Narrow Escape of Interacting Diffusing Particles

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The narrow escape problem deals with the calculation of the mean escape time (MET) of a Brownian particle from a bounded domain through a small hole on the domain's boundary. Here we develop a formalism which allows us to evaluate the nonescape probability of a gas of diffusing particles that may interact with each other. In some cases the nonescape probability allows us to evaluate the MET of the first particle. The formalism is based on the fluctuating hydrodynamics and the recently developed macroscopic fluctuation theory. We also uncover an unexpected connection between the narrow escape of interacting particles and thermal runaway in chemical reactors.

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The narrow escape problem (NEP) [1–6] is ubiquitous in physics, chemistry, and biology. It deals with the calculation of the mean time it takes a Brownian particle inside a bounded domain to escape through a narrow window on the domain's boundary; see Fig. 1. In the past two decades this beautiful and mathematically intricate problem has received much attention, as it was realized that the mean escape time (MET) controls the rates of many important processes in molecular and cellular biology, such as arrival of a receptor at a reaction site on the surface of a cell [7], transport of RNA molecules from the nucleus to the cytoplasm through nuclear pores [8], diffusion of calcium ions in dendritic spines [9], and other processes [3]. When the size of the escape hole ϵ is much smaller than the domain size L, the MET of a Brownian particle can be expressed via the principal eigenvalue of the Laplace's operator inside the domain with the absorbing (Dirichlet) boundary condition on the escape hole and the reflecting (Neumann) condition on the rest of the boundary; see, e.g., [2]. The latter problem goes back to Helmholtz [10] and Lord Rayleigh [11]. Recent theoretical developments addressed the role of the initial position of the Brownian particle [12], complicated geometries [13–21], finite lifetime of the escaping particle [22,23], and the presence of a kinetic bottleneck at the escape hole [24].

In a host of situations of biological importance there are many Brownian particles, which attempt to escape through a small hole (or reach a small site). If they are treated as noninteracting, the escape statistics can be expressed via the one-particle statistics [25,26]. Quite often, however, the particles interact with each other, such as in a highly crowded intracellular environment [3]. Although the importance of interactions may have been recognized earlier, there have been no attempts to include them in the theory. This is our main objective here, but the formalism proves useful also for ensembles of noninteracting particles.

One approach to solving the NEP for a single Brownian particle with diffusivity D_0 relies on the calculation of the particle's nonescape probability until time T, $\mathcal{P}_1(T)$. In the small-window limit, $\epsilon/L \ll 1$, the problem simplifies because the particle's escape becomes a relatively rare event [2]. For times much longer than the diffusion time across the escape hole, $T \gg \epsilon^2/D_0$, and for a uniformly distributed random initial position of the particle, $\mathcal{P}_1(T)$ decays exponentially in time [1–5],

$$-\ln \mathcal{P}_1(T) \simeq T D_0 \mu_0^2, \tag{1}$$

where μ_0^2 is the principal eigenvalue of the eigenvalue problem $\boldsymbol{\nabla}^2\Psi + \mu^2\Psi = 0$ inside the domain with the mixed boundary conditions $\Psi(\mathbf{x}\in\Omega_a,t) = \boldsymbol{\nabla}\Psi(\mathbf{x}\in\Omega_r,t)\cdot\hat{n} = 0$. Here Ω_r is the reflecting part of the domain's boundary, Ω_a is the complementary absorbing part (the small escape hole), and $\hat{n}$ is the local normal to the boundary. Correspondingly, the MET is equal to $\langle T_1\rangle \simeq 1/D_0\mu_0^2$, and this result holds up to small corrections in ϵ/L [19]. In the leading order, which is $O(\epsilon/L)$, μ_0^2 (found already by Lord Rayleigh [11]) can be expressed through the electrical capacitance C_ϵ of the conducting patch Ω_a in an otherwise

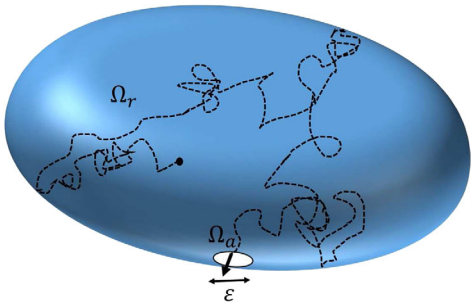

FIG. 1. Narrow escape of a single Brownian particle. Ω_a is a small hole of linear size ϵ. Ω_r is the reflecting part of the boundary.

empty space: $\mu_0^2 \simeq 2\pi C_\epsilon/V$, where V is the domain's volume. The capacitance C_ϵ scales as ϵ. If Ω_a is a disk of radius ϵ, then $C_\epsilon = 2\epsilon/\pi$ [27] leading to $\langle T_1\rangle \simeq V/(4\epsilon D_0)$, which is independent of the domain shape [2].

