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Extinction of a bacterial colony under forced convection in pie geometry

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The extinction of a bacterial colony, as it is forced to migrate into a hostile environment, is analyzed in pie geometry. Under convection, separation of the radial and the azimuthal degrees of freedom is not possible, so the linearized evolution operator is diagonalized numerically. Some characteristic scales are compared with the results of recent experiments, and the ''integrable'' limit of the theory in the narrow growth region is studied.

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The time evolution of bacterial colonies on a petri-dish has been studied recently both theoretically and experimentally [1–4]. The colony is a relatively simple biological system, and its basic component, an individual bacterium, involves only ''elementary'' biological processes such as diffusion, food consumption, multiplication, death, and some interaction like chemotaxis. Studies of several bacteria strains have shown a wide variety of complex pattern formation, in most cases due to either competition for food resources or chemical interaction. With a uniform, inexhaustible background of nutrients and without the presence of mutations and chemical signaling, these simple strains are suppose to invade an empty region as a front which propagates with some typical velocity, known as the Fisher front [5–7].

Biological problems of colony growth in *inhomogeneous* environment and under forced convection have been modeled recently by Nelson and Shnerb [8] and by Dahmen, Nelson, and Shnerb [9]. These studies have focused on the spectral properties of the linearized evolution operator, which becomes non-Hermitian in the presence of convection [10]. An experiment designed to test these predictions has been carried out recently by Neicu *et al.* [4].

In the experiment, a colony of *Bacillus subtilis* bacteria is forced to migrate in order to ''catch up'' with a shielded region on the petri-dish, where all the other parts of the dish are exposed to an ultraviolet (uv) light, which makes the unshielded bacteria immotile. It was assumed that the adaptation of the bacterial colony to the rotating shielded region has nothing to do with information processing or mutual signaling in the colony, but is attributed solely to the combined effect of ''dumb'' diffusion of individual bacteria and the larger growth rate under the shelter. Theoretically, it was predicted that the adaptation of the colony to the moving environment fails if the drift is faster than the Fisher front velocity, as the colony lags behind the shelter and an extinction transition takes place.

In order to get the flavor of the theory, let us consider a one-dimensional example, where bacteria are diffusing on a line parametrized by x, and are subject to some environmental heterogeneity that implies fluctuating growth rate. If the bacteria diffuses, multiply, and are forced to migrate with some convection velocity v, the differential equation which describes the evolution of the colony is

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} + v\frac{\partial c}{\partial x} + a(x)c - bc^2, \tag{1}$$

where $a(x)$ is the local growth rate. When the hostile environment outside an ''oasis'' of size x_0 causes the immediate death of any bacteria, and inside the oasis there is some positive growth rate, $a(x)$ takes the form

$$a(x) = \begin{cases} a & 0 \leqslant x \leqslant x_0 \\ -\infty & \text{elsewhere.} \end{cases} \tag{2}$$

In the absence of a drift, i.e., $v=0$, the linearized version of this problem is equivalent to the (imaginary time) evolution of a quantum particle in an infinite potential well. The growth pattern is determined by the eigenvalues of the evolution operator, giving a colony localized on the oasis if it has a minimal width $x_0 > \pi\sqrt{D/a}$. (This width scales like the width of the Fisher front). The introduction of the drift term $v\partial_x$ into Eq. (1) may be compensated by a ''gauge'' of the evolution (Liouville) operator eigenfunctions

$$\phi_n = \sin(n\pi x/x_0) \rightarrow e^{\pm vx/2D}\sin(n\pi x/x_0) \tag{3}$$

together with a rigid shift of the eigenvalues,

$$\Gamma_n(v) = \Gamma_n(v=0) - \frac{v^2}{4D}. \tag{4}$$

The theory, thus, predicts an extinction transition when all the eigenvalues of Eq. (4) become negative, i.e., as $v_c = 2\sqrt{aD} - O(1/x_0)$, which is the Fisher velocity [11]. Right above the extinction transition, only the largest growth eigenvalue (the ''ground state'') is positive, and the nonlinear term $-bc^2$ is suppressed. Accordingly, the analysis of the transition is focused on the features of the ground state of the linearized operator.

