

An (almost) solvable model for bacterial pattern formation

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Abstract

We present a simple model for the description of ring-like concentric structures in bacterial colonies. We model the differences between *Bacillus subtilis* and *Proteus mirabilis* colonies by using a different dependence of the duration of the consolidation phase on the concentration of agar. We compare our results to experimental data from these two bacterial species colonies and obtain a good agreement. Based on this analysis, we formulate a hypothesis on the connection of the diffusion constant that appears in the model to the experimental agar concentration.

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1. Introduction

The study of pattern formation in bacterial colonies is of particular interest both from the biological and physical points of view (for a review see [15]). Since patterns are ubiquitous in biological systems, the study of very simple biological objects, like colonies of bacteria, provides an excellent starting point in our attempt to elucidate the complicated mechanisms which operate in biological pattern formation. For the physicist, these systems are equally interesting since they present a very rich behaviour, as far as patterns are concerned, while the number of control parameters stays manageable. In many cases, experiments involving bacterial colonies can be conducted like a physics experiment, where one has to ensure just the proper physical conditions in order to obtain a certain behaviour. It is thus quite natural that a very extensive literature exists on the matter (for reviews see [2,17,21,24]). In this paper, we shall focus on two kinds of bacteria which, under certain conditions, form concentric ring-like colonies: *Proteus mirabilis* and *Bacillus subtilis*. In the case of *P. mirabilis*, the ring-like patterns are the standard behaviour over a large range of parameters [19]. By contrast, for *B. subtilis* these patterns appear only for special conditions of nutrient (usually peptone)

abundance and substrate density (which is controlled by the agar concentration of the medium) [9,20,25]. As a matter of fact, in the case of *B. subtilis* colonies, the variety of possible patterns is impressive. In a nutrient-rich medium the observed patterns evolve with diminishing hardness from a very compact colony with a fractal-like border to concentric rings and to a disk-like, homogeneously spread colony. In a nutrient-poor medium, the colony grows branches which become more and more dense as the agar concentration diminishes.

The modelling of pattern formation in bacterial colonies has been the object of numerous papers. Most of them are based on coupled reaction–diffusion-like equations [11] with various assumptions, like for instance, different populations [12], chemotaxis [3,12] or nonlinear diffusion of bacteria [18]. Different approaches do also exist involving cellular automata [3] or hydrodynamics-based models [14]. Only one of these older approaches [13] has succeeded in reproducing concentric-ring colonies.

Recently, models involving more microscopic aspects of swarming have appeared and manage to successfully reproduce ring patterns [1,6,8,16]. Mimura's model [16] assumes the existence of two types of bacterial cells, active and inactive. Active cells become inactive when nutrient density becomes poor or cell density becomes low. Other models [1,6,8] are based on kinetic equations which describe the transition active–inactive (differentiation) as a function of bacterial

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density, and the spatial evolution of active cells. These models also take into account the finite lifetime of active cells (swarmers) and manage to reproduce many experimental results for *P. mirabilis*. However, they are more complicated than the reaction–diffusion models, and involve a lot of parameters, which are sometimes difficult to estimate from experiments.

Moreover, all these models concentrate on one bacterial species, and none of them describe both *B. subtilis* and *P. mirabilis*; nor do they give any explanation for differences: it is not clear why *P. mirabilis* form ring-like patterns over a large range of parameters, whereas *B. subtilis* form these patterns over a very narrow range (in a nutrient-rich medium). We believe that this difference should be easy to reproduce in a model, just by a minimal change of parameters. The present paper has been conceived as a challenge: how simple can a model be and still reproduce the ring-like pattern as well as the differences in the morphological diagrams of these two bacterial species in a nutrient-rich medium?

2. The model

Before proceeding to the proposal of the model, let us summarise a few points which are essential for its construction. Two kinds of cells seem to be present in both *P. mirabilis* and *B. subtilis* colonies: active cells, elongated and hyperflagellated, and less motile cells, shorter and oligoflagellated [5,16,27]. The growth of a bacterial colony proceeds typically in two phases. During the phase known as “migration” or “swarming”, the colony expands rapidly due to the more motile cells. (In the case of a very hard medium, this phase is greatly inhibited and the colony expands essentially by division of the cells located at the border.) In the phase known as “consolidation” or “proliferation”, the outwards migration stops and the number of cells increases rapidly. The two phases alternate with clockwork regularity. A possible explanation of this two-phase mechanism may be sought in the optimal use of the nutrients in order to maximise the biomass of the colony. Detailed experiments have shown that nutrient diffusion does not play an important role in the process. Also, the characteristic migration and consolidation times do not depend crucially on the nutrient concentration [23,26]. On the other hand the agar concentration, which conditions the hardness of the medium, does play an important role: migration time decreases and consolidation time increases with increasing hardness. As a result, the width of the concentric rings (which is roughly constant over the colony) decreases strongly with increasing hardness [23,26].

