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Generalized transition state method and continuous diffusion in multi-dimensional systems with relation to ion transport in channels of biological membranes

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Abstract. An exact expression for the escape rate of a particle in a multi-dimensional system, with respect to an arbitrary reaction coordinate, is derived from first principles according to the transition state method, using a simple geometrical argument. It is shown how the mutual coupling of all degrees of freedom due to the interaction forces leads to the appearance of an effective mass and the potential of the mean force. The same relevant quantities dominate the effective one-particle Fokker-Planck equation, which is derived by a similar projection procedure from the multi-dimensional transport equation. In the limit of a large, position-dependent friction the respective effective Smoluchowski equation is obtained. It allows for the discussion of a diffusing particle which is subject to a temperature bath only through the coupled motion with the constituent lattice particles, or ligands in the case of a molecular ion channel. This treatment is of particular importance for the analysis of ion transport in membrane pores in which the ionic motion is mediated by internal ligand motion.

Key words: Multi-dimensional rate theory, escape rates, continuous diffusion, Fokker-Planck equation, Smoluchowski equation

Introduction

The calculation of transition rates is an old problem of classical statistical mechanics and has gained widespread popularity not least because of the simple form of its result in form of the Arrhenius law

$$\Gamma = \nu_0 \exp(-\beta \cdot \Delta E), \quad (1)$$

where ν_0 is the attempt frequency, and ΔE is the energy barrier between a local minimum and the nearest saddle point (Pelzer and Wigner 1932; Eyring 1935; Glasstone et al. 1941). The transition state method can easily be applied by means of the principle of detailed balance, where in the case of one variable the procedure is trivial (Schröder 1983a). In an historic paper, Kramers (1940) discussed the relation between the Fokker-Planck formalism and the transition state method in one dimension. Since then there have been repeated attempts to calculate transition rates for various multidimensional systems either directly by the transition state method or via Kramers' approach (Wert and Zener 1949; Wert 1950; Zener 1951; Vineyard 1957; Langer 1968; Gardiner 1981; Weidenmüller and Jing-Shing 1984; Young 1984). Throughout the literature the procedures can be found either to be complicated, or to be based on incisive approximations (as, for example, the harmonic approximation), or they are given as rather formal recipes.

In a many-particle system the discussion of one degree of freedom usually leads to a temperature dependent effective potential, which may be decomposed into activation energy and entropy of activation. The latter is of increasing importance with an increasing number of degrees of freedom. However, in the harmonic approximation the entropic contribution to the rate consists of a constant factor which either may be part of the exponent or the attempt frequency. Moreover, the harmonic approximation assumes a linear response of the system with respect to the degrees of freedom under consideration, for example, with respect to a lattice deformation under the influence of a diffusing particle. It is clear that the harmonic approximation is not a sufficient description for a large number of systems. Examples are the nucleation and decay of small clusters as well as the transport of ions and small compounds in biological systems, especially the transmembrane motion of ions (Gay and Berne 1982; Woodbury 1971; Hille 1975; Levitt 1978a;

Levitt 1978 b; Levitt 1982; Läuger 1979; Läuger et al. 1980; Läuger 1981; Läuger and Apell 1982). In these cases nonlinear deformation effects may be important and could be responsible for some of the conductivity properties of transmembrane channels.

Certain protein complexes and polypeptides embedded in bilayer membranes serve as ionic conductors with ion-specific transport rates varying by orders of magnitude for one and the same channel and different ion species. There is evidence that conformational changes caused by moving ions participate in selectivity effects, which may be reflected in certain entropy contributions (Brickmann and Fischer 1983). It is also known that the polarization of a pore by diffusing ions may play an important role in the transport mechanism (Schröder 1983 b, 1983 c, 1984, 1985). Therefore, the migrating particles must be viewed as complexly built polarons rather than point-like Coulomb particles. A prototype candidate for such a system is the gramicidin A (GA) channel, which is probably the best known object of its kind, since it has been subject to extensive studies, both experimental and theoretical. Special interest has been devoted to computer simulations of GA channel systems (Mackay et al. 1984; Kim et al. 1985), and it has become obvious that Eyring's rate theory is not adequate for the description of those processes. Only recently Clementi et al. (1985) have stressed the need for a proper transport theory in biological systems. Despite their complex nature the description of ion transport in GA channel systems is a relatively simple matter; simply because the diffusion is spontaneous. The situation is quite different for a large class of important channel systems, the so called electrogenic ion pumps. In these systems the ion transport is probably mediated by large scale conformational changes, which are not necessarily induced by the ion itself (Läuger 1983). Usually these processes are much slower than the local, ion-induced polarization processes and moreover, they are superimposed on the latter. The theoretical handling of all these phenomena, as far as they have been discussed in the literature at all, is found to be limited either to Eyring's rate theory, i.e. Eq. (1), or to the one-dimensional Smoluchowski equation. Whereas the phenomenological rate theory requires empirical input parameters and cannot make predictions, the one-dimensional continuous diffusion approach is inapt, because ion transport in the respective systems is a multi-dimensional reaction process.

The purpose of this article is the development of a theoretical framework which allows for an adequate and unified discussion of a wide range of the aformentioned transport phenomena. The basic idea is to view the transport mechanism as a multi-dimensional reaction process which will be mapped onto a selected reaction coordinate for both discrete and continuous diffusion, rendering effective one-dimensional expressions. This procedure allows one to incorporate an arbitrary large number of degrees of freedom, which may either be subject to a response to the migrating particle or to external excitations. In the first section the escape rates in multi-dimensional systems are derived from the general definition of the unidirectional current across saddle points along the respective potential hyper-surface. In the second section the canonical representation of the corresponding Hamiltonian is used to present an equivalent procedure leading to the description of the continuous transport process, which is discussed in the third section. There an effective one-particle Fokker-Planck equation is derived using the local equilibrium approximation, which assumes that memory effects are not important. Under the same condition the effective Smoluchowski equation is obtained in the limit of large friction. After the preparation of these theoretical tools there seem to be various possible applications, some of which are planned to be discussed in future communications.

