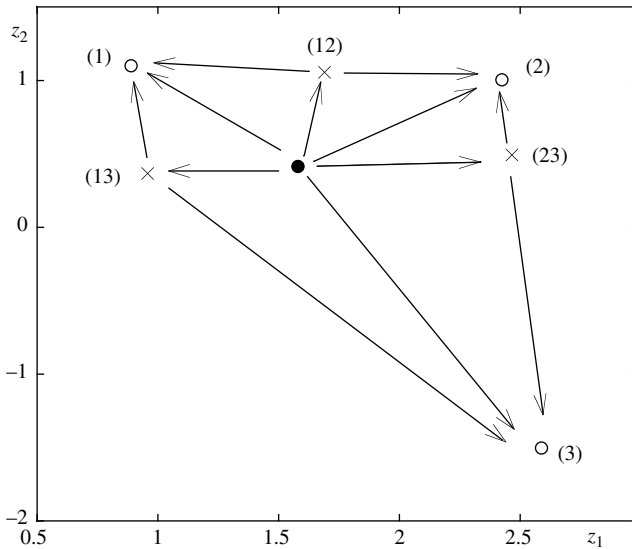
Figure 2. Location of steady states of Eq. (30) and of the unstable manifolds in the two-dimensional phase space (z_1, z_2) for $c = 0.1$. Other parameter values as in Fig. 1.

with the qualitative arguments advanced above. Notice that from the standpoint of phase transition theory four coexisting stable phases is compatible with the Gibbs phase rule [30] as long as one is dealing with a two-component system, as is the case of a protein solution.

The location of the steady states in phase space in the range of three simultaneously stable states is indicated in Fig. 2, where the unstable manifolds of the other fixed points are also sketched. We obtain a configuration corresponding exactly to what was anticipated in the beginning of Section IVB showing clearly the existence of two *a priori* competing pathways, of transitions from state 1 to state 3, $1 \to (13) \to 3$ and $1 \to (12) \to 2 \to (23) \to 3$. This configuration also suggests associating in the particular case of protein crystallization order parameter z_1 to "concentration" and order parameter $-z_2$ to "structure" or "crystallinity."

Naturally, the transitions between the stable states present in the bifurcation diagram of Fig. 1 will be governed by the augmented version of Eq. (30) in which fluctuations are incorporated, see Eq. (18a):

$$\frac{dz_1}{dt} = -z_1^3 - az_1^2 - \lambda z_1 - cz_2 - u + r_1(t)$$

$$\frac{dz_2}{dt} = -z_2^3 - \mu z_2 - cz_1 - v + r_2(t) \qquad (33)$$

where the random forces r_1, r_2 satisfy conditions (18b).

V. KINETICS OF TRANSITIONS BETWEEN STATES: MAPPING INTO A DISCRETE MARKOV PROCESS

As stressed in Sections II and III, a case of special interest when studying transitions between states is the weak noise limit. For a system whose evolution is generated by a kinetic potential U, in the notation of Eq. (18b) and in the light of the comments following Eq. (20), this means that ϵ is much smaller than the various potential barriers ΔU_{ij}. The latter are given by the differences of the value $U(ij)$ of U on the unstable (transition) state (ij) across which the system will leave attraction basin of stable state i to enter that of stable state j, and of the value $U(i)$ of U on the reference stable state i.

The mean waiting time τ_{ij} for a transition from state i across state (ij) is given by an extension of a classic theory originally elaborated for one-variable systems by Kramers [2, 3] in the multi (here two-) dimensional case. In what follows we will be especially interested in the corresponding transition rates $k_{ij} = \tau_{ij}^{-1}$ that in the above specified limits take the form [11, 31]

$$k_{ij} = \frac{1}{2\pi} \left(\sigma_i^{(1)} \sigma_i^{(2)} \right)^{1/2} \left(\frac{\sigma_{(ij)}^+}{|\sigma_{(ij)}^-|} \right)^{1/2} \exp\left(-\frac{\Delta U_{ij}}{\epsilon} \right) \tag{34}$$

Here $\sigma_i^{(1)}, \sigma_i^{(2)}$ are the eigenvalues of the Hessian of U (or equivalently the solutions of Eq. (32) on the stable reference state i); and $\sigma_{(ij)}^\pm$ stand, respectively, for the unstable and stable eigenvalue of the Hessian [or equivalently the solutions of Eq. (32)] evaluated on the unstable (saddle) transition point.

