Fractal scaling of microbial colonies affects growth

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The growth dynamics of filamentary microbial colonies is investigated. Fractality of the fungal or actinomycetes colonies is shown both theoretically and in numerical experiments to play an important role. The growth observed in real colonies is described by the assumption of time-dependent fractality related to the different ages of various parts of the colony. The theoretical results are compared to a simulation based on branching random walks.

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I. INTRODUCTION

Filamentary micro-organisms, like fungi and actinomycetes, draw much attention because of their widespread appearance. They are to be found everywhere from the soil to our own body [1,2]. Their role as decomposers is important, e.g., in the global carbon cycle. Through their symbiotic connections with plant root systems they take part in the redistribution and transfer of nutrients and minerals [3]. Moreover, their importance is underlined by the fact that a significant portion of enzymes, antibiotics, and vitamins are produced by their cultivation [1,4–6].

Filamentary micro-organisms start their life cycle as a single spore. Under favorable environmental conditions, the budding spore produces a long filament called a *germ tube* [1,2,4,7], which explores the surroundings for available nutrients. To better utilize the available resources the germ tube undergoes branching, producing new filaments called *hyphae*, which themselves also start branching. The hyphae grow at their apex, while nutrients are gained along the total length of the branches [1,2,4,7–11]; thus there is a continuous transportation of materials inside the filaments. In particular, cell wall building materials are transported toward the extending tip [1,2,4,7,10,11]. This process eventually leads to a colony of densely packed hyphae called a *mycelium* [1,2,7]. At the initial stage of growth, when the nutrients are in abundance and the hyphae are not impeding each others growth, the growth of the colony has been measured to be exponential [2,4,7,8,12,13]. Later, as the resources in the center of the colony are exhausted and the hyphae in that region start to overlap, growth is limited to the edge of the colony and vegetative growth in the center decays [2,4,7,8,12,13]. The decaying colony provides the necessary nutrients for *aerial growth* [1,2,7], where aerial branches grow out of the (usually planar) mycelium. At this stage antibiotics are produced to prevent other micro-organisms from utilizing the decaying mycelium (moreover, the eliminated competitors are utilized for the aerial growth) [2]. Finally, the aerial branches start pinching and produce new spores to restart the life cycle [1,2,7].

In this paper the main goal is to model the growth of the whole colony. Recent models have either concentrated on the initial exponentially growing stage of the colony [4,7,9,14–17] or on the later stage when growth in the center has already ceased [4,7,8,18–22]. Although measurements [1,12,13] and simulations [23] show the crossover between these two stages, so far no model has given a quantitative account for the slowing down of the growth. It has been pointed out that the intricate topology of the colony formed by the branching filaments is best described by the concept of *fractality* [24,25]; see also Fig. 1. It has been suggested that fractality could provide a means to characterize different species [26,27]. However, no attempt has been made to incorporate the observed fractal scaling in describing the details of growth, even though the growth of a colony can be simply modeled by a *branching random walk*, which is known to generate fractal patterns with time-dependent fractality [28].

Recent results [29–35] in the fields of chemical or biological activity on fractal sets, however, have provided an appropriate framework to incorporate fractality into the study of growth processes. In these works open chaotic hydrodynamical flows are shown to produce stable filamental fractal patterns of advected chemically or biologically active species. The description of activity on fractals requires a dramatic change to the traditional reaction equations: a nontrivial, singular term appears in the equations [29–31,33]. It has been shown that this term provides a possible solution to problems related both to plankton population dynamics [32,34] and to prebiotic evolution [32,35,36].