I. Current-based calculation of escape rates

In this section the correct expression for the transition rate is derived from first principles, retaining the full potential and allowing for a physical interpretation of all appearing terms. The well known basic assumption of rate theory is the only one used here. If a configuration is initially near a minimum on the hyper-surface of a multidimensional potential, $V(\boldsymbol{x})$,

$$\boldsymbol{x} = \{x_\mu\} \quad \mu = 1, \ldots, n,$$

it will eventually reach the saddle point by thermal activation and pass on to the next minimum. With this condition, the general expression for the rate, Γ, is obtained from the total unidirectional flux across the saddle (Vineyard 1957):

$$\Gamma = \int \varrho(\dot{\boldsymbol{x}}, \boldsymbol{x}) \cdot (\dot{\boldsymbol{x}} \mathrm{d}\boldsymbol{S}) \, \mathrm{d}^n \dot{x}, \quad \dot{\boldsymbol{x}} \, \mathrm{d}\boldsymbol{S} > 0. \tag{I.1}$$

Here $\varrho(\dot{\boldsymbol{x}}, \boldsymbol{x})$ is the Boltzmann distribution function and $\mathrm{d}\boldsymbol{S}$ is a hyper-surface element of dimensionality $n-1$ with $\mathrm{d}S = \mathrm{d}^{n-1}x$, cutting through the saddle point parallel to the respective reaction coordinate. The flux across the saddle may be written as

$$\Gamma = \int \boldsymbol{j}(\boldsymbol{x}) \, \mathrm{d}\boldsymbol{S}, \tag{I.2}$$

where the unidirectional current density must be given beforehand:

$$\boldsymbol{j}(\boldsymbol{x}) = \int \varrho(\dot{\boldsymbol{x}},\boldsymbol{x}) \cdot \dot{\boldsymbol{x}}\, \mathrm{d}^n \dot{x}\,. \tag{I.3}$$

The constraint $\dot{\boldsymbol{x}}\,\mathrm{d}\boldsymbol{S} > 0$ is rather weak and automatically fulfilled for the correct orientation of $\boldsymbol{j}(\boldsymbol{x})$. The unidirectional current itself is defined by an appropriate integration in velocity space, such that its orientation is given by the direction of the steepest descent from the saddle point, i.e. the direction $\boldsymbol{n}$ in $\boldsymbol{j}(\boldsymbol{x}) = \boldsymbol{n}\cdot j(\boldsymbol{x})$ is completely determined by the equilibrium properties of the potential landscape. Let us assume that the potential $V(\boldsymbol{x})$ describes the mutual interaction of all constituent particles rather than the interaction of a system of non-interacting particles with an external force. Let us further assume that the system has at least one equilibrium configuration. If one component, x_n, is forced out of equilibrium, all other components will respond with the occupation of new positions. Associating x_n with the reaction coordinate, a set of $n-1$ equilibrium coordinates depending on x_n, namely

$$\hat{\boldsymbol{x}}(x_n) = \{\hat{x}_\mu(x_n)\}\,, \quad \mu = 1,\dots,n-1\,,$$

can be obtained from the roots of $n-1$ equations

$$\frac{\partial V(\boldsymbol{x})}{\partial x_\mu} = f_\mu(\hat{\boldsymbol{x}}(x_n), x_n) = 0\,. \tag{I.4}$$

Then the direction of the steepest descent along the potential hyper-surface is given by the unit vector

$$\boldsymbol{n} = \left\{\frac{\partial \hat{\boldsymbol{x}}}{\partial x_n}, 1\right\} \frac{1}{\sqrt{1+\left(\frac{\partial \hat{\boldsymbol{x}}}{\partial x_n}\right)^2}}\,. \tag{I.5}$$

Since the hyper-surface element $\mathrm{d}\boldsymbol{S}$ is, by definition, parallel to the reaction coordinate, the total unidirectional flux across the saddle with respect to x_n is simply given by the projection of the reaction path in configuration space onto the reaction coordinate:

$$\Gamma = \int j(\boldsymbol{x}) \cdot \boldsymbol{n}\, \mathrm{d}\boldsymbol{S}\,. \tag{I.6}$$

It is obvious that the current density cannot be obtained from a simple half-range integration over the velocities as in the one-dimensional case, because all components $j_\mu(\boldsymbol{x})$ but $j_n(\boldsymbol{x})$ would vanish, i.e. the current density would always be parallel to any arbitrarily chosen reaction coordinate:

$$\begin{aligned} j_\mu(\boldsymbol{x}) &= \int \varrho(\dot{\boldsymbol{x}},\boldsymbol{x}) \cdot \dot{x}_\mu\, \mathrm{d}^{n-1}\dot{x} \int_0^\infty \mathrm{d}\dot{x}_n = 0\,, \quad \mu = 1,\dots,n-1 \\ j_n(\boldsymbol{x}) &= \int \varrho(\dot{\boldsymbol{x}},\boldsymbol{x})\, \mathrm{d}^{n-1}\dot{x} \int_0^\infty \dot{x}_n\, \mathrm{d}\dot{x}_n = \sqrt{k_B T/2\pi m_n}\, \varrho(\boldsymbol{x})\,. \end{aligned} \tag{I.7}$$

This result is obviously incompatible with the observation that $\boldsymbol{j}(\boldsymbol{x})$ follows the reaction path, which has the direction of the steepest descent from the saddle point. Only in the case of a system of non-interacting particles – $V(\boldsymbol{x})$ would be an external potential – would the current vector coincide with the selected reaction coordinate. Since the mutual interaction between constituent particles of the ensemble can be switched on continuously, at least with the aid of some fictitious parameter, the direction of the current is rotated continuously off the principal axis x_n with increasing mutual interaction. If the variation of the magnitude of the current with varying direction was known, it would be possible to use the half-range integration along the desired principal axis in velocity space, (I.7), and then to rotate the current into the $\boldsymbol{n}$-direction. In order to establish the relation between magnitude and direction of the current density let us assume that $\boldsymbol{j}(\boldsymbol{x})$ has been evaluated as a definite integral according to (I.3) and that it possesses the correct orientation, $\boldsymbol{n}$. Using the generalized coordinates

$$z_\mu = \sqrt{m_\mu} \cdot \dot{x}_\mu$$

as new integration variables, the components of the current are given by

$$j_\mu(\boldsymbol{x}) = \varrho(\boldsymbol{x}) \int \mathrm{d}^n z\, \varrho(z) \cdot z_\mu/\sqrt{m_\mu}\,, \tag{I.8}$$

where the equilibrium distribution function has been factorized:

$$\begin{aligned} \varrho(\boldsymbol{x}) &= \exp(-\beta \cdot V(\boldsymbol{x}))/\int \mathrm{d}^n x \exp(-\beta \cdot V(\boldsymbol{x})) \\ \varrho(z) &= \exp(-\tfrac{1}{2}\cdot\beta\cdot\sum_\mu z_\mu^2)/ \\ &\qquad \int \mathrm{d}^n z \exp(-\tfrac{1}{2}\cdot\beta\cdot\sum_\mu z_\mu^2)\,. \end{aligned} \tag{I.9}$$