Under the same assumptions the diffusion type of stochastic process described by Eq. (33) can be mapped into a jump process between the (discrete) stable states, in which the transition probabilities per unit time are given by Eq. (34), see Refs 2, 26, 27. This leads to the following simple kinetic schemes, it being understood that state 3 is by far the most stable state and thus plays the role of an absorbing barrier.

A. Three Simultaneously Stable States (Seven-Steady-State Region)

$$
\begin{array}{c}
1 \underset{k_{12}}{\overset{k_{21}}{\rightleftharpoons}} 2 \\
k_{13} \searrow \quad \swarrow k_{23} \\
3
\end{array}
\tag{35}
$$

The pobabilities p_1 and p_2 to be in the attraction basins of states 1 and 2 satisfy the rate equations

$$\frac{dp_1}{dt} = -(k_{12} + k_{13})p_1 + k_{21}p_2$$

$$\frac{dp_2}{dt} = k_{12}p_1 - (k_{21} + k_{23})p_2 \tag{36a}$$

with

$$p_3 = 1 - p_1 - p_2 \tag{36b}$$

The overall transition rates from 1 to 3 will be determined by the eigenvalues $\omega_\pm$ of the transition matrix associated to Eq. (36a),

$$\omega_\pm^2 + (k_{12} + k_{21} + k_{23} + k_{13})\omega_\pm + k_{12}k_{23} + k_{21}k_{13} + k_{23}k_{13} = 0$$

Actually, following a short initial transient the dominant time scale of the transition will be determined by the smallest (in absolute value) eigenvalue ω_-,

$$\omega_- = \frac{1}{2}\{-(k_{12} + k_{21} + k_{23} + k_{13})$$
$$+ \sqrt{(k_{12} + k_{21} + k_{23} + k_{13})^2 - 4(k_{12}k_{23} + k_{21}k_{13} + k_{23}k_{13})}\} \tag{37}$$

B.   Two Simultaneously Stable States (Five-Steady-State Region)

$$1 \underset{k'_{13}}{\overset{k_{13}}{\rightleftarrows}} 3 \tag{38}$$

This configuration arises past the limit point where states (23) and 2 merge in the bifurcation diagram of Fig. 1. There are two independent pathways leading from 1 to 3, a first past unstable state (13) exactly as in case A and a second past unstable state (13)$'$ that is actually a smooth continuation of unstable state (12) of case A. The probability p_1 to be in the attraction basin of state 1 satisfies the equation

$$\frac{dp_1}{dt} = -(k_{13} + k'_{13})p_1 \tag{39a}$$

with

$$p_3 = 1 - p_1 \tag{39b}$$

The overall transition rate from 1 to 3 is here determined by

$$|\omega| = (k_{13} + k'_{13}) \tag{40}$$

C. Two Simultaneously Stable States (Three-Steady-State Region)

This configuration arises past the limit point where states (12) and N merge in the bifurcation diagram of Fig. 1. It corresponds to the simple kinetic scheme