The experiment [4] takes place in a two-dimensional geometry. Part of a petri-dish was shielded from the uv source, and then this shield was given a constant *angular* velocity with respect to the petri-dish. The corresponding convection velocity $v(r) = \omega r$ was chosen to interpolate between zero (at the rotation axis) and about $2v_c$ at the edge of the dish. It turned out that the colony indeed fails to keep rotating with the shield at about half the radius. On the other hand, the velocity profile for the bacterial density $c(r,\omega)$ did not reach equilibrium during the experiment (~3 days).

In this paper, I consider the differences between the one-dimensional system (1,2) and the actual experimental setup. In particular, the two-dimensional nature of the experiment

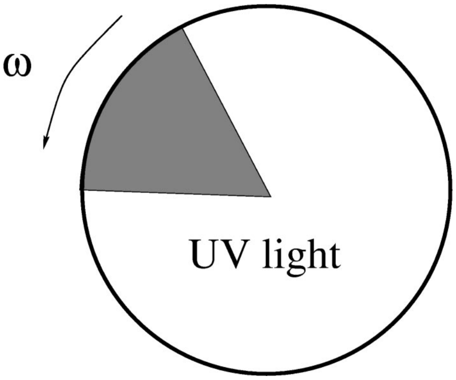

FIG. 1. Pie geometry: the growth rate in the shaded region is a, and any bacteria outside this area ''die'' (or become immotile) instantly due to the UV light. The shaded region is then rotated at angular velocity ω.

and the effect of *radial* diffusion are considered explicitly. The typical time scales for the stabilization of the ground state are then compared with the experiment.

In order to capture the essential physics using the simplest geometry, the extinction transition is considered on a pie, a section of the two-dimensional disc (see Fig. 1). Although the shielded region of the experiment [4] was not pie shaped, it turns out that even in this simple geometry there is a coupling between the radial and the azimuthal degrees of freedom, and the spectrum becomes ''chaotic'' when convection takes place. Accordingly, the results presented here are also relevant to the more complicated geometry of the experiment.

The basic equation which governs the bacterial growth problem on a nonuniform substrate, in the absence of mutation and chemical interactions, is [8]

$$\frac{\partial c(\mathbf{x},\mathbf{t})}{\partial t} = D\nabla^2 c(\mathbf{x},\mathbf{t}) + a(\mathbf{x})c(\mathbf{x},\mathbf{t}) + \mathbf{v}\cdot\nabla c - bc^2. \tag{5}$$

With no convection and homogeneous, positive a this equation supports Fisher front propagation with velocity $2\sqrt{Da}$. The experimental situation corresponds to $D\sim10^{-6}$ cm^2/s and $a\sim10^{-3}$/s, so the Fisher velocity is of order $0.1-1$ μm/s, as has been observed experimentally. The Fisher *width*, which is the characteristic scale of spatial correlations, is $\sqrt{D/a}\sim10^{-2}$ cm, much smaller than the petri-dish radius of a few centimeters.

In cylindrical geometry, Eq. (5) takes the form

$$\frac{\partial c(r,\theta,t)}{\partial t} = D\nabla^2 c(r,\theta,t) + a(\theta)c(r,\theta,t) + \mathbf{v}\cdot\nabla c - bc^2, \tag{6}$$

and for a rotating petri-dish the convection term is [12]

$$\mathbf{v}\cdot\nabla c = \omega\frac{\partial c}{\partial\theta}. \tag{7}$$

Pie geometry is defined by

$$a(\theta) = \begin{cases} a & 0\leq\theta\leq\theta_0 \\ -\infty & \text{elsewhere,} \end{cases} \tag{8}$$

i.e., we have absorbing boundary conditions [13]

$$c(r,\theta_0,t) = c(r,0,t) = 0. \tag{9}$$

As for the petri-dish edge at $r=R$, it is reasonable to take the von Neumann boundary and to impose the no-slip condition on the bacterial density at the surface. However, the data of [4] seems to indicate extinction of the bacteria at the edge of the dish. This is perhaps due to the fact that the width of the boundary layer (which is expected due to the no-slip condition) is approximately the Fisher width, which has been shown above to be very small. Accordingly, we further simplify the problem by using

$$c(R,\theta,t) = 0. \tag{10}$$

Dropping the term $-bc^2$ at Eq. (5), one has the linearized evolution operator, and for the no-drift ($\omega=0$) case, the density of bacteria at time t is given by

$$c(r,\theta,t) = \sum_{m,n} A_{m,n} e^{(a-\Gamma_{m,n})t}\phi_{m,n}(r,\theta), \tag{11}$$

with the eigenstates of the evolution operator,

$$\phi_{m,n}(r,\theta) = \eta_{m,n} J_{n\pi/\theta_0}(r/\sqrt{D/\Gamma_{m,n}})\sin\left(\frac{n\pi\theta}{\theta_0}\right), \tag{12}$$