Independent of the integration limits in (I.8) one can write:

$$n_\mu \cdot \sqrt{m_\mu} \cdot j(\boldsymbol{x}) = \varrho(\boldsymbol{x}) \cdot \langle z_\mu \rangle\,. \tag{I.10}$$

Accordingly the quantity

$$\sum_\mu \langle z_\mu \rangle^2$$

is an invariant under the rotation

$$\langle z' \rangle = \boldsymbol{R}(\boldsymbol{n}) \cdot \langle z \rangle \tag{I.11}$$

in configuration space. In particular, a principal axes transformation can be applied, such that all components $\langle z_\mu \rangle$ but $\langle z_n \rangle$ vanish. From (I.7) we have:

$$\sum_\mu \langle z_\mu \rangle^2 = k_B T/2\pi\,. \tag{I.12}$$

Hence:

$$j(\boldsymbol{x})^2 \cdot \sum_\mu (n_\mu^2 m_\mu) = k_B T/2\pi \cdot \varrho(\boldsymbol{x})^2\,. \tag{I.13}$$

Thus the desired expression for the current density is found to be:

$$j_\mu(x) = n_\mu \sqrt{\frac{k_B T}{2\pi \cdot \sum\limits_\mu (n_\mu^2 m_\mu)}}\; \varrho(x)\,. \tag{I.14}$$

Since the only non-vanishing component of the hyper-surface element $\mathrm{d}\boldsymbol{S}$ is $\mathrm{d}S_n = \mathrm{d}^{n-1}x$, the escape rate with respect to the n-th reaction channel is easily presented:

$$\begin{aligned} \Gamma = {} & \sqrt{k_B T/2\pi m^*} \cdot \exp(-\beta \cdot V^*(c)) / \\ & \int_a^c \exp(-\beta \cdot V^*(x_n))\, \mathrm{d}x_n\,. \end{aligned} \tag{I.15}$$

This expression for the escape rate in a multi-dimensional system is formally identical with the expression in the one-dimensional case except for the fact that the former contains the effective mass

$$m^* = m_n + \sum_\mu{}' m_\mu \left(\frac{\partial \hat{x}_\mu}{\partial x_n}\right)^2 \tag{I.16}$$

instead of m_n, and the potential of the mean force $V^*(x_n)$ instead of the single particle potential. Throughout this article the conventions

$$\sum_{\mu=1}^{n-1} \ldots = \sum_\mu{}' \ldots \quad \text{and} \quad \sum_{\mu=1}^{n} \ldots = \sum_\mu \ldots$$

are used. $V^*(x_n)$ is defined by the restricted sum of states

$$\begin{aligned} Q &= \int \exp(-\beta \cdot V(\boldsymbol{x}))\, \mathrm{d}^{n-1}x \\ &= Q_0 \cdot \exp(-\beta \cdot V^*(x_n))\,, \end{aligned} \tag{I.17}$$

where Q_0 is the sum of states in the absence of the n-th particle. The crucial point is the appearance of the effective mass, m^*, stating that the diffusing particle behaves as a dressed particle, for example as a polaron, the properties of which are determined by the masses of all other particles as well as by their mutual interaction. It is evident that the multi-dimensional escape rate has a non-local character, i.e., the possibility of a jump across a given barrier may in principle depend on the presence of other barriers. This feature is certainly of particular interest in systems with long range interaction. The result in the form of (I.15) and (I.16) has been discussed in an earlier publication (Schröder 1983b), where, in contrast to the present general proof, it was derived from a purely mechanical analysis of the transport problem.

In its present form (I.15) is not restricted to a certain temperature range, and the low temperature approximation is easily derived. Let $V^*(b)$ be the minimum between two enclosing saddles at $x_n = a$ and $x_n = c$. Then the low temperature limit yields the rate in the familiar form of Eq. (1):

$$\begin{aligned} &\Gamma = 1/2\pi \cdot \sqrt{\varkappa(T)/m^*} \cdot \exp(-\beta \cdot \Delta E) \\ &\varkappa(T) = \mathrm{d}^2 V^*(x_n)/\mathrm{d}x_n^2|_{x_n=b}\,, \quad \Delta E = V^*(c) - V^*(b)\,. \end{aligned} \tag{I.18}$$

Note that $\varkappa$ is temperature dependent due to possible anharmonic contributions of $V(x)$, and that ΔE is the free energy with the entropy of activation

$$\Delta S = k_B \frac{\partial}{\partial T} \{T \cdot \ln(Q(c)/Q(b))\}\,. \tag{I.19}$$

II. Canonical representation

The procedure discussed in this chapter has been applied before by the author (Schröder 1983a, 1983b, 1983c, 1984, 1985) to special, simple systems modelling ion transport through membrane channels. The application of this method, however, is neither restricted to certain models nor to certain systems. The only requirement is a Hamiltonian, defining distinct, time-independent states. The expression for the rate in the form of (I.15) or (I.18) is effectively that of a one-dimensional problem, since the entire process has been mapped onto the reaction coordinate. The idea, therefore, is to find the corresponding effective Hamiltonian which represents the quasi one-dimensional problem and renders the formulation of the continuous diffusion problem.

The starting point of the procedure is the reformulation of the energy in terms of a set of new variables $\boldsymbol{q}$ and $\dot{\boldsymbol{q}}$ which are defined by

$$\begin{aligned} &x_\mu = \hat{x}_\mu(q_n) + q_\mu\,, \quad \mu = 1, \ldots, n-1 \\ &x_n = q_n \end{aligned} \tag{II.1}$$

where the $\hat{x}_\mu(q_n)$ are obtained from the equilibrium conditions (I.4). Then the kinetic energy reads:

$$E_{\mathrm{kin}} = \tfrac{1}{2} \sum_\mu{}' m_\mu \cdot \left(\frac{\partial \hat{x}_\mu}{\partial q_n}\, \dot{q}_n + \dot{q}_\mu\right)^2 + \tfrac{1}{2} m_n \cdot \dot{q}_n^2\,. \tag{II.2}$$

The canonical momenta are defined by the first derivative of E_{kin} with respect to the velocities:

$$\begin{aligned} p_\mu &= m_\mu \left(\frac{\partial \hat{x}_\mu}{\partial q_n}\, \dot{q}_n + \dot{q}_\mu\right) \\ p_n &= \dot{q}_n \cdot \left\{m_n + \sum_\mu{}' m_\mu \left(\frac{\partial \hat{x}_\mu}{\partial q_n}\right)^2\right\} + \sum_\mu{}' m_\mu \frac{\partial \hat{x}_\mu}{\partial q_n}\, \dot{q}_\mu\,. \end{aligned} \tag{II.3}$$