The nonescape probability $\mathcal{P}(T,N)$ of N noninteracting Brownian particles, randomly distributed over the domain, is the product of their single-particle nonescape probabilities (1). Therefore, at long times, it also decays exponentially in time, $-\ln \mathcal{P}(T,N) \simeq Ts(n_0,\epsilon)$, with the decay rate

$$s(n_0,\epsilon) = ND_0\mu_0^2 \simeq 2\pi C_\epsilon D_0 n_0, \tag{2}$$

where $n_0 = N/V$ is the particle number density. For very low densities, $n_0\epsilon^3 \ll 1$, Eq. (2) yields the MET of the first particle, $\langle T\rangle \simeq 1/s(n_0,\epsilon)$ [25]. Indeed, in this regime $\langle T\rangle$ is much longer than the diffusion time across the hole, ϵ^2/D_0.

At higher densities, $n_0\epsilon^3 \gg 1$, we have $\langle T\rangle \ll \epsilon^2/D_0$. As the diffusion length scale $\sqrt{D_0T}$ is now much smaller than ϵ, the process is effectively one dimensional (1D) in the direction normal to the hole. Here the nonescape problem reduces to a well-studied problem of finding the survival probability $\mathcal{P}_{1D}$ of a gas of noninteracting Brownian particles of density n_{1D} (per unit length), randomly placed on a half-line $x > 0$, against absorption at $x = 0$ [28–37]. Here $\mathcal{P}_{1D}$ decays as a stretched exponential, $-\ln \mathcal{P}_{1D} \simeq (2/\sqrt{\pi})n_{1D}\sqrt{D_0T}$ [29,37]. To evaluate $\mathcal{P}(T,N)$, one should set $n_{1D} = n_0A_\epsilon$, where A_ϵ is the area of Ω_ϵ [37]. For a circular hole of radius ϵ this leads to

$$-\ln \mathcal{P}(T,N) \simeq 2\sqrt{\pi}n_0\epsilon^2\sqrt{D_0T}, \tag{3}$$

and one obtains $\langle T\rangle \simeq (2\pi D_0 n_0^2\epsilon^4)^{-1}$ [25].

For interacting particles the nonescape probability $\mathcal{P}(T,N)$ is not equal to the product of single-particle probabilities, and a new approach is required. We develop such an approach here and calculate the nonescape probability $\mathcal{P}(T,N)$ of $N \gg 1$ interacting particles at long and short times. At long times, $\mathcal{P}(T,N)$ decays exponentially in time,

$$-\ln \mathcal{P}(T,N) \simeq Ts(n_0,\epsilon). \tag{4}$$

The dependence of $s(n_0,\epsilon)$ on the geometry factorizes up to small corrections in ϵ/L. In the leading order in ϵ/L we obtain

$$s(n_0,\epsilon) \simeq \pi C_\epsilon f^2(n_0). \tag{5}$$

The nonlinear function $f(n_0)$, which we show how to calculate, encodes particle interactions and is model dependent.

At short times we obtain

$$-\ln \mathcal{P}(T,N) \simeq A_\epsilon g(n_0)\sqrt{D_0T}, \tag{6}$$

with a model-dependent nonlinear function $g(n_0)$.