$$1 \xrightarrow{\ k_{13}\ } 3 \qquad\qquad (41)$$

with

$$\frac{dp_1}{dt} = -k_{13}p_1 \qquad\qquad (42a)$$

$$p_3 = 1 - p_1 \qquad\qquad (42b)$$

The transition rate is simply determined by

$$|\omega| = k_{13} \qquad\qquad (43)$$

Equations (37), (40), and (43) in conjunction with Eqs. (34), (29), and (31) allow one to determine the mean transition times $\tau_{13} = 1/|\omega_-|$, $1/(k_{13} + k'_{13})$, and $1/k_{13}$ as the parameter c runs from left to right across the bifurcation diagram of Fig. 1. The result is represented by the curve in full line in Fig. 3. For reference we also plot (dashed line) the transition times $\tau_{13}^{(0)}$ from 1 to 3 ignoring the presence or not of state 2, evaluated as $\tau_{13}^{(0)} = k_{13}^{-1}$. Finally, the crosses in Fig. 3 stand for the result of a simulation of the full stochastic differential equations (33). As can be seen the analytic and the simulation results agree remarkably well. Deviations do occur but they are limited to situations near transition points where the potential barrier is small, a case for which Eq. (34) needs to be amended as one of the assumptions of the theory ($\epsilon \ll \Delta U$) is no longer fulfilled. More importantly, we see that as one is entering the region of existence of stable state 2 the transition times decrease dramatically as compared to those that would prevail had the direct path $1 \to 3$ via unstable state (13) been the only one available. In particular, for values of c slightly less that 0.1 state 2 turns out to be less stable than state 1 and the barrier ΔU_{23} less than ΔU_{13}. The transition from 1 to 3 occurs then in an accelerated way through a "secondary nucleation" mediated by state 2. Remarkably, state 2 has an accelerating effect even in the vicinity of the transition point where it merges with unstable state (23). This occurs near $x \approx 0.16$ in the bifurcation diagram of Fig. 1 and may be referred to as "transient intermediate state nucleation," see also chapter by J. Lutsko in this volume. These conclusions are in accord with the results of observations [13], simulations [12], and microscopic approaches [14, 15] according to which the presence of an intermediate dense fluid phase enhances the nucleation of protein crystals. It also shows that intermediate state-mediated
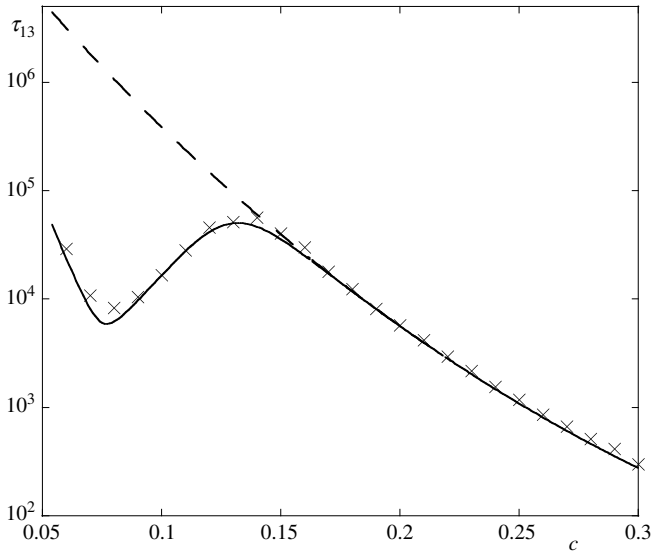
Figure 3. Mean transition times τ_{13} between states 1 and 3 versus parameter c. Full line: analytic result [Eqs. (34) and (37)]; crosses: result of the simulation of the full stochastic differential equations (33); dashed line: direct transition from 1 to 3 ignoring the presence of state 2. Noise strength $2\epsilon = 0.025$. Number of realizations is 1000 and other parameter values as in Fig. 1.

enhancement is a generic phenomenon, extending beyond the specific case of protein crystallization.

VI. IRREVERSIBLE THERMODYNAMICS OF FLUCTUATION-INDUCED TRANSITIONS

According to the setting adopted throughout this chapter, the transition between the initial state 1 and the final state 3 (direct or indirect via state 2) is a transient irreversible process: starting from state 1 with probability equal to one the state is gradually depleted and eventually state 3 invades the entire system, owing to its higher stability ($U(3) \ll U(1)$) in conjunction with the weak noise limit $\epsilon < \Delta U_{13} \ll \Delta U_{31}$. In this section, we analyze this transition from the standpoint of irreversible thermodynamics by evaluating the entropy production [8, 9] associated to the different scenarios considered in the previous sections.

As a reference we start with the direct transition scenario (cf. Section VC)

$$1 \underset{k_{31}}{\overset{k_{13}}{\rightleftharpoons}} 3 \tag{44}$$

where we introduce a small backward transition rate ($k_{31} \ll k_{13}$) in order to avoid the complication arising from the presence of purely irreversible steps. We also adopt a "chemical" interpretation where the variables associated to 1 and 3 are the mass fractions x and s of the material in these states [see also comment prior to Eq. (11)]. The rate equation associated to scheme (44) is then [to be compared with Eq. (42)]

$$\frac{dx}{dt} = -k_{13}x + k_{31}s \tag{45a}$$

with

$$s = 1 - x \tag{45b}$$

The solutions of Eqs. (45) corresponding to the initial conditions $x(0) = 1$, $s(0) = 0$ read

$$x(t) = \frac{k_1'}{k_1 + k_1'} + \frac{k_1}{k_1 + k_1'} \exp[-(k_1 + k_1')t]$$

$$s(t) = \frac{k_1}{k_1 + k_1'} - \frac{k_1}{k_1 + k_1'} \exp[-(k_1 + k_1')t] \tag{46}$$

The instantaneous entropy production (normalized by the gas constant) associated to this "direct" transformation is

$$\sigma_{\mathrm{d}}(t) = (k_{13}x - k_{31}s) \ln \frac{k_{13}x}{k_{31}s}$$

where for simplicity we adopted the assumption of an ideal mixture. Integrating this expression from time $t = 0$ to $t = \infty$ and using Eq. (46) one obtains the total dissipation undergone by the system to complete the transition,

$$\Sigma_d = \int_0^\infty dt \sigma_{\mathrm{d}}(t) = \ln \frac{k_{13} + k_{31}}{k_{31}} = \ln(K_{\mathrm{eq}} + 1) \tag{47}$$

where $K_{\mathrm{eq}} = k_{13}/k_{31}$ is the equilibrium constant of the "reaction" in Eq. (44). In the limit $k_{31} \ll k_{13}$ this expression reduces to $\ln K_{\mathrm{eq}}$, that is, to the standard free energy change associated to the reaction.