The inversion yields:

$$\begin{aligned} \dot{q}_\mu &= p_\mu/m_\mu - \left(p_n - \sum_\nu{}' \frac{\partial \hat{x}_\nu}{\partial q_n}\, p_\nu\right) / m_n \\ \dot{q}_n &= \left(p_n - \sum_\mu{}' \frac{\partial \hat{x}_\mu}{\partial q_n}\, p_\mu\right) / m_n\,. \end{aligned} \tag{II.4}$$

Obviously canonical and kinetic momenta are only identical if the distortion field vanishes, i.e., in the interaction-free case. With the use of (II.4) in (II.2) the Hamiltonian follows as

$$H = \tfrac{1}{2} \sum_{\mu}{}' p_{\mu}^2/m_{\mu} + \tfrac{1}{2}\left(p_n - \sum_{\mu}{}' \frac{\partial \hat{x}_{\mu}}{\partial q_n} p_{\mu}\right)^2 / m_n + V(\boldsymbol{q}) \,, \tag{II.5}$$

where $\{\boldsymbol{p}, \boldsymbol{q}\}$ are the proper pairs of canonical variables spanning the $2n$-dimensional phase space. The sum of states is the $2n$-fold integral

$$Z = \int \mathrm{d}^n p \int \mathrm{d}^n q \exp(-\beta \cdot H) \,.$$

As discussed in an earlier paper (Schröder 1985), the escape rate with respect to the reaction coordinate $q_n = x_n$ can be directly evaluated by a half-range integration in phase space, namely:

$$\Gamma = \int_0^{\infty} \mathrm{d}p_n \, \dot{q}_n \int \mathrm{d}^{n-1} p \int \mathrm{d}^{n-1} q \exp(-\beta \cdot H)/Z \,. \tag{II.6}$$

The result of (II.6) is, of course, (I.15). Evidently a one-dimensional formulation with the aid of an effective one-dimensional equilibrium distribution function $\varrho^*(p_n, q_n)$ can be used to obtain the same result:

$$\begin{aligned} \Gamma &= \int_0^{\infty} \mathrm{d}p_n \, \dot{q}_n \, \varrho^*(p_n, q_n) \\ \varrho^*(p_n, q_n) &= 1/\sqrt{2\pi m^* k_B T} \\ &\quad \cdot \exp(-\beta \cdot H^*)/\int Q(q_n) \, \mathrm{d}q_n \,. \end{aligned} \tag{II.7}$$

Thus the effective Hamiltonian is

$$H^* = \tfrac{1}{2} p_n^2/m^* + V^*(q_n) \tag{II.8}$$

with

$$p_n = \dot{q}_n \cdot \left\{ m_n + \sum_{\mu}{}' m_{\mu} \left(\frac{\partial \hat{x}_{\mu}}{\partial q_n} \right)^2 \right\} .$$

$V^*(q_n)$ is the potential of the mean force as defined in (I.17). An alternative formulation is possible if the velocity instead of the momentum is used:

$$\begin{aligned} \Gamma &= \sqrt{m^*/(2\pi k_B T)} \int_0^{\infty} \dot{q}_n \, \mathrm{d}\dot{q}_n \\ &\quad \cdot \exp(-\beta \cdot E^*(q_n, c))/\int_a^c Q(q_n) \, \mathrm{d}q_n \,. \end{aligned}$$

Hence

$$\begin{aligned} \Gamma &= \sqrt{k_B T/2\pi m_n} \, \frac{\mathrm{d}q_n}{\mathrm{d}s_n} \exp(-\beta \cdot V^*(c))/ \\ &\quad \int_a^c \exp(-\beta \cdot V^*(q_n)) \, \mathrm{d}q_n \,, \end{aligned} \tag{II.9}$$

where $\mathrm{d}s_n$ is the arc length in phase space as defined by

$$\mathrm{d}q_n^2 \cdot m^* = \mathrm{d}s_n^2 \cdot m_n$$

in

$$E^* = \tfrac{1}{2} m_n \cdot \dot{s}_n^2 + V^*(q_n) \,. \tag{II.10}$$

The occurrence of the effective mass m^* tells us that it may become rather meaningless to talk about a certain diffusing particle, because all particles are in mutually coupled motion. Relevant is the motion of the quasi-particle which involves the motion of all constituent particles in the system. Thus the escape rate, representing the inverse dwelling time of a particle in the neighbourhood of a potential minimum in the one-dimensional case, must be associated with the mean lifetime of the quasiparticle in the multi-dimensional case.

The very concept of rate theory is also reflected in the effective mass. It assumes that an equilibrium configuration of all other degrees of freedom can be ascribed to each value of the reaction coordinate, q_n. This assumption is certainly true for any appropriate potential, $V(\boldsymbol{x})$. Nevertheless, fluctuations around equilibrium appear and are taken into account by averaging over the subspace perpendicular to q_n, (I.6) and (II.6). At any given instant the contour of the potential hyper-surface may look very different from the equilibrium contour. Consequently the mean reaction path is the average of all possible passages from one minimum to the next, where any deviation from the mean can contribute to the entropy, ΔS. However, whereas it is true that an equilibrium configuration is assumed by the system for any given value of q_n, it is generally not true that this happens instantaneously following a change of q_n. It is a well known deficiency of the transition state method that it ignores the history of the system prior to a possible transition. But memory effects can become important if the time needed for an adjustment of the system is comparable with the dwelling time in the potential well (or the lifetime of the quasi-particle) or is large compared to it. This is the case if the characteristic frequencies associated with the conformational changes are not large compared to the typical frequency in the well. For a given set of elastic constants

$$\varkappa_{\mu} = \left. \frac{\partial^2 V(\boldsymbol{q})}{\partial q_{\mu}^2} \right|_{q_{\mu} = 0}$$

the frequencies decrease with increasing masses, m_{μ}. Therefore, it cannot be expected that (I.15) describes the transition correctly if the m_{μ} become too large. A quantitative estimation can be obtained from any individually given potential if the relation between the distortion field

$$\frac{\partial \hat{\boldsymbol{x}}}{\partial q_n}$$

and the characteristic coupling constants $\varkappa_\mu$ is derived. Model calculations show that the correction term in m^* due to all masses may become rather large for comparable masses and reasonable frequencies (Schröder et al. 1983).