Now we present our results in some detail. Assuming a large number of particles in the relevant regions of space, we employ fluctuating hydrodynamics: a coarse-grained description in terms of the (fluctuating) particle number density $\rho(\mathbf{x},t)$ [38,39]. The average particle density obeys a diffusion equation $\partial_t\rho = \boldsymbol{\nabla}\cdot[D(\rho)\boldsymbol{\nabla}\rho]$, whereas macroscopic fluctuations are described by the conservative Langevin equation

$$\partial_t\rho = -\boldsymbol{\nabla}\cdot\mathbf{J}, \qquad \mathbf{J} = -D(\rho)\boldsymbol{\nabla}\rho - \sqrt{\sigma(\rho)}\boldsymbol{\eta}(\mathbf{x},t), \tag{7}$$

where $D(\rho)$ and $\sigma(\rho)$ are the diffusivity and mobility of the gas of particles, and $\boldsymbol{\eta}(\mathbf{x},t)$ is a zero-mean Gaussian noise, delta correlated in space and time. The density ρ and flux $\mathbf{J}$ satisfy the boundary conditions

$$\rho(\mathbf{x}\in\Omega_a,t) = 0, \qquad \mathbf{J}(\mathbf{x}\in\Omega_r,t)\cdot\hat{n} = 0. \tag{8}$$

To proceed further we employ the recently developed macroscopic fluctuation theory (MFT) [40]. The MFT grew from the Martin-Siggia-Rose path integral formalism in physics [41–43] and the Freidlin-Wentzell large-deviation theory in mathematics [44]. It follows from a path integral formulation for Eq. (7), which describes the probability of observing a joint density and flux histories $\rho(\mathbf{x},t)$, $\mathbf{J}(\mathbf{x},t)$, constrained by the conservation law (7),

$$\mathcal{P} = \int \mathcal{D}\rho\mathcal{D}\mathbf{J}\prod_{\mathbf{x},t}\delta(\partial_t\rho + \boldsymbol{\nabla}\cdot\mathbf{J})\exp(-\mathcal{S}),$$
$$\mathcal{S}[\rho(\mathbf{x},t),\mathbf{J}(\mathbf{x},t)] = \int_0^T dt\int d^3\mathbf{x}\,\frac{[\mathbf{J}+D(\rho)\boldsymbol{\nabla}\rho]^2}{2\sigma(\rho)}. \tag{9}$$

The next step in the derivation, by now fairly standard [40,42,43], exploits the large parameter $N \gg 1$ to perform a saddle-point evaluation of the path integral. The dominant contribution to $\mathcal{P}$ comes from the optimal fluctuation: the most probable history $(\rho,\mathbf{J})$ ensuring the particle nonescape up to the specified time T and obeying the conservation law. The ensuing minimization procedure yields the Euler-Lagrange equation and the problem-specific boundary conditions. With the solutions at hand, one calculates the action S, which yields the nonescape probability $\mathcal{P}(T,N)$ up to a preexponential factor,

$$-\ln \mathcal{P}(T,N) \simeq S \equiv \min_{\rho,\mathbf{J}}\mathcal{S}[\rho(\mathbf{x},t),\mathbf{J}(\mathbf{x},t)]. \tag{10}$$

The resulting problem simplifies in the limits of very long and very short times (we elaborate on the relevant time scales below). At long times, the optimal gas density and

flux, conditioned on nonescape, become stationary, in analogy with a closely related problem of survival of particles inside domains with fully absorbing boundaries [45]. As a result, $\mathcal{P}(T,N)$ exponentially decays with time T; see Eq. (4). A similar property lies at the origin of the "additivity principle" [46], proposed in the context of stationary fluctuations of current in systems driven by density reservoirs at the boundaries.

In the stationary formulation, Eq. (7) yields $\boldsymbol{\nabla}\cdot\mathbf{J}=0$, so the optimal flux $\mathbf{J}$ is a solenoidal vector field. In the nonescape problem, $\mathbf{J}$ must also have zero normal component at the entire domain's boundary. Using these properties, one can show (see Ref. [45] and Appendix A of Ref. [47]) that $\mathbf{J}$ is also vortex free and thus vanishes identically. This means that the fluctuating contribution to the optimal flux exactly counterbalances the deterministic contribution, thus preventing the particles from escaping. Now we have to find the optimal density profile. Upon the ansatz $\mathbf{J}=0$ and $\rho=\rho(\mathbf{x})$ in Eq. (9), the action $\mathcal{S}$ becomes proportional to T, and the problem reduces to minimizing the action rate functional

$$\mathfrak{s}[\rho(\mathbf{x})]=\int d^3\mathbf{x}\,\frac{[D(\rho)\boldsymbol{\nabla}\rho]^2}{2\sigma(\rho)}, \tag{11}$$