$\eta_{m,n}$, the normalization factors,

$$\eta_{n,m} = \frac{2}{R\sqrt{\theta_0}}\frac{1}{J_{[(n\pi/\theta_0)+1]}(R/\sqrt{D/\Gamma_{m,n}})}, \tag{13}$$

and the constants $A_{m,n}$ are determined by the initial density distribution $c(r,\theta,t=0)$. The eigenvalues of the Hermitian problem are

$$\Gamma_{m,n} = D\left(\frac{j^m_{n\pi/\theta_0}}{R}\right)^2, \tag{14}$$

where $j^m_{n\pi/\theta_0}$ is the mth zero of the corresponding Bessel function.

Let us get an order of magnitude estimate for the time scales that are relevant to the experiment [4]. The characteristic times needed for the ''ground state'' to control the system are given by the typical difference between two eigenvalues. In our case, since the first zeroes of the Bessel functions are of order 1, the times involved are $\sim(R^2/D)$. For an experimental system with $R\sim0.01$ m and $D\sim10^{-10}$ m^2/s, the typical relaxation times are $O(10^6\ \text{s})\sim11$ days, which is larger than the typical time of the actual experiment.

Consider now the non-Hermitian case, where $\omega\neq0$. Unlike its Cartesian analogous [8,9], there is no simple gauge which relates the ''tilted'' and the ''untilted'' wave functions, as the separation of variables is impossible. Spanning the space of normalizable functions by a set of Hermitian eigenstates, the perturbative term $\omega\partial_\theta$ mixes both quantum numbers m and n. The matrix elements of the convection term are

$$\langle n,m|\omega\partial_\theta|k,l\rangle = 2\omega R^2 \gamma_{nmkl}, \tag{15}$$

where γ_{nmkl} is

$$\gamma_{nmkl} = \begin{cases} k+n=\text{even} & 0 \\ k+n=\text{odd} & \dfrac{2kn}{n^2-k^2}\eta_{n,m}\eta_{k,l}I_{nmkl} \end{cases} \tag{16}$$

and

$$I_{nmkl} = \int_0^1 J^m_{n\pi/\theta_0}(y) j^l_{k\pi/\theta_0}(y) y\, dy. \tag{17}$$

In order to calculate the eigenvalues and eigenfunctions at finite angular velocity one should diagonalize the full non-Hermitian Liouville operator. The extinction transition takes place as the ground state (smallest) eigenvalue, $\Gamma_{1,1}$, becomes larger than the growth rate, a, on the pie.

As the rotating system is not integrable, it should be studied numerically using some computer diagonalization of the linearized evolution operator. Essentially, one should look at the ground state of this operator, since this state dominates the system close to the extinction transition.

The numerical analysis, however, may lead to erroneous results if the continuum limit is not taken carefully. In the most general case, a discretized version of a model with local growth rate and hopping between sites may be represented numerically as a matrix, where the growth rates are the coefficients on the diagonal and the hopping process gives the off-diagonal terms. As any hopping term is positive semidefinite, the only negative terms are the local growth rate, and for any finite matrix, by adding an appropriate multiplication of the unit matrix, one may get a positive semidefinite matrix with the *same* eigenvectors. Perron-Frobenius theorem [14] then implies that the ground state should be a nodeless, positive eigenvector. There is a simple physical interpretation to this result: since the ground state dominates the system at long times, and the number of bacteria should not become negative, the Perron-Frobenius theorem should hold. Numerical diagonalization of the evolution operator, on the other hand, may give a ground state with nodes, which is physically impossible.