III. Continuous diffusion

Most importantly, the application of rate theory requires distinct, well separated minima on the potential hyper-surface. As discussed previously, this condition does not automatically restrict its validity to the low temperature limit. But there are certain situations where the rate theoretical approach fails because barriers become too small. This is a difficult problem, especially when, in a sequence of binding sites and barriers, some wells vanish whereas neighbouring ones are still dominant. It is clear that the concept of a discrete random walk is not very useful here. For instance, such situations are found in ion-conducting membrane channels, where the potential profile for one and the same channel varies with the ion's size, i.e., activation energies and the number of binding sites may decrease with increasing ionic radius. Therefore it is necessary to develop a theory for the continuous analogy of the discrete jump process, where the desired one-dimensional description is a result of an appropriate projection of the multi-dimensional phenomenon.

A standard approach of the one-dimensional continuous diffusion problem is given in form of the Smoluchowski equation (SE)

$$\dot{P}(x,t) = k_B T/(\zeta m) \cdot \frac{\mathrm{d}}{\mathrm{d}x}\left(\frac{\mathrm{d}}{\mathrm{d}x} + \beta \cdot \frac{\mathrm{d}V}{\mathrm{d}x}\right) P(x,t)\,, \tag{III.1}$$

which can be derived from the Fokker-Planck equation (FPE)

$$\begin{aligned}\dot{P}(\dot{x},x,t) = &-\left(\dot{x} \cdot \frac{\partial}{\partial x} - \frac{1}{m} \cdot \frac{\partial V}{\partial x} \cdot \frac{\partial}{\partial \dot{x}}\right) P(\dot{x},x,t) \\ &+ \beta^{-1} \zeta \frac{\partial}{\partial \dot{x}}\left(\frac{1}{m} \cdot \frac{\partial}{\partial \dot{x}} + \beta \dot{x}\right) P(\dot{x},x,t)\end{aligned} \tag{III.2}$$

in the limit of a large friction coefficient (Resibois 1983; van Kampen 1984). The SE has the advantage that a stationary, analytical solution is available. With the aid of the continuity equation one obtains for the stationary current (Levitt 1982)

$$J = -k_B T/(\zeta m) \cdot \left(\frac{\mathrm{d}}{\mathrm{d}x} + \beta \cdot \frac{\mathrm{d}V}{\mathrm{d}x}\right) P(x)\,, \tag{III.3}$$

which is an ordinary differential equation for the stationary distribution, $P(x)$.

In this section an effective one-dimensional SE is derived from the multi-dimensional FPE, taking into account a projection of the conformational change of the entire many particle system during a diffusive process onto the selected reaction coordinate. In the first step of the derivation a one-dimensional FPE is obtained which contains an effective, position-dependent friction coefficient. Presently only the large friction limit is considered, yielding differential equations in the form of (III.2) and (III.3). In the intermediate region of friction the result of the transition state method, (I.15), renders an adequate description, whereas the region of small friction requires different methods, especially since the effective friction coefficient is position dependent. It seems, however, that the limiting case of small friction is of particular interest for ion transport in membrane channels. A future communication on this subject is planned.

The multi-dimensional FPE with individually different friction coefficients, ζ_μ, is given by:

$$\begin{aligned}\dot{P}(\dot{\boldsymbol{x}},\boldsymbol{x},t) = &-\sum_\mu \left(\dot{x}_\mu \frac{\partial}{\partial x_\mu} - \frac{1}{m_\mu} \cdot \frac{\partial V}{\partial x_\mu} \cdot \frac{\partial}{\partial \dot{x}_\mu}\right) P(\dot{\boldsymbol{x}},\boldsymbol{x},t) \\ &+ \beta^{-1} \sum_\mu \zeta_\mu \frac{\partial}{\partial \dot{x}_\mu}\left(\frac{1}{m_\mu} \cdot \frac{\partial}{\partial \dot{x}_\mu} + \beta \dot{x}_\mu\right) P(\dot{\boldsymbol{x}},\boldsymbol{x},t)\,.\end{aligned} \tag{III.4}$$

As in the case of the transition state method, the goal is to obtain an effective one-particle distribution function, $P^*(p_n, q_n, t)$, by averaging over $n-1$ pairs of variables $\{p_\mu, q_\mu\}$.

$$P^*(p_n, q_n, t) = \int P(\boldsymbol{p}, \boldsymbol{q}, t)\, \mathrm{d}^{n-1}p\, \mathrm{d}^{n-1}q\,. \tag{III.5}$$

For this purpose the canonical transformation according to (II.3) and (II.4) must be carried out, and (III.4) expressed by the position variables q_μ and the canonical momenta p_μ with the aid of the relations

$$x_\mu = \hat{x}_\mu(q_n) + q_\mu\,, \quad x_n = q_n$$

and

$$\dot{x}_\mu = p_\mu / m_\mu\,, \quad \dot{x}_n = \left(p_n - \sum_\mu{}' p_\mu \frac{\partial \hat{x}_\mu}{\partial q_n}\right) / m_n\,.$$

Evidently, this procedure is unique. If a stationary solution of the differential equation for $P(\boldsymbol{p}, \boldsymbol{q}, t)$ is

$$\varrho(\boldsymbol{p}, \boldsymbol{q}) = \exp(-\beta H)/Z$$

with H from (II.5), then

$$\varrho^*(p_n, q_n) = \int \varrho(\boldsymbol{p}, \boldsymbol{q})\, \mathrm{d}^{n-1}p\, \mathrm{d}^{n-1}q$$

as given by (II.7) must be the stationary solution of the effective one-particle problem. It can easily be seen that the averaging process applied to the FPE for $P(\boldsymbol{p}, \boldsymbol{q}, t)$ would be of no advantage, because it requires the knowledge of the full distribution function in the first place. The problem can be reduced to only known quantities if the n-particle distribution function is replaced by the following product which represents the local equilibrium approximation:

$$P(\boldsymbol{p},\boldsymbol{q},t) \approx \varrho(\boldsymbol{p},\boldsymbol{q}) \cdot \tilde{P}(p_n, q_n, t) . \qquad \text{(III.6)}$$

This mean field type approximation neglects memory effects completely, which would still be present in $P^*(p_n, q_n, t)$ as the average of the exact solution, $P(\boldsymbol{p},\boldsymbol{q},t)$. A rigorous treatment of the reduction of $P(\boldsymbol{p},\boldsymbol{q},t)$ to an effective distribution function would be reflected in the presence of a memory function in the effective Fokker-Planck equation. At this level the Markov approximation could be applied to the appearing force-autocorrelation function, i.e. its time-dependence would be approximated by a δ-function. The remaining term is in general equivalent to a renormalization of the effective friction coefficient. The purpose of the present discussion, however, is to demonstrate the mechanism of the reduction procedure in multi-dimensional systems for both discrete and continuous diffusion processes on a generalized rate theoretical level, the basis of which is the local equilibrium approximation. With this assumption it follows immediately that

$$P^*(p_n, q_n, t) = \varrho^*(p_n, q_n) \cdot \tilde{P}(p_n, q_n, t) , \qquad \text{(III.7)}$$

thus $\tilde{P}(p_n, q_n, t)$ represents the deviation of the effective one-particle solution from equilibrium.