subject to the boundary conditions (8) and the mass conservation constraint

$$\int d^3\mathbf{x}\rho(\mathbf{x})=n_0V. \tag{12}$$

Let us introduce the new variable $u(\mathbf{x})=f[\rho(\mathbf{x})]$, where the function f is defined by the integral [48],

$$f(\rho)=\int_0^\rho dz\,\frac{D(z)}{\sqrt{\sigma(z)}}. \tag{13}$$

We denote the inverse function, f^{-1}, by F. Expressed through $u(\mathbf{x})$, the action rate (11) is reduced to the effective "electrostatic action"

$$\mathfrak{s}[u(\mathbf{x})]=\frac{1}{2}\int d^3\mathbf{x}[\boldsymbol{\nabla}u(\mathbf{x})]^2, \tag{14}$$

which, remarkably, is universal for all interacting particle models described by Eq. (7). Now we minimize this action, incorporating the mass conservation (12),

$$\int d^3\mathbf{x}F[u(\mathbf{x})]=n_0V, \tag{15}$$

via a Lagrange multiplier Λ. The Euler-Lagrange equation has the form of a nonlinear Poisson equation [45],

$$\boldsymbol{\nabla}^2u+\Lambda\frac{dF(u)}{du}=0, \tag{16}$$

with the mixed boundary conditions [49],

$$u(\mathbf{x}\in\Omega_a)=0,\qquad \boldsymbol{\nabla}u(\mathbf{x}\in\Omega_r)\cdot\hat{n}=0. \tag{17}$$

The action rate (14), evaluated on the solution to the problem (15)–(17), yields the decay rate $s(n_0,\epsilon)$ from Eq. (4), specific to each gas model. If there are multiple solutions, the minimum-action solution must be chosen.

Now we apply the steady-state formalism to the diffusive lattice gases [38,39,50]. This is a class of microscopic models, defined by a prescribed stochastic particle dynamics on a lattice. The diffusivity $D(\rho)\geq 0$ and the mobility $\sigma(\rho)\geq 0$ should be obtained from the microscopic model. The simplest example is a gas of noninteracting random walkers (RWs). On large scales and at long times these are indistinguishable from the noninteracting Brownian particles [51]. For the RWs one has $D(\rho)=D_0=\text{const}$, and $\sigma(\rho)=2D_0\rho$ [38].

A more interesting example is the symmetric simple exclusion process (SSEP), which accounts for excluded-volume interactions. In the SSEP each particle can hop to a neighboring lattice site only if that site is vacant [38]. In the coarse-grained description of the SSEP one has $D(q)=D_0=\text{const}$ and $\sigma(\rho)=2D_0\rho(1-\rho a^3)$ [38,39]. We set the lattice constant a to unity, so that $0\leq\rho\leq 1$.

Let us first see that the formalism (13)–(17) reproduces the classical narrow-escape results for the RWs. In this case Eq. (13) yields $f(\rho)=\sqrt{2D_0\rho}$, while Eq. (16) reduces to the Helmholtz equation

$$\boldsymbol{\nabla}^2u+\mu^2u=0, \tag{18}$$

with $\mu^2\equiv\Lambda/D_0$ playing the role of the eigenvalue. The minimum action is achieved for the fundamental mode of this equation. We denote it by $\Psi_0(\mathbf{x})$ and normalize it to unity, $\int d^3\mathbf{x}\Psi_0^2(\mathbf{x})=1$. Subject to the mass conservation (15), the solution can be written as $u(\mathbf{x})=\sqrt{2ND_0}\Psi_0(\mathbf{x})$. Now we plug it into Eq. (14), use the identity $(\boldsymbol{\nabla}\Psi_0)^2=\boldsymbol{\nabla}\cdot(\Psi_0\boldsymbol{\nabla}\Psi_0)-\Psi_0\boldsymbol{\nabla}^2\Psi_0$, apply the divergence theorem to the first term on the right, and use Eqs. (17) and (18) for $\Psi_0(\mathbf{x})$. The resulting $\mathfrak{s}[u(\mathbf{x})]=s(n_0,\epsilon)$ is equal to $ND_0\mu_0^2$ in agreement with the exact result cited in Eq. (2). The case of RWs is important because here one can also exactly solve the full time-dependent MFT equations [45]. The time-dependent solution shows that, for $T\gg\epsilon^2/D_0$, the leading-order contribution to the action indeed comes from the steady-state solution. Furthermore, only a vicinity of the escape hole contributes. That is, to leading order in ϵ/L, the solution for a finite domain coincides with the one for a gas of particles occupying the infinite half-space on one side of an infinite reflecting plane with the hole Ω_a on it.