In open flows, fractal patterns are generated by an external physical process and the activity occurs on this fractal skeleton. In the case of filamentary micro-organisms, however, the complicated geometry is generated by the growth process itself, governed by the search for and efficient utilization of resources. Another important difference is that while advection in open chaotic flows produces a fractal whose dimension does not depend on time, in the case of fungi and actinomycetes the fractality is *time dependent* [24,25,37]. Furthermore, the mycelium is densest in the center of the colony, and rarest close to the edges. This results in the colony having a higher fractal dimension in its aging center and a lower dimension close to the colony edge. This inhomogeneity suggests that models based on a continuous distribution of biomass [4,7,8,17–20,38–40] have to be re-

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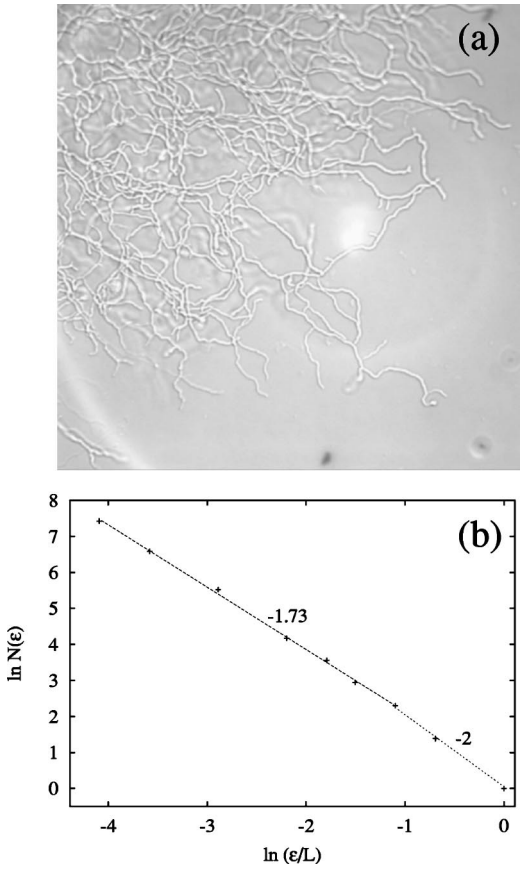

FIG. 1. (a) Part of a *Streptomyces Coelicolor A*3(2) colony. Picture taken in the Arizona Research Lab is courtesy of Alain Goriely and Michael Tabor. (b) Number $N(\varepsilon)$ of boxes of linear size ε covering filaments in picture (a) scales as $N \sim \varepsilon^{-D}$, where $D = 1.73 \pm 0.03$ is the fractal dimension of this part of the colony. The horizontal axis is rescaled by the linear size L of image (a). For large boxes, ε reaches the size of image (a) (right side, with tangent −2).

vised. The assumption that the hyphal surface, where nutrient uptake takes place, is proportional to biomass [38,39] must also be revised due to fractality. In this paper we propose a simple model of nutrient uptake and filament growth, which is designed to incorporate the effect of the fractal distribution of biomass.

In Sec. II a model of colony growth is developed, which takes into account the age-dependent fractality of the colony. In Sec. III the theoretical results are compared with data obtained from numerical simulations. We present our conclusions in Sec. IV.

II. MODEL FOR COLONY GROWTH

Chemical or biological processes occurring along a fractal boundary are associated with significantly enhanced activity as compared to processes occurring along regular boundaries [29–31,33]. In the case of filamentary micro-organisms the activity is nutrient uptake; the main advantage of the intricate and complicated geometry of the colony is the greatly increased surface area of the hyphae, which is where the nutrient resources are gained. In this paper we assume that there is only one resource limiting growth and that all other resources are in abundance. In our model a simple autocatalytic utilization of the limiting resource is assumed; i.e., a certain fixed portion of the consumed nutrients are directly converted to biomass [39].

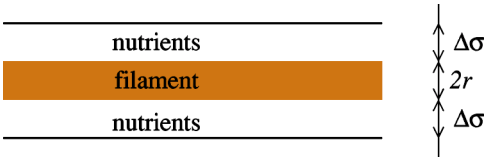

FIG. 2. (Color online) Nutrients are consumed from a narrow stripe of width $\Delta\sigma$ along the hyphae of radius r during time Δt.