The transformation of the FPE, (III.4), into its canonical form, is straightforward but lengthy and is therefore not shown here. After this operation has been carried out, the integration over the $2(n-1)$ variables can easily be performed:

$$\begin{aligned}
\int \dot{P}\, \mathrm{d}\Omega = & - \int \left(\frac{\partial H}{\partial p_n} \cdot \frac{\partial}{\partial q_n} - \frac{\partial H}{\partial q_n} \cdot \frac{\partial}{\partial p_n}\right) P \,\mathrm{d}\Omega \\
& + \beta^{-1} \sum_{\mu}{}' \zeta_\mu m_\mu \int \left(\frac{\partial}{\partial p_\mu} + \frac{\partial \hat{x}_\mu}{\partial q_n} \cdot \frac{\partial}{\partial p_n}\right)^2 P \,\mathrm{d}\Omega \\
& + \sum_{\mu}{}' \zeta_\mu \int \left(\frac{\partial}{\partial p_\mu} + \frac{\partial \hat{x}_\mu}{\partial q_n} \cdot \frac{\partial}{\partial p_n}\right) p_\mu P \,\mathrm{d}\Omega \\
& + \beta^{-1} \zeta_n m_n \int \frac{\partial^2 P}{\partial p_n^2} \,\mathrm{d}\Omega \\
& + \zeta_n \frac{\partial}{\partial p_n} \int \left(p_n - \sum_{\mu}{}' p_\mu \frac{\partial \hat{x}_\mu}{\partial q_n}\right) P \,\mathrm{d}\Omega \qquad \text{(III.8)}
\end{aligned}$$

with $\mathrm{d}\Omega = \mathrm{d}^{n-1}p\, \mathrm{d}^{n-1}q$. Inserting the factorization (III.6) into (III.8) enables us to make use of the following identities:

$$\left(\frac{\partial}{\partial p_\mu} + \frac{\partial \hat{x}_\mu}{\partial q_n} \cdot \frac{\partial}{\partial p_n}\right) P = - \varrho \left(\beta \cdot \tilde{P} \cdot p_\mu / m_\mu - \frac{\partial \hat{x}_\mu}{\partial q_n} \cdot \frac{\partial \tilde{P}}{\partial p_n}\right)$$

$$\frac{\partial P}{\partial p_n} = \varrho \left[\frac{\partial \tilde{P}}{\partial p_n} - \beta / m_n \left(p_n - \sum_{\mu}{}' p_\mu \frac{\partial \hat{x}_\mu}{\partial q_n}\right) \tilde{P}\right] .$$

The surviving terms are:

$$\begin{aligned}
\varrho^* \cdot \dot{\tilde{P}} = & - \int \varrho \left(\frac{\partial H}{\partial p_n} \cdot \frac{\partial}{\partial q_n} - \frac{\partial H}{\partial q_n} \cdot \frac{\partial}{\partial p_n}\right) \tilde{P} \,\mathrm{d}\Omega \\
& + \beta^{-1} \varrho^* \cdot \left[\zeta_n m_n + \sum_{\mu}{}' \zeta_\mu m_\mu \left(\frac{\partial \hat{x}_\mu}{\partial q_n}\right)^2\right] \\
& \cdot \left(\frac{\partial^2}{\partial p_n^2} - \beta \cdot p_n / m^* \cdot \frac{\partial}{\partial p_n}\right) \tilde{P} . \qquad \text{(III.9)}
\end{aligned}$$

The integral on the RHS of (III.9) requires some special attention. Here one has to consider integrals of the type

$$\begin{aligned}
\int \varrho(\boldsymbol{p},\boldsymbol{q}) \frac{\partial H}{\partial q_n} \mathrm{d}\Omega & = - \beta^{-1} \frac{\partial}{\partial q_n} \int \varrho(\boldsymbol{p},\boldsymbol{q}) \,\mathrm{d}\Omega \\
& = - \beta^{-1} \frac{\partial}{\partial q_n} \varrho^*(p_n, q_n) ,
\end{aligned}$$

where $\varrho^*(p_n, q_n)$ is identical with the quantity defined in (II.7). Up to an only temperature-dependent function, F_0, the distribution function $\varrho^*(p_n, q_n)$ can be written as

$$\varrho^* = \exp(-\beta(F^* + F_0))$$

where

$$F^* = H^* + \tfrac{1}{2}\beta^{-1} \cdot \ln(m^*/m_n) . \qquad \text{(III.10)}$$

Hence:

$$\int \varrho(\boldsymbol{p},\boldsymbol{q}) \frac{\partial H}{\partial q_n} \mathrm{d}\Omega = \varrho^* \cdot \frac{\partial F^*}{\partial q_n} ,$$

$$\int \varrho(\boldsymbol{p},\boldsymbol{q}) \frac{\partial H}{\partial p_n} \mathrm{d}\Omega = \varrho^* \cdot \frac{\partial F^*}{\partial p_n} .$$

Thus the effective one-particle FPE takes the form

$$\begin{aligned}
\dot{\tilde{P}} = & - \left(\frac{\partial F^*}{\partial p_n} \cdot \frac{\partial}{\partial q_n} - \frac{\partial F^*}{\partial q_n} \cdot \frac{\partial}{\partial p_n}\right) \tilde{P} \\
& + \beta^{-1} \left[m_n \zeta_n + \sum_{\mu}{}' m_\mu \zeta_\mu \left(\frac{\partial \hat{x}_\mu}{\partial q_n}\right)^2\right] \\
& \cdot \left(\frac{\partial^2}{\partial p_n^2} - \beta \cdot p_n / m^* \frac{\partial}{\partial p_n}\right) \tilde{P} . \qquad \text{(III.11)}
\end{aligned}$$