We next evaluate the dissipation in the "secondary nucleation" scenario, where the 1 to 3 transition occurs via state 2. The corresponding scheme, rate equations and entropy production are (compare with Section VA)

$$1 \underset{k_{21}}{\overset{k_{12}}{\rightleftharpoons}} 2 \underset{k_{32}}{\overset{k_{23}}{\rightleftharpoons}} 3 \tag{48}$$

$$\frac{dx}{dt} = -k_{12}x + k_{21}y$$

$$\frac{dy}{dt} = k_{12}x - (k_{21} + k_{23})y + k_{32}s$$

$$s = 1 - x - y \tag{49}$$

$$\sigma = (k_{12}x - k_{21}y)\ln\frac{k_{12}x}{k_{21}y} + (k_{23}y - k_{32}s)\ln\frac{k_{23}y}{k_{32}s}$$

Integrating again σ from 0 to ∞ we obtain for $x(0) = 1$ and in the limit of small k_{21}, k_{32} the following expression for the total dissipation during the transformation:

$$\Sigma = \Sigma_1 + \Sigma_2 \tag{50a}$$

with

$$\Sigma_1 = \ln\frac{k_{12}}{k_{21}} + \ln\frac{k_{23}}{k_{32}} \tag{50b}$$

and

$$\Sigma_2 = -k_{12}\int_0^\infty dt\,\exp[-k_{12}t]\ln\frac{k_{12}(1 - \exp[-(k_{23} - k_{12})t])}{k_{23} - k_{12}} + \frac{k_{12}k_{23}}{k_{12} - k_{23}}$$

$$\times \int_0^\infty dt(\exp[-k_{12}t] - \exp[-k_{23}t])$$

$$\times \ln\frac{k_{23} - k_{12} - k_{23}\exp[-k_{12}t] + k_{12}\exp[-k_{23}t]}{k_{12}(\exp[-k_{12}t] - \exp[-k_{23}t])} \tag{50c}$$

Here part Σ_1 corresponds to the contribution of the standard part of the chemical potentials in the entropy production and part Σ_2 to the contribution of the composition-dependent part. Clearly,

$$\Sigma_1 = \ln\frac{k_{12}k_{23}}{k_{21}k_{32}} = \ln K_{eq}$$

where K_{eq} was already introduced in Eq. (47). In the limit of small k_{32}, Σ_1 becomes thus identical to Σ_d. On the other hand, as it turns out $\Sigma_2 = 0$ for all values of the ratio k_{23}/k_{12}. We therefore conclude that

$$\Sigma = \Sigma_d \tag{51}$$

that is, at least in the limits considered the total dissipation associated to transition from 1 to 3 is independent of whether the transition is direct or occurs via the intermediate state 2. This is at variance with some results reported in the literature in a somewhat different context [32], where the presence of intermediate steps

seems to lower the entropy production. What it happening here is, rather, that the contribution to dissipation due to the distance from equilibrium of the ratio x/y counteracts exactly that due to the distance from equilibrium of the ratio y/s. We emphasize that nonequilibrium is manifested here as a transient phenomenon, as eventually the whole system is invaded with probability one by the single final state 3, whatever the pathway for reaching this state might have been.

VII.   CONCLUSIONS

In this chapter we outlined a general approach for analyzing the transitions between simultaneously stable steady states in the presence of thermodynamic or externally driven fluctuations. Emphasis was placed on transitions between two given states taking place under conditions allowing for the presence of a third one, which could be metastable with respect to the other states or even appear as a transient in the vicinity of criticalities of certain kinds. Conditions were defined under which the presence of such "intermediate" states can enhance the rate of transitions between the two "reference" states. We have shown that these mechanisms are likely to be generic and underlie a wide range of phenomena including the nucleation of crystalline materials from a liquid mixture in the presence of a second liquid phase as observed, in particular, in the crystallization of globular proteins or colloids.