For simplicity and for ease of comparison with the result of the simulations described in the next section, we will consider a two-dimensional (2D) colony. Besides the fact that filamentary micro-organism colonies, when grown on a surface (like moist bread, damp soil, or synthetic solid medium), are effectively two dimensional, the same derivation can be applied in three dimensions. We concentrate on a part, A_0, of the colony, like the one in Fig. 1, which is small compared to the total colony size. This colony part possesses a well-defined scaling with (time-dependent) fractal dimension D. Let $\mathcal{L}(t)$ denote the total hyphal length (which is proportional to biomass due to the constant cross-sectional area of the filaments) in the reference area A_0 of the colony at time t after the first branch has grown into it. The filaments within A_0 can utilize the nutrients contained in the growth medium of this region. During a short time Δt, resources in a narrow strip of width $\Delta\sigma$ along the hyphae are assumed to be consumed by the filaments (Fig. 2). This means that during time Δt the total consumed nutrient mass in 2D is

$$\Delta m_n = \mathcal{L} c \Delta\sigma \varrho, \tag{1}$$

where ϱ is the average concentration of the limiting resource which depends on time, decreasing as the nutrients are consumed. The geometrical factor c would be 2 for ideal parallel, straight filaments; however, it deviates from this value to some extent due to the bending of the hyphae, as explained in Refs. [29–31,33].

A portion, $\gamma < 1$, of the consumed nutrients Δm_n are directly converted to biomass, which increases the hyphal length; the rest maintains the metabolism of the already existing filaments. If the average density of the filaments is ϱ_f, then filaments of radius r during time Δt will grow in length by

$$\Delta\mathcal{L} = \frac{\gamma \Delta m_n}{\varrho_f c r} = \gamma \Delta\sigma \frac{\varrho}{\varrho_f} \frac{\mathcal{L}}{r}. \tag{2}$$

We can take the limit $\Delta\sigma \to 0$ and $\Delta t \to 0$, while keeping their ratio constant:

$$v = \lim_{\Delta t \to 0, \Delta\sigma \to 0} \frac{\Delta\sigma}{\Delta t}. \tag{3}$$

This is the rate of nutrient consumption (which can be related, for example, to diffusion through the cell membrane). This implies that

$$\frac{d\mathcal{L}}{dt} = \gamma v \frac{\varrho}{\varrho_f}\frac{\mathcal{L}}{r}. \tag{4}$$

The available nutrient pool is reduced by consumption; its concentration ϱ decreases while the colony becomes increasingly dense. However, it is not only the biomass density that changes during growth; for fractals a better measure is the fractal dimension, which changes with time [25,27,41,42]. It makes sense to assume that the available resource concentration ϱ will depend on the fractal dimension D of the colony. This means that as the colony becomes denser (i.e., D increases as a result of growth) the availability of the resources decreases (as they are consumed). When the grown is on a solid surface and the linear size ℓ_0 of the region of observation A_0 is much larger than the diffusion distance for typical limiting nutrients (like glucose, phosphorus, minerals), we can safely neglect nutrient diffusion into A_0, because it has only a minor effect on the available nutrients [7] (N.B. internal nutrient translocation seems to have a more important effect [39]). The decrease in the available nutrient concentration during time Δt is $-\Delta m_n/(\Delta t \ell_0^2)$. Taking the limit $\Delta t \to 0$ as before, we find

$$\frac{d\varrho(D)}{dt} = -\frac{\mathcal{L} c v \varrho(D)}{\ell_0^2}. \tag{5}$$