In order to solve this problem the discrete limit of the continuum theory should be taken carefully. When θ is discretized in quanta of $\Delta\theta$, the azimuthal hopping rate becomes $D/(r^2\Delta\theta^2)$ and the drift is $\pm\omega/\Delta\theta$. In order to avoid the (physically impossible) negative hopping rates, one should keep $\Delta\theta$ small, thus restricting the minimal value of the quantum number n. If the effective discretization is given by $\Delta\theta=\theta_0/n$, the matrix (16) may be truncated only for

$$n \geqslant \frac{\omega R^2\theta_0}{D}. \tag{18}$$

On the other hand, the truncation of the infinite matrix may be justified only if the elements are arranged by order of their "energies," $\Gamma_{n,m}$, and the matrix is truncated if this energy is much larger than the ground state ($\Gamma_{1,1}$) eigenvalue. As the eigenvalues of the unperturbed problem are related to the zeroes of the corresponding Bessel functions, it is impossible to satisfy these two conditions at small wedge angles, since as $\theta_0\to 0$, the higher m zeroes of any Bessel of order n are smaller than the $m=1$ zero of the $n+1$ state, and the condition (18) implies the diagonalization of an infinite matrix. Accordingly, I present here the numerical results for the case $\theta_0=\pi$. This situation does not coincide with the experimental conditions in [4], but there seems to be no prevention to perform the same experiment with a large shielded area.

In Fig. 2, contour plots of the ground state for different angular velocities are shown. One may identify clearly the large deviations from the ground state from its shape at $\omega=0$. The largest 100 spectral points for each case are shown in Fig. 3.

Figure 4 presents the ground state eigenvalue, $\Gamma_{0,}$ in units of D/R^2, as a function of the angular velocity of the dish. The extinction transition takes place when this eigenvalue is larger than the growth rate on the "pie," $a/D/R^2$, as has been found earlier.

Let us show now how to get a problem equivalent to Eqs. (1) and (2) on a rotating petri-dish. In order to do that, the geometry should be taken on a narrow shell as in Fig. 5, i.e., the boundary conditions are

$$\begin{gathered} c(r,\theta_0,t)=c(r,0,t)=0, \\ c(R_1,\theta_0,t)=c(R_2,0,t)=0, \end{gathered} \tag{19}$$

with $\Delta R=R_2-R_1$. In the limit $R_1\to\infty$ at constant n, the asymptotic expansion of the Bessel functions J_ν and Y_ν at large argument gives the eigenfunctions of the unperturbed Liouville operator,

$$\phi_{m,n}(r,\theta) \approx \frac{(\Gamma_{n,m}/D)^{1/4}}{\Delta R\sqrt{R_1\theta_0}} \sin\left(\frac{m\pi r}{\Delta R}+\alpha_n\right)\sin\left(\frac{n\pi\theta}{\theta_0}\right), \tag{20}$$

where the phase α_n ensures the boundary conditions at R_1 and the eigenvalues, $\Gamma_{n,m}=D[m^2\pi^2/(\Delta R)^2]$, are *independent* of n. The matrix elements of the operator $\omega\partial_\theta$ are given by

$$\langle n,m|\omega\partial_\theta|k,l\rangle = \omega\delta_{m,l}\gamma_{nk}, \tag{21}$$

with

$$\gamma_{nk} = \begin{cases} k+n=\text{even} & 0 \\ k+n=\text{odd} & \dfrac{2kn}{n^2-k^2}, \end{cases} \tag{22}$$