Throughout the analysis we considered a closed system evolving eventually toward the state of thermodynamic equilibrium and satisfying the condition of detailed balance, entailing a vanishing probability flux in each phase space point and the proportionality between the Onsager matrix of kinetic coefficients and the diffusion matrix of the fluctuations. Under the additional condition that these matrices are state independent we showed that the evolution of the state variables could be mapped into a form deriving from a kinetic potential. We have constructed generic potentials compatible with various nucleation scenarios, some of which are identical to experimentally observed scenarios in the context of crystallization of globular proteins or colloids, see Ref. 13 and the Chapters by Vekilov and by Dinsmore et al. in this volume. These potentials provide also valuable information on the nature of the free energy surface of the system concerned which, despite its complex dependence on microscopic-level properties, is ultimately topologically equivalent to them.

More than one century ago, Wilhelm Ostwald proposed a *step rule* to explain certain observations on the formation of crystalline materials from the melt [33]. According to this rule, typically it is not the most stable form of the material but the least stable one that crystallizes first. The status of this rule in the light of present day knowledge on nucleation has been discussed recently in the literature [34, 35]. Our analysis shows that Ostwald's step rule is a consequence of a general underlying mechanism: the transition from an initial state (a liquid phase) to a final

one (a stable crystalline phase) may occur preferably via a pathway involving an intermediate state (a second, metastable liquid phase), possessing the necessary properties (e.g., high concentration of a key substance) for the appearance and growth of nuclei possessing the structure of the final phase. The analysis also shows that this is only one out of several scenarios and provides information on its realizability depending on the values of the parameters present in the problem.

Transitions between states are a generic phenomenon observed in a multitude of systems of interest in physical, life, engineering, and environmental sciences [36]. It constitutes one of the principal signatures of the dynamics of complex systems as it endows them with the ability to evolve, to choose, and to adapt and extends in this respect beyond the examples of protein or colloid crystallization and similar phase transition phenomena. Viewed in all its generality it constitutes a largely open problem likely to witness important developments in the future.

A first direction would be to account for the presence of several intermediate states as it may be the case, for instance, in transitions between different conformations of proteins and other biomolecules [37].

From the standpoint of stochastic processes and thermodynamics an interesting extension would be to assess whether some of our conclusions subsist when the condition of detailed balance breaks down. There are two broadly different mechanisms at the origin of such a breakdown.

(i) The evolution vector $\mathbf{v}$ in Eq. (1) contains an additional contribution beyond the one involving the thermodynamic or the kinetic potential. Typically, this will reflect the presence of constraints in, for instance, the form of concentration or temperature gradients, that do not allow the system to reach the state of equilibrium as provided by the extremum of the potential, even in the long time limit.

(ii) The diffusion matrix D_{ij} of the fluctuations accounts for the fact that the medium in which the system of interest is embedded is itself maintained out of equilibrium—for instance, by an external time-periodic driving.

In both cases, while Eqs. (6) and (7) will remain valid Eqs. (18) will break down and much of the analysis of Sections III–V will need to be extended. In particular, the exit from the attraction basin of a stable state need no longer follow a path across an intermediate unstable state of the saddle point type.

The influence of intermediate states on the kinetics of the transitions between two reference states can also be viewed as a new mechanism of control and optimization of the rate of production of the "material" associated to the final state. In this perspective, it would be of interest to study its interference with other known control mechanisms. Most prominent among them is stochastic resonance [38, 39], whereby the passage over a potential barrier is facilitated by the presence of a weak external periodic forcing. In the context of phase transitions and in particular

of protein crystallization a coupling of nucleation kinetics with an external field is expected to exist and play a nontrivial role in view of the presence of charged groups in the individual molecules [26]. Ordinarily, studies in stochastic resonance focus on the case of two simultaneously stable states separated by an unstable state of the saddle point type. Recently, an extension to the case of several stable states in the presence of a spatially periodic potential has been reported [40]. It would undoubtedly be interesting to adapt this work to the type of potentials considered in this chapter and assess the additional effect of the external periodic forcing in different parts of the bifurcation diagram of Fig. 1.

Finally, future developments in this area should aim at the elucidation of the microscopic basis of the mesoscopic-level approach developed in this chapter. This should clarify the limits of validity of some of the assumptions adopted, such as the use of spatially lumped variables and the independence of matrices L and D on the state variables $\{x_i\}$ in Eqs. (14) and onward, and provide the basis for appropriate refinements and generalizations.

Acknowledgments

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