As supported by observations [24,26] (see also Fig. 1) and computer simulations [23,26], filaments form a fractal set in A_0 in a certain scaling region $r \leqslant \epsilon \leqslant \ell_0$, bounded by the filament width r from below and by ℓ_0, the linear size of the observation region A_0, from above. The length of the filaments is measured as $\mathcal{L} = \epsilon N(\epsilon)$, where $N(\epsilon)$ is the number of boxes of linear size ϵ covering the mycelium. For a fractal of dimension D, $N(\epsilon) = \mathcal{H}(\epsilon/\ell_0)^{-D}$ [41], where $\mathcal{H}$ is a proportionality constant called the *Hausdorff measure* [43]. Choosing $\epsilon = r$ (the lower bound of the fractal scaling interval), we find

$$\mathcal{L} = \mathcal{H} r^{1-D} \ell_0^D. \tag{6}$$

Taking the derivative of Eq. (6) and inserting it into Eq. (4) leads to[1]

$$\frac{dD}{dt} = \frac{\gamma v \varrho(D)}{r \varrho_f \ln \delta}, \tag{7}$$

where $\delta = \ell_0/r \gg 1$ is the size of the region of observation relative to filament radius. Using Eq. (5) a differential equation can be obtained for $\varrho(D)$ as

$$\frac{d\varrho(D)}{dD} = -\frac{\mathcal{H} c \varrho_f \ln \delta}{\gamma} \delta^{D-2}. \tag{8}$$

This can be solved with the condition that initially there is only a single hypha in A_0, having dimension $D(t=0)=1$, when the nutrient concentration is $\varrho(t=0) = \varrho(D=1) = \varrho_0$, to give

$$\varrho(D) = \varrho_0 + \frac{\mathcal{H} c \varrho_f}{\gamma \delta^2}(\delta - \delta^D). \tag{9}$$

From Eq. (7) the time dependence of the fractal dimension in A_0 is obtained with initial condition $D(0)=1$ as

$$D(t) = \frac{1}{\ln \delta} \ln \left\{ \frac{\mathcal{H} c \varrho_f \delta + \delta^2 \gamma \varrho_0}{\mathcal{H} c \varrho_f + \gamma \varrho_0 \delta \exp\left[-\frac{v}{r}\left(\frac{\mathcal{H} c}{\delta} + \frac{\gamma \varrho_0}{\varrho_f} \right) t \right]} \right\}. \tag{10}$$

As filaments grow into the different regions of the colony at different times, thus initiating growth in those regions, the fractal dimension will be different in each of the various regions, in agreement with observations [25].

Using Eq. (6) again, the total length of the hyphae can be written as

$$\mathcal{L}(t) = \mathcal{H} r \frac{\mathcal{H} c \varrho_f \delta + \gamma \varrho_0 \delta^2}{\mathcal{H} c \varrho_f + \gamma \varrho_0 \delta \exp\left[-\frac{v}{r}\left(\frac{\mathcal{H} c}{\delta} + \frac{\gamma \varrho_0}{\varrho_f} \right) t \right]}. \tag{11}$$

Being closely related to the total biomass, it is easy to measure $\mathcal{L}(t)$ in either experiments or simulations.

Formula (11) can be rewritten in a dimensionless form. We introduce $R = \gamma \varrho_0/\varrho_f$, the ratio of utilizable initial resource concentration to the density of the filaments, and $H = \mathcal{H} c/\delta = \mathcal{H} c r/\ell_0$, which is proportional to the ratio of the filament diameter and the linear size ℓ_0 of the region of observation. Then the dimensionless hyphal length $L = \mathcal{L}/r\mathcal{H}\delta = \mathcal{L}/\mathcal{H}\ell_0$ as a function of the dimensionless time $\tau = vt/r$ is

$$L(\tau) = \frac{H + R}{H + R \exp[-(H+R)\tau]}. \tag{12}$$

Since $H \sim 1/\delta \ll 1$, we have that $R \gg H$. This means that, besides the rate of nutrient uptake v, it is the ratio of the utilizable nutrient concentration to the filament density that has the major role in determining the biomass growth:

$$L(\tau) = \frac{R}{H + Re^{-R\tau}}. \tag{13}$$

For small τ, the second term in the denominator is much larger than the first term. This means that $L(\tau) \approx e^{R\tau}$—that is, $\mathcal{L}(t) \approx \mathcal{H}\ell_0 \exp(\gamma t v \varrho_0/r\varrho_f)$—which implies an *initial exponential growth* as observed for filamentary colonies [2,8,12,13]. Later, as τ increases, the exponential vanishes in the denominator, leading to $L(\tau) \approx R/H$—that is, $\mathcal{L}(t) \approx \gamma r \delta^2 \varrho_0/c\varrho_f$; i.e., there is *no growth after a long enough time*. As the total hyphal length to cover A_0 would be $\mathcal{L} = \ell_0^2/(cr) = r\delta^2/c$, this stage corresponds to an almost filled

[1]Here we have assumed that $\mathcal{H}$ does not depend on time. A more precise treatment would show that an additional term containing $-\dot{\mathcal{H}}/(\mathcal{H} \ln \delta)$ would appear in the right-hand side of Eq. (7). This, through $\dot{\mathcal{H}} < 0$, would increase the growth of D, that is, of the biomass, especially in the initial stage when $|\dot{\mathcal{H}}|$ is expected to be larger.

region of observation ($\gamma\varrho_0/\varrho_f<1$). At this late stage the remaining available resource concentration is $\varrho=0$. The fractal dimension is expected to saturate around $D=2+\ln(\gamma\varrho_0/\mathcal{H}c\varrho_f)/\ln(\delta)$, for $\delta\gg1$. This value for D is expected to be somewhat below 2, which would be the fractal dimension of a plane-filling mycelium. Finally the growth in the region of observation ceases due to a lack of nutrients [2,4,7,8,12,13]. Altogether, the graph of Eq. (13) shows good qualitative agreement with observations of biomass growth in experiments studying fungi (see, for example, Fig. 2 of [6], Fig. 7 of [8], Fig. 1 of [13], Fig. 5 of [21], and Fig. 9 of [27]).

The advantage of our model is that the parameters are directly measurable in experiments. The initial resource concentration ϱ_0 is an environmental variable, easily tunable in experiments. The average internal density ϱ_f of the hyphae, the portion γ of resources spent on growth, the rate v of nutrient consumption, and the radius r of the hyphae are specific to species and can be measured. The geometrical constants $\mathcal{H}$ and c are determined by the shape of the colony, while δ depends on the size of the chosen region of observation. This means that the validity of Eq. (11) can be readily checked in an experiment. In the next section the validity of Eq. (13) is checked using a simple numerical model of filamentary colony growth based on a branching self-avoiding random walk.

III. SIMULATION RESULTS

To check the validity of the model developed in the previous section computer-simulated filamentary colonies were investigated. The simulation of a colony starts from a single point at the origin; this models the initiation of growth from a single spore. Growth occurs in discrete time steps. The exact position of the tip of each growing filament is stored, along with its position at all previous time steps. A segment of filament is drawn from each of these points back to the position of the same tip in the preceding time step. The region of observation is covered by a grid. A value is stored for each grid cell that is equal to the number of filament segments in that cell. This grid then characterizes the density of the mycelium.

One step of the growth process consists of three stages: bending, growth, and branching. During the *bending stage*, all tips choose a new growth direction from 18 different directions, an angle $2\pi/18$ apart. First, a probability is assigned to each of the 18 directions. The default probability is highest in the same direction as the growth direction of the tip during the previous growth step and decreases linearly so as to reach zero in the opposite direction. This default probability is decreased linearly with the mycelial density around the tip in each directions. The mycelial density is taken from the values stored in the grid cells covering A_0.

The dependence of the probabilities on the mycelial density models that the tip will try to avoid regions of high hyphal content where the nutrients have been depleted [14]. One of the 18 directions is chosen randomly according to their corrected probabilities. If all directions have zero probability, then the tip does not grow any longer.