Based on these data, we proceed now to formulate our model. Since we are interested essentially in the formation of concentric rings (and not of branch-like structures), we do not need to consider a full 2-dimensional model, but can assume circular symmetry. Moreover, even the curvature effect does not alter the results significantly (as we have explicitly checked in some test cases), and thus we could even have neglected it. Still, including the curvature term does not overburden the model, and in any case we have a 1-dimensional problem describing the bacteria (and nutrient) density along the radius

of the colony. We shall clearly distinguish the two phases, the migration phase and the consolidation phase, each of which has specific dynamics and a characteristic duration (respectively T_m and T_c), with $T_m + T_c$ taken constant.

During the migration phase, we assume that the bacteria move following a simple diffusion law and at the same time they consume nutrients at a rate proportional to their number. We have thus the equations:

$$\frac{\partial b}{\partial t} = D \left(\frac{\partial^2 b}{\partial r^2} + \frac{2}{r} \frac{\partial b}{\partial r} \right) \quad (1a)$$

$$\frac{\partial n}{\partial t} = -\kappa b \quad (\text{for } n > 0) \quad (1b)$$

where b and n are the bacteria and nutrient concentrations respectively. The constraint $n > 0$ means that Eq. (1b) (and similarly (2b), below) holds only if the nutrient concentration is non-zero. Once n reaches zero, there is no further evolution of its value. During the consolidation phase there is no spatial evolution, and the number of bacteria grows locally due also to the existence of nutrient. We have now the equations:

$$\frac{\partial b}{\partial t} = \alpha n b \quad (2a)$$

$$\frac{\partial n}{\partial t} = -\lambda b \quad (\text{for } n > 0). \quad (2b)$$

Rescaling n and the two characteristic times, T_m and T_c , of migration and consolidation, we can put the constants α , κ and λ as 1. We could also have scaled out the diffusion constant D , which would lead to redefining the size of the box we are working in, but we prefer to keep it as such, since it will make the analysis simpler. (We expect D to be related to the hardness of the medium and thus to the agar concentration, with D diminishing when the concentration increases, but the precise relation is not available. We shall return to this point in the following sections.) The two characteristic times, T_m and T_c , are given, with the constraint $T_m + T_c$ constant, as well as the box radius L . At $t = 0$, we introduce initial conditions $b(r, 0)$, in the form of a lump at the centre of the box, and $n(r, 0)$ which is taken as constant all over the box.

System (1) and (2) can “almost” be solved explicitly. The diffusion equation can be reduced to a simple quadrature using the Green’s function of (1a), $G(r, r', t) = (4\pi Dt)^{-3/2} e^{-\frac{(r-r')^2}{4Dt}}$. However, we have found it simpler and faster to use an explicit algorithm (sacrificing the possibility of a fully analytic solution). Once $b(r, t)$ is obtained, we can compute the corresponding change in the nutrient by $\Delta n = -\int_{t_0}^{t_0+\Delta t} b dt$. The consolidation equation (2) can be solved in an even simpler way. Combining the two equations, we obtain $\frac{\partial b}{\partial t} + n \frac{\partial n}{\partial t} = 0$, and integrating it we find

$$b + \frac{1}{2} n^2 = \frac{1}{2} c^2 \quad (3)$$

where c is a constant, $c = \sqrt{2b_0 + n_0^2}$, which depends, of course, on the position in space. Using (1b) and (3) we can integrate for n . We find for its increment ($\Delta n = n - n_0$), the

expression

$$\frac{\Delta n}{c - n_0} = 1 - \frac{2c}{(c - n_0) + (c + n_0)e^{-c\Delta t}} \quad (4)$$

and consequently, from (3),

$$\Delta b = -\Delta n \left(n_0 + \frac{\Delta n}{2} \right). \quad (5)$$

Thus, the integration of the equations of migration–consolidation is reduced to two quadratures in the former phase with explicit solutions in the latter one.

Two quantities will also appear in our analysis: biomass and density. The biomass B is defined as the total number of bacteria in the colony. At time t , it is computed as:

$$B = \int_0^t b 2\pi r dr. \quad (6)$$

The density is defined as the biomass per colonized surface area, $d = B/S$.