For interacting particles Eq. (16) is nonlinear, but we can exploit the small parameter ϵ/L in the same spirit. The nonescape probability of the gas in the infinite half-space until a long time T can be obtained from an unconstrained minimization procedure where, instead of Eq. (15), we use the boundary condition $u(\mathbf{x}\to\infty)=f(n_0)$. Setting $\Lambda=0$ in Eq. (16), we arrive at the Laplace's equation for $u(\mathbf{x})$. The solution can be expressed through the electrostatic potential $\phi(\mathbf{x})$ of a conducting patch Ω_a kept at unit voltage on an otherwise insulating infinite plane,

$$u(\mathbf{x}) = f(n_0)[1-\phi(\mathbf{x})]. \tag{19}$$

In simple cases (e.g., when Ω_a is a disk), $\phi(\mathbf{x})$ can be found explicitly [27]. Equation (19) yields the stationary density profile, optimal for the particle nonescape, $\rho(\mathbf{x})=F\{f(n_0)[1-\phi(\mathbf{x})]\}$. Plugging Eq. (19) in Eq. (14) yields the announced result (5) for the decay rate of the nonescape probability to order ϵ/L. It is given by the electrostatic energy created by a conductor Ω_a held at voltage $f(n_0)$, where C_ϵ is the electrical capacitance of the conductor Ω_a. The entire effect of interactions is encoded in the density dependence $f(n_0)$, coming from the nonlinear transformation (13). The geometry dependence is universal for all gases of this class and is given by the capacitance C_ϵ. The latter is determined by the shape of the hole and is independent of the domain shape. A dependence on the domain shape emerges in higher orders in ϵ/L. When specialized to the RWs, Eq. (5) yields the approximate result cited in Eq. (2), as to be expected.

For the SSEP Eq. (13) yields $f(\rho)=\sqrt{2D_0}\arcsin(\sqrt{\rho})$, whereas for a small circular window of radius ϵ we have $C_\epsilon = 2\epsilon/\pi$. The resulting decay rate of $\mathcal{P}(T,N)$ is

$$s(n_0,\epsilon) \simeq 4D_0\epsilon \arcsin^2(\sqrt{n_0}). \tag{20}$$

Figure 2 shows the density dependence of the ratio of this decay rate to the decay rate for the RWs, Eq. (2). At finite densities this ratio is always larger than 1, as to be expected because of the effective mutual repulsion of the SSEP particles. The finite value of the ratio, $\pi^2/4$, at close packing of the SSEP should not be taken too seriously,

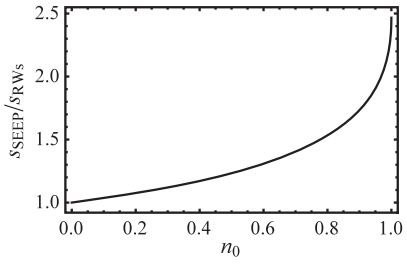

FIG. 2. The ratio of the decay rate of the nonescape probability for the SSEP, Eq. (20), to the same quantity for the RWs, Eq. (2), vs the gas density $n_0 = N/V$.

because fluctuating hydrodynamics breaks down here [45]. For low densities $n_0\epsilon^3 \ll 1$, the MET of the first particle is given by $\langle T\rangle \simeq 1/s(n_0,\epsilon)$.

Higher-order corrections (with respect to ϵ/L) to Eq. (5) can be obtained by matched asymptotic expansions [52]. The inner expansion of $u(\mathbf{x})$ is valid at distances from the escape hole that are much smaller than L. The outer expansion holds at distances much larger than ϵ. The two expansions can then be matched in their joint region of validity to yield a composite expression valid across the entire domain. This method yields subleading corrections in ϵ/L for the noninteracting Brownian particles [1,19]. For interacting particles we can adopt a different formalism. Remarkably, Eqs. (16) and (17) also serve as a simple model of thermal runaway in cooled chemical reactors, where $u(\mathbf{x})$ is the stationary temperature field across a reactor that is insulated by its boundary except for a small cooling patch on it [53,54]. The (important) difference is that in the NEP one also should evaluate the action and minimize it over possible multiple solutions.