where the approximation

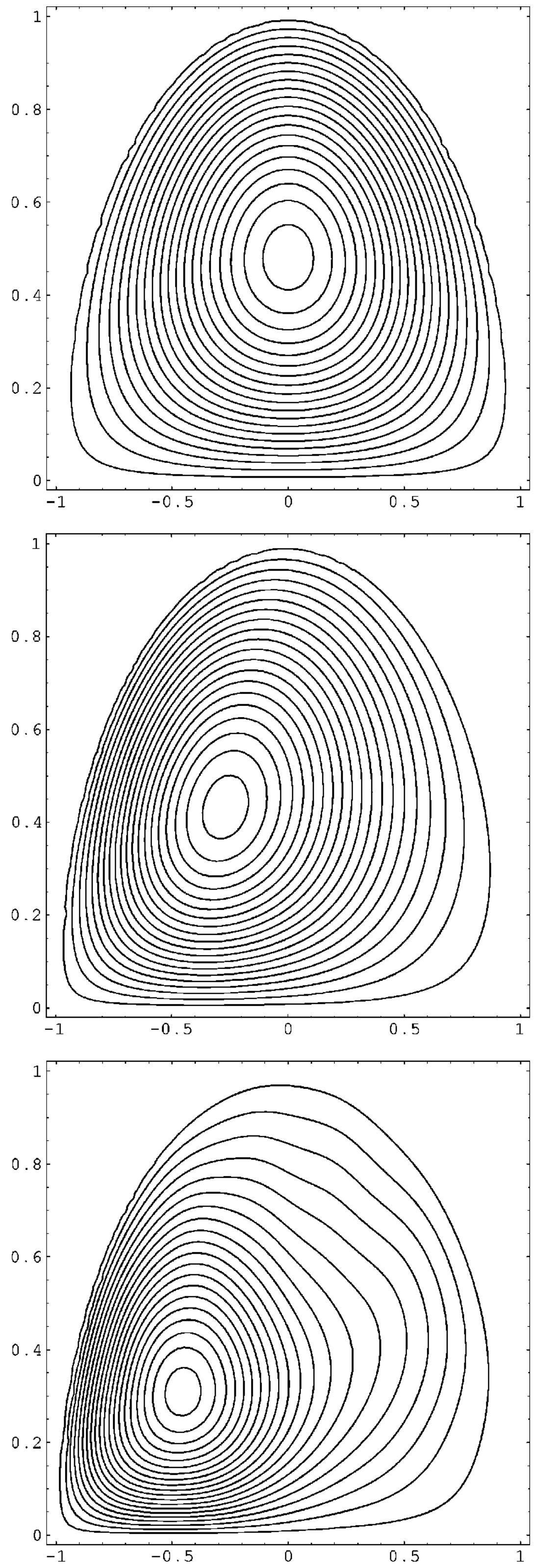

FIG. 2. Contour plot of the bacterial density at $\theta_0 = \pi$. Upper panel, $\omega/D/R^2 = 0$; middle, $\omega/D/R^2 = 10$; and lower panel, $\omega/D/R^2 = 30$.