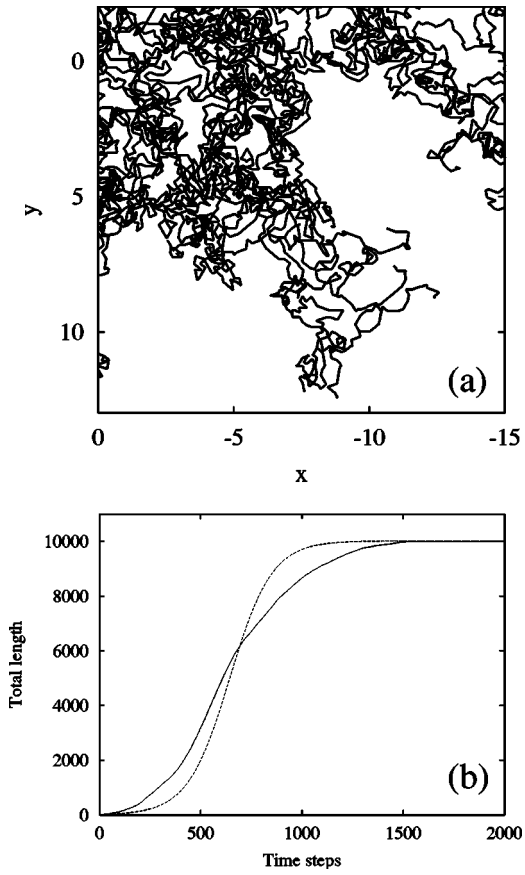

FIG. 3. (a) Part of the simulated colony. Applied parameters are in the text. (b) Comparison of the measured total hyphal length (solid line) in the course of time with that obtained from Eq. (11) (dashed line). Units used for length are converted to the dimensionless units of the simulation; thus total length is measured and computed inside region A_0 with hyphal diameter 0.04 (see main text).

The *growth stage* follows after a new growth direction has been chosen for each of the tips. Each tip which has not ceased to grow is moved in its chosen direction a distance that is selected randomly, with uniform probability, from an interval. This gives new tip positions, and the mycelial content stored for each grid cell is also updated. Finally, in the *branching stage*, there is a small chance that any nonceased filaments branch, forming a new growing tip at any of the previous tip locations.

Altogether, this is a simple, but realistic simulation of filamentary colonies, based on an implementation of branching random walks where intersections of trajectories are restricted by density. If the maximum density is 1—that is, the probability of growth falls to zero in directions containing a single hypha—this is a self-avoiding, branching random walk. This model can be considered a simplified version of the model in Ref. [23] and produces colonies qualitatively similar to realistic fungal or actinomycetes colonies; compare Figs. 1 and 3(a).

The measured total filament length as a function of time is shown in Fig. 3(b), together with the prediction obtained from Eq. (11). The parameters in Eq. (11) can be approximated from the computer model parameters. In the computational model, the grid size defined on the region of obser-