Reverting to the corresponding equation for $P^*(p_n, q_n, t)$ with the aid of (III.7) and using the velocity $\dot{q}_n = p_n / m^*$ instead of the canonical momentum p_n yields

$$\begin{aligned}
& \dot{P}^*(\dot{q}_n, q_n, t) \\
& = - \left(\dot{q}_n \frac{\partial}{\partial q_n} - \frac{1}{m^*} \cdot \frac{\partial F^*}{\partial q_n} \cdot \frac{\partial}{\partial \dot{q}_n}\right) P^*(\dot{q}_n, q_n, t) \\
& \quad + \beta^{-1} \zeta^*(q_n) \frac{\partial}{\partial \dot{q}_n} \left(\frac{1}{m^*} \cdot \frac{\partial}{\partial \dot{q}_n} + \beta \dot{q}_n\right) P^*(\dot{q}_n, q_n, t) , \qquad \text{(III.12)}
\end{aligned}$$

where

$$\zeta^*(q_n) = \frac{m_n \zeta_n + \sum_\mu{}' m_\mu \zeta_\mu \left(\frac{\partial \hat{x}_\mu}{\partial q_n}\right)^2}{m_n + \sum_\mu{}' m_\mu \left(\frac{\partial \hat{x}_\mu}{\partial q_n}\right)^2} \tag{III.13}$$

is the effective, position-dependent friction coefficient. As the basic starting point of all further discussions we will take the FPE in form of (III.12). The effective one-particle FPE for $P^*(\dot{q}_n, q_n, t)$ is formally identical with the single-particle FPE, (III.2), where mass and friction coefficient have been replaced by the corresponding effective quantities, and the potential V has been replaced by the potential of the mean force, V^*. Therefore it is to be expected that a standard procedure in the form of an asymptotic expansion for large friction leads to the respective, effective SE. This is indeed the case. Using van Kampen's method (van Kampen 1984), the effective distribution function is written as an asymptotic expansion for large τ after $\zeta^*(q_n)$ has been replaced by $\tau \cdot \zeta^*(q_n)$:

$$P^*(\dot{q}_n, q_n, t) = \sum_{j=0}^{\infty} \tau^{-j} \Phi_j(\dot{q}_n, q_n, t) \, . \tag{III.14}$$

Insertion of this expansion into the FPE, (III.12), leads to a hierarchy of differential equations for the $\Phi_j(\dot{q}_n, q_n, t)$, given by the recursion relation

$$\begin{aligned} \dot{\Phi}_j = & -\left(\dot{q}_n \cdot \frac{\partial}{\partial q_n} - \frac{1}{m^*} \cdot \frac{\partial F^*}{\partial q_n} \cdot \frac{\partial}{\partial \dot{q}_n}\right) \Phi_j \\ & + \beta^{-1} \zeta^* \frac{\partial}{\partial \dot{q}_n} \left(\frac{1}{m^*} \cdot \frac{\partial}{\partial \dot{q}_n} + \beta \cdot \dot{q}_n\right) \Phi_{j+1} \, , \end{aligned} \tag{III.15}$$

which can be solved successively, starting with

$$\begin{aligned} \Phi_0(\dot{q}_n, q_n, t) = & \, \sigma(q_n) \cdot \sqrt{\beta m^*/2\pi} \\ & \cdot \exp\left(-\tfrac{1}{2} \beta m^* \cdot \dot{q}_n^2\right) . \end{aligned}$$

The relation between $\sigma(q_n)$ and the next higher member of the expansion (III.14), $\Phi_1(\dot{q}_n, q_n, t)$, is readily established as

$$\begin{aligned} & \int \Phi_1(\dot{q}_n, q_n, t) \, \mathrm{d}\dot{q}_n \\ & = \beta^{-1} \cdot \frac{\mathrm{d}}{\mathrm{d}q_n} \left\{ 1/(m^* \zeta^*) \left(\frac{\mathrm{d}}{\mathrm{d}q_n} + \beta \frac{\mathrm{d}V^*}{\partial q_n}\right) \sigma(q_n) \right\} . \end{aligned} \tag{III.16}$$

Setting $\tau = 1$ and averaging (III.14) over $\dot{q}_n$ one obtains:

$$P^*(q_n, t) = \sigma(q_n) + \int \Phi_1(\dot{q}_n, q_n, t) \, \mathrm{d}\dot{q}_n + O(\zeta^{*-2}) \, .$$

With the aid of (III.16) the desired, final equation is found, which is structurally identical with the single particle SE, (III.1):

$$\begin{aligned} & \dot{P}^*(q_n, t) \\ & = \beta^{-1} \frac{\mathrm{d}}{\mathrm{d}q_n} \left\{ 1/(m^* \zeta^*) \left(\frac{\mathrm{d}}{\mathrm{d}q_n} + \beta \cdot \frac{\mathrm{d}V^*}{\mathrm{d}q_n}\right) P^*(q_n, t) \right\} . \end{aligned} \tag{III.17}$$

Introducing an effective diffusion coefficient

$$D^*(q_n) = \frac{k_B T}{m_n \zeta_n + \sum_\mu{}' m_\mu \zeta_\mu \left(\frac{\partial \hat{x}_\mu}{\partial q_n}\right)^2} \tag{III.18}$$

the SE, (III.17), can be written as

$$\begin{aligned} \dot{P}^* = \frac{\mathrm{d}}{\mathrm{d}q_n} \Big\{ & D^* \cdot \exp(-\beta \cdot V^*) \\ & \cdot \frac{\mathrm{d}}{\mathrm{d}q_n} (P^* \cdot \exp(\beta \cdot V^*)) \Big\} \end{aligned} \tag{III.19}$$

with its respective stationary solution satisfying

$$J \cdot \exp(\beta \cdot V^*)/D^* = -\frac{\mathrm{d}}{\mathrm{d}q_n} (P^* \cdot \exp(\beta \cdot V^*)) \, . \tag{III.20}$$