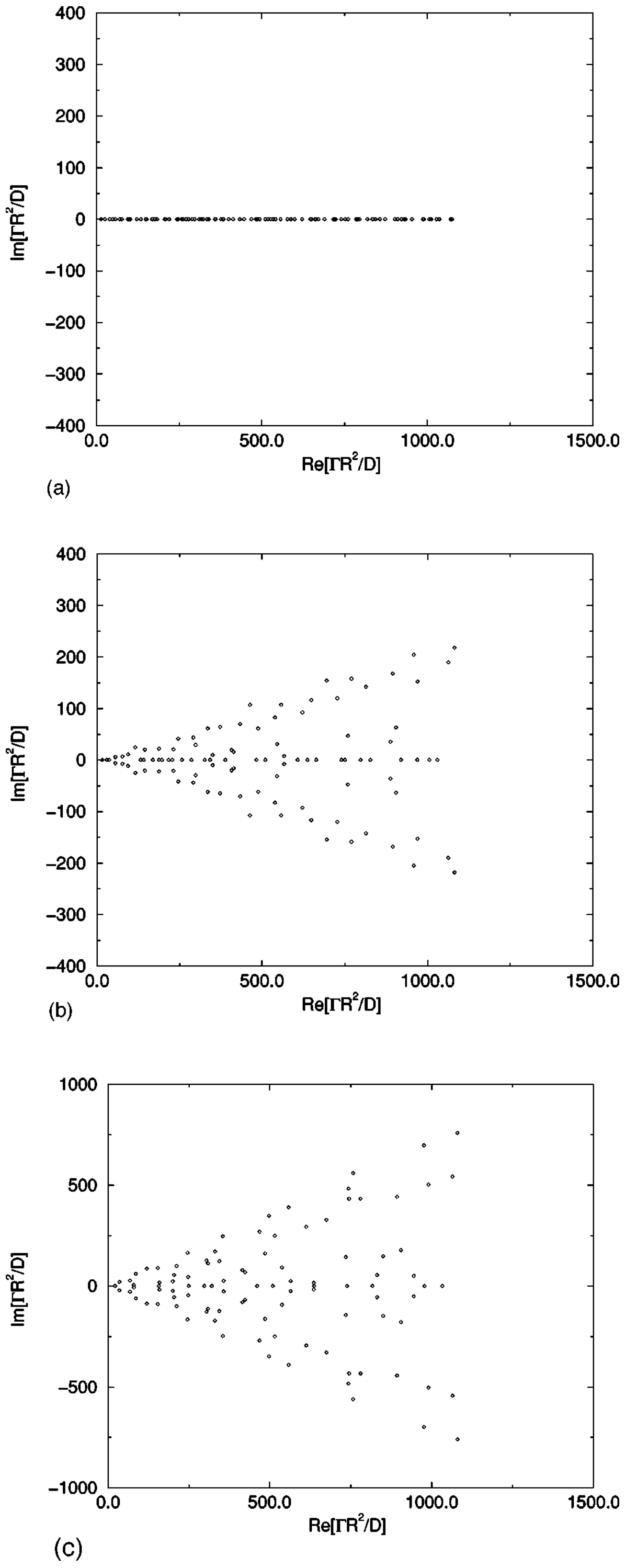

FIG. 3. First 100 spectral points $\{\mathrm{Im}[\Gamma/D/R^2]$ vs $\mathrm{Re}[\Gamma/D/R^2]\}$ at $\theta_0 = \pi$. Upper panel, $\omega/D/R^2 = 0$; middle $\omega/D/R^2 = 10$; and lower panel, $\omega/D/R^2 = 30$.

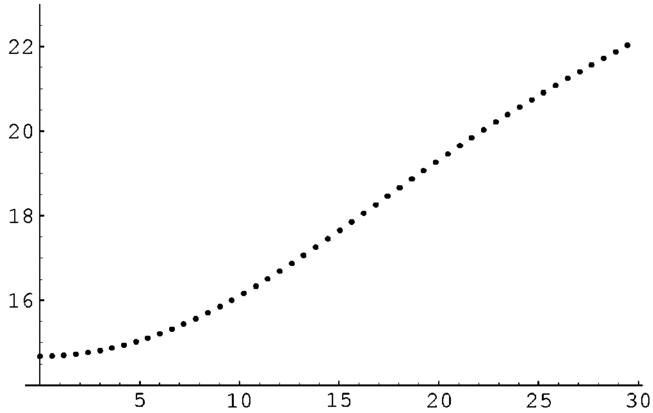

FIG. 4. Highest eigenvalue, $\Gamma_0/D/R^2$, as a function of the angular velocity, $\omega/D/R^2$, for $\theta_0=\pi$. The extinction happens as this eigenvalue is larger than $a/D/R^2$, the growth rate inside the pie.

$$\int_{R_1}^{R_2}\sin\left(\frac{m\pi r}{\Delta R}+\alpha_n\right)\sin\left(\frac{l\pi r}{\Delta R}+\alpha_k\right)\sqrt{r}dr \sim \sqrt{R_1}\int_{R_1}^{R_2}\sin\left(\frac{m\pi r}{\Delta R}+\alpha_n\right)\sin\left(\frac{l\pi r}{\Delta R}+\alpha_k\right)dr \tag{23}$$

for $\Delta R/R_1 \ll 1$ has been used. Accordingly, for any m sector, both the diagonal and the off-diagonal matrix elements are identical with the corresponding one dimensional problem, and the results should be the same.

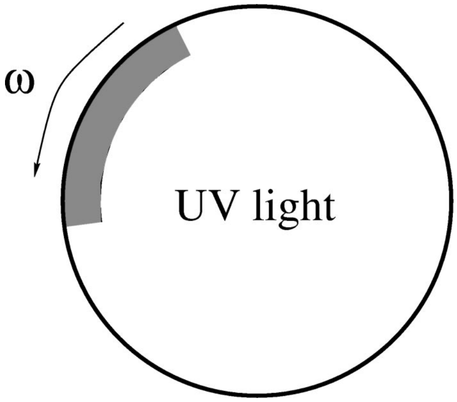

FIG. 5. Narrow shell geometry, where the two-dimensional problem converges to the ‘‘integrable’’ case.

In conclusion, the mathematical problem which corresponds to the experiment [4] has been found to be nonintegrable, and no simple gauge transformation connects the eigenvectors of the static and the dynamic problems. The actual critical velocity and ground state properties have to be studied numerically, and the limit of very narrow wedge angle ($\theta_0 \to 0$) involves diverging numerical loads. The time scales needed for the ground state to dominate the system are larger than the duration of the actual experiment, and this explains the observed inequilibration.

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