vation $A_0=[-20,20]\times[-20,20]$ ($\ell_0=40$) was 1000×1000. It means that the approximate diameter of the hyphae was $2r\approx0.04$ (linear size of one grid cell), while $\delta\approx1000$. The length of the growth steps was chosen randomly from the interval [0.04, 0.4] (one to ten grid cells). The dimensionless combination of the parameters $R=\gamma\varrho_0/\varrho_f$ appearing in Eq. (13) was taken to be unity; i.e., in the computer model the resources are turned directly into biomass. In reality this term is below 1, but in this simple model the consumed resources are used only for growth; the effects of processes such as the upkeep of existing nutrients, internal translocation of nutrients, etc., are not considered. The geometrical constants are usually of the order of 1; for a simple choice we take $\mathcal{H}=1$ and $c=2$, leading to $H=0.002$. Hence the only parameter remaining to be fitted is v/r, the dimensionless time unit, which was identified as $v/r=0.009\,62\pm0.000\,03$ (with one time unit being one simulation time step). This means that during one growth time step Δt, the nutrients are utilized to a distance of $\Delta\sigma\approx r/100$ from the hyphae. In reality, this parameter should also be related to the transport rate through the cell membrane and to the diffusion of resources in the medium that transports the available resources close to the hyphae, but these mechanisms are not included in the computational model. Despite its simplicity, Eq. (11) approximates well the computational results with the estimated parameter values. Allowing for the time dependence of $\mathcal{H}$ (see footnote 1) in the theoretical description would increase the activity (and biomass) at the initial stage of growth. This is expected to give an even better correspondence between the numerical and the theoretical curves of Fig. 3(b), where the theoretical prediction is below the measured biomass. In the late stages, the measured biomass is smaller than that predicted by Eq. (11), because the numerical simulation neglected the effect that filaments, in reality, may return to the examined region after having previously left it. This causes the break in the measured curve around the 700th time step. A more elaborated numerical experiment, which follows more closely the growth of real colonies, would be expected to follow the prediction given by Eq. (11).

IV. CONCLUSIONS AND DISCUSSION

The main goal of the model developed in this paper is the incorporation of time-dependent fractality into the study of colony growth. Without any further assumptions about the details of the activity (growth and nutrient uptake) the model is able to describe the initial exponential and the later saturating stages of growth. To achieve this no artificial crossover terms or saturating activity terms were necessary, like those used in Refs. [4,13,17,19,20,22,38,39]. Also, contrary to Refs. [18,21,22], it was not assumed that growth is restricted to the perimeter of the colony. The main ingredients of the model are the time-dependent fractality, which is connected to resource consumption, and that growth is restricted to the hyphal tips, while resources are taken up all along the filaments.

In our model, the biological activity is described, with only a few parameters, by the speed v of resource consumption and the rate γ of resource utilization for growth. In order to model different types of colonies and various pattern formations observed in fungal colonies [38–40]. It may be necessary to extend this model in order to describe different types of colonies and the various pattern formations observed in fungal colonies [20,38–40,42]. Other variables (like density of growing tips, mass of inactive mycelium, internal resource translocation, external resource diffusion, effects of more than one resource, etc.) can also be incorporated in the model.

Although the derivation of Eq. (11) was based on the assumption of a two-dimensional colony, it is quite straightforward to extend it to colonies in three dimensions. In dimensionless units, the length of the filaments as a function of time is described by the same expression (13) as in the 2D case, with the exception that the constants R and H are different: $R=\gamma c\varrho_0/\varrho_f$, $H=\mathcal{H}c\pi/\delta^2=\mathcal{H}c\pi r^2/\ell_0^2$. The qualitative features of the equations thus remain the same, and the important ideas (to incorporate time-dependent fractality and consumption of nutrients) and findings (saturation of growth after exponential extension) remain valid.

The results were derived for a part A_0 of the colony; Eq. (11) gives the time dependence of the biomass in this region of observation. When growth reaches the edges of this region, the total biomass will consist of the hyphal content in both the initial and its neighboring regions. However, growth in the neighboring regions will be retarded as compared with that in the initial region. To obtain the total hyphal length of the colony it is necessary to sum up Eq. (11) over the regions, but using a *different inoculation time* for each region.

Most previous growth models started from the assumption that biomass is evenly distributed, thus neglecting totally the microscopic distribution of materials [4,7,8,17–20,38–40]. This paper shows how to incorporate the microscale details (fractality) into a macroscopic description. The effect of this alone provides realistic growth profiles for the colonies.

The model introduced in this paper is also relevant to the study of active processes in flows. Activity in fluids can occur along filamental fractals formed by the stretching and folding action of the flow. In *open* flows, this produces fractal filaments of stationary fractal dimension [44]. However, there is numerical evidence [45] that, for a transient time, there is a time dependence in the fractality of the advected ingredients. It is in this situation that our model may be applicable.

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