If the environment is assumed not to respond to the motion of a particle along the given reaction coordinate, (III.19) and (III.20) simply reduce to (III.1) and (III.3), respectively. However, this description is highly unrealistic in systems where the mobility of the environment leads to a coupled motion with the diffusing particle. Moreover, it might not even be clear which of the particles is actually the diffusing one. A good candidate for such a system is the GA channel. Here the diffusing particle is a polaron (rather than the ion itself), built by an ion and the surrounding flexible dipoles. Since there is no contact of the ion with the temperature bath represented by the membrane other than its interaction with the fluctuating dipoles, it does not make sense to consider the ion as a Brownian particle in the limit of a rigid channel. Any diffusive motion should thus come to rest if the dipoles become immobile. In this limiting case the ionic motion is purely deterministic, i.e., $\zeta_n = 0$! Assuming in addition that all $n-1$ particles are subject to the same temperature bath, and thus experience the same random force, one may use identical friction coefficients $\zeta_\mu = \zeta$ and the effective friction coefficient, (III.13), reads:

$$\zeta^*(q_n) = \zeta \cdot (1 - m_n/m^*) \, . \tag{III.21}$$

The quantity defined in (III.21) is obviously the relevant parameter which sets the conditions for an approximate solution of the effective FPE, (III.12). If, for example, the molecular channel becomes more and more rigid, then the effective mass approaches the naked mass m_n and $\zeta^*(q_n)$, (III.21), tends to zero. In this case the effective SE in the form of (III.19) cannot be used. It is also possible that the friction coefficient ζ tends to zero, so that $\zeta^*(q_n)$ becomes very small anyway. In both the cases of a more or less rigid channel or small ζ, an appropriate solution of the FPE for small friction according to Kramers' method (Kramers 1940) should be searched for. By contrast, in a more or less "soft" channel the effective mass may be significantly larger than m_n (Schröder 1983b, 1983c). If, in addition, ζ can be considered not to be too small, the effective SE

$$\dot{P}^* = \frac{\mathrm{d}}{\mathrm{d}q_n} \left\{ \frac{k_B T}{\zeta\,(m^* - m_n)} \cdot \exp\,(-\beta \cdot V^*) \cdot \frac{\mathrm{d}}{\mathrm{d}q_n} (P^* \cdot \exp\,(\beta \cdot V^*)) \right\} \tag{III.22}$$

can be used. If all ligand masses are identical, $m_\mu = m$, then the stationary solution simply reads:

$$J \cdot \exp\,(\beta \cdot V^*) \cdot \left(\frac{\partial \hat{\mathbf{x}}}{\partial q_n}\right)^2 = -D_0 \cdot \frac{\mathrm{d}}{\mathrm{d}q_n} (P^* \cdot \exp\,(\beta \cdot V^*))\,, \tag{III.23}$$

where $D_0 = k_B T/\zeta m$ is the rotational diffusion coefficient of the ligands. For a given concentration gradient across the membrane of thickness L the integration of (III.23) yields:

$$J = D_0 \cdot \frac{P^*(0) \cdot \exp\,(\beta \cdot V^*(0)) - P^*(L) \cdot \exp\,(\beta \cdot V^*(L))}{\int_0^L \exp\,(\beta \cdot V^*(q_n)) \cdot \left(\frac{\partial \hat{\mathbf{x}}}{\partial q_n}\right)^2 \mathrm{d}q_n} \,. \tag{III.24}$$

If the channel is rigid, i.e., all $\partial \hat{x}_\mu / \partial q_n$ vanish, then (III.23) automatically yields the equilibrium solution

$$P_{eq} = \exp\,(-\beta \cdot V^*)\,,$$

whereas from (III.12) it follows that the respective time-dependent solution is deterministic. Thus (III.24) would, for example, represent the ionic current along a molecular channel mediated only by the ligand's fluctuative motion. It is certainly no problem to calculate the transport quantity J, (III.24), for a given model system, as long as the distortion field can be evaluated, at least numerically. This is possible in the case of simple model channel systems as discussed previously (Schröder 1985) and will be carried out in a future communication. The application of the present transport theory to such GA-like systems is a necessity because a general handling on a rate theoretical basis is not possible. However, a priori it is not clear what regimes of friction are actually described by the quantities (III.13) and (III.21). For $\zeta_n = 0$, $\zeta^*(q_n)$, (III.13), can always be made arbitrarily small if the environment is assumed to be rigid, although the individual friction coefficients ζ_μ may be large in the sense of an overdamped motion. On the other hand, the strong friction limit in form of (III.24) can always be used if ζ is chosen to be sufficiently large, even though the distortion field $(\partial \hat{\mathbf{x}} / \partial q_n)^2$ might be rather small. Therefore it seems necessary to compare analytical model calculations resulting either from the present rate theory, or from the strong friction limit, or even from the corresponding small friction limit, to appropriate computer simulations which finally rule out inadequate approximations.

Summary

The subjects of this discussion have been rate processes and continuous diffusion in multi-dimensional systems consisting of mutually interacting particles with a total of n degrees of freedom. The systems under consideration possess well-defined, distinct states which are separated by barriers on the potential hyper-surface. If the system is initially near a local minimum, a transition to a neighbouring minimum can be induced by the motion of any of the particles along one degree of freedom. During this process the positions of all constituent particles assume new equilibrium values due to their mutual coupling. Thus it is possible to map the variation of an equilibrium configuration involving $n-1$ degrees of freedom onto one independent variable which defines the reaction coordinate. The characteristic quantity accompanying the cooperative motion in configuration space is the distortion field with respect to the selected reaction coordinate. It defines the direction of the steepest descent across saddle points on the potential hyper-surface. In the rate theoretical approach, the knowledge of this quantity has directly been used to calculate the escape rate with respect to the chosen reaction coordinate as the density of unidirectional flux projected onto the former. The total flux is then obtained by an integration over the $(n-1)$-dimensional subspace perpendicular to the reaction coordinate. This procedure defines the potential of the mean force appearing in the exponential, whereas the prefactor containing the effective mass, is defined by the cosine between reaction coordinate and reaction path, i.e., direction of the steepest descent.

The expression obtained for the jump rate is effectively one-dimensional and reveals a systematic approach for the analogous handling of continuous diffusion. An effective one-dimensional equilibrium distribution function yielding the jump rate in a standard procedure is obtained from the average of the multi-dimensional e.d.f. over $n-1$ pairs of canonical variables spanning the phase space perpendicular to the reaction coordinate. This projection renders an effective Hamiltonian with effective mass and potential of the mean force.

The starting point for the derivation of an effective one-dimensional transport equation is the multi-dimensional Fokker-Planck equation. In the first step the FPE is written in terms of canonical variables as defined before. In the second step the distribution function is split into a product of the Boltzmann distribution function containing all dynamical variables and a time-dependent function with the reaction coordinate and its conjugate momentum. Averaging again over $n-1$ pairs of variables yields the effective one-dimensional FPE. Its significant quantities are the potential of the mean force, position-dependent effective mass and friction coefficient, respectively. The latter consists of all individual friction coefficients, all masses and the distortion field. It allows for the discussion of a large variety of scenarios. In particular, the large friction limit leading to an effective Smoluchowski equation has been discussed. In the case of ion-conducting membrane channels it is realistic to consider only the fluctuating ligands as coupled to the temperature bath which in turn thermalize the ion. This can easily be achieved by a vanishingly small direct friction for the ion. In this case, the diffusive motion of the ion comes to rest with vanishing distortion field.

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