The leading-order composite expression for $u(\mathbf{x})$ coincides with Eq. (19) [53,54]. As we checked, the action (4) remains proportional to $f^2(n_0)$ up to, and including, the second order in ϵ/L, with a geometry-dependent proportionality constant. The latter is given by the second-order expansion of the principle eigenvalue of the Laplace's operator μ_0^2 [55]. For a small absorbing disk of radius ϵ on the boundary of a sphere of radius L one obtains $\mu_0^2 V = 4\epsilon[1+(\epsilon/\pi L)\ln(\epsilon/L)+\cdots]$ [55]. In the context of the NEP of the SSEP, this leads to

$$s(n_0,\epsilon) \simeq 4D_0\epsilon\left[1+\frac{\epsilon}{\pi L}\ln\left(\frac{\epsilon}{L}\right)\right]\arcsin^2(\sqrt{n_0}). \tag{21}$$

Equations (20) and (21) hold for $D_0T \gg \epsilon^2$. However, they yield the MET of the first particle only for very low densities, $n_0\epsilon^3 \ll 1$, where the interparticle interactions can be neglected. For moderate and high densities, $n_0\epsilon^3 \gg 1$, the MET of the first particle is much shorter than ϵ^2/D_0. Here the optimal fluctuation for the nonescape is nonstationary, and we must return to the time-dependent MFT formulation (9). The problem boils down to finding the survival probability $\mathcal{P}_{1\mathrm{D}}$ of a gas of interacting particles, randomly distributed on a half-line $x>0$, against absorption at $x=0$. This problem was studied via the MFT [37]. The stretched-exponential decay with time, $-\ln\mathcal{P}_{1\mathrm{D}} \simeq \sqrt{D(n_0)Ts_{1\mathrm{D}}(n_0)}$, holds in spite of the interactions. For the SSEP, the MFT yields a low-density expansion $s_{1\mathrm{D}}(n_0)=(2/\sqrt{\pi})[n_0+(\sqrt{2}-1)n_0^2+\cdots]$ [37,56]. For higher densities $s_{1\mathrm{D}}(n_0)$ can be computed numerically [37]. This brings us to the result announced in Eq. (6) with $g(n_0)\equiv s_{1\mathrm{D}}(n_0)$, and we obtain $\langle T\rangle \simeq 2[A_\epsilon^2 D_0 g^2(n_0)]^{-1}$.

A plausible setup, where our predictions can be compared to experiment, is a "pore-cavity-pore" device of μm

dimensions with a nanoscale hole [57]. It allows for a controlled entrapment of particles of a nanoscale size, which, once trapped, can freely diffuse. Fluorescence imaging is used to track their positions. The authors of Ref. [57] reported measurements of the decay rate of the average number of particles inside the device, and noticed deviations from a purely Brownian behavior. It would be interesting to also measure, for different initial number of particles, and different hole sizes, the MET of the first particle from the device.

Finally, our general framework for the NEP, rooted in the MFT, can be extended to more complicated geometries [5,13–20] and boundary conditions at the escape hole [24]. It can also accommodate reactions among, and a finite lifetime of, the particles [58–62].

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[48] Convergence of this integral puts some limitations on the behavior of $D(\rho)$ and $\sigma(\rho)$ at small densities. As an example, let $D(\rho \to 0) \sim \rho^{\alpha}$ and $\sigma(\rho \to 0) \sim \rho^{\beta}$. Then the integral converges at $\rho \to 0$ if and only if $2\alpha - \beta + 2 > 0$. This condition holds in the examples we consider here.

[49] The condition $u(\mathbf{x} \in \Omega_a) = 0$ is inherited from $\rho(\mathbf{x} \in \Omega_a) = 0$ due to the definition (13). The condition $\boldsymbol{\nabla} u(\mathbf{x} \in \Omega_r) \cdot \hat{n} = 0$ results from a boundary term that appears when minimizing the action (14).
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