Since we have decided to solve the diffusion equation by using a numerical algorithm rather than an analytic quadrature using the Green's functions, we must decide on the precise algorithm and the space–time discretisation. The integration routine used is an implicit scheme described in [22]. We have taken $\Delta x = 0.1$ mm $\Delta t = 0.05$ h = 3 min. The box radius for the integration was $L = 150$ mm, which proved adequate in every case, even for large diffusion parameters. The latter was varied over several orders of magnitude from 2×10^{-5} to 2×10^{-2} mm² h⁻¹. The initial “seed” bacterial colony was assumed to have constant concentration $b_0 = 1$ mm⁻² in a circle of radius $r_0 = 2$ mm. The nutrient concentration was taken constant throughout the box, and equal to $n_0 = 4$ h⁻¹/α.

The total time of migration + consolidation was taken as constant and equal to $T_M + T_C = 10$ h. In the case of *P. mirabilis*, this time was equally split between the two processes i.e. $T_M = T_C = 5$ h. For the *B. subtilis* case, the ratio of the two times was varied as a function of the diffusion constant (following a logarithmic dependence). Thus starting from $T_C = 9.5$ h for $D = 2 \times 10^{-5}$ mm² h⁻¹, we arrived at $T_C = 1$ h for $D = 2 \times 10^{-2}$ mm² h⁻¹.

3. Results

In Fig. 1 below, we give the density profile of the bacteria along the radius after 5 migration plus consolidation cycles for *P. mirabilis* (left, Fig. 1a, b and c) and *B. subtilis* (right, Fig. 1d, e and f) respectively. In Fig. 1d, we remark that when the diffusion parameter is very small, the *B. subtilis* colony expands very little and has a compact aspect with no ring structure. As the diffusion parameter grows (and the migration times with it), Fig. 1e, the colony expands periodically going through migration–consolidation phases, leading to concentric ring formation. However when the diffusion parameter grows further (Fig. 1f), the colony spreads out without ring formation and without substantial growth, since the consolidation times are now rather small. For the *P. mirabilis* colonies (Fig. 1a, b, c), since migration and

consolidation times are balanced, ring formation is present in every case. Simply, when the diffusion constant D is small, the colony does not spread much and the bacterial concentration maxima are close together, with the opposite being true for large D .

Having obtained the concentration profiles of the bacterial colonies, it is interesting to extract characteristic quantities which can be compared to well-established experimental findings. The first quantity we present in Fig. 2 is the dependence of the radius of the colony on time for both *P. mirabilis* (Fig. 2a) and *B. subtilis* (Fig. 2b) for various values of the diffusion constant. The radii given in Fig. 2 were recorded at the end of each full migration + consolidation cycle. It is interesting to note that the experimental results give a similar evolution, with a linear growth with a sharp increase in slope, after a slow-growing first phase (lag-time), the slope depending strongly on the agar concentration [23]. Since the growth in our model begins with a consolidation phase, a lag-time is present before the large growth phase. By the construction of the model, both for *P. mirabilis* and *B. subtilis*, the number of terraces (that we define as the latest formed maximum of the bacterial profile) formed in a given total time do not depend on the agar concentration, as in experiments with *P. mirabilis* [23] (cf. Fig. 3). The duration of each step is also constant as a function of the agar concentration, since it reflects the time cycle $T_M + T_C$.

As can be assessed from Fig. 1, the distance between two successive maxima is roughly constant over the concentration profile for a given value of the diffusion constant, which allows us to define a period for the ring-like pattern. For *P. mirabilis*, this period is defined over the whole range of the diffusion constant, whereas for *B. subtilis* the period is not defined for the two extreme values of the diffusion constant because of the absence of oscillations. Fig. 4 represent the variation of the logarithm of the period p with the logarithm of the diffusion constant D , for both *P. mirabilis* (Fig. 4a) and *B. subtilis* (Fig. 4b). In the latter case, only the values of D for which we obtain rings are considered, of course. In Fig. 4, the values of the ordinate have been normalized to the radius of the original spot r_0 , whereas the abscissa values have been normalized to the smallest value of D (which is $D_0 = 2 \times 10^{-5}$ mm² h⁻¹). The continuous line corresponds to the best fit, which is linear in both cases. For *P. mirabilis* (Fig. 4a), the equation of the line is: $\log(p/r_0) = a \log(D/D_0) + b$ with $a = 0.47$ and $b = -0.27$ and for *B. subtilis*, (Fig. 4b), we find $a = 0.43$ and $b = -0.24$.

At this point, it would be interesting to try to deduce the possible relation of the effective diffusion constant D to the agar concentration C on the basis of the observed periods of concentration profiles for *P. mirabilis*. Analysing the results of [23], we present in Fig. 5 the dependence of the logarithm of the period of a *P. mirabilis* colony (normalized to the radius of the original spot) on the logarithm of the agar concentration C (normalized to the smallest value of the concentration of agar, which is $C_0 = 2\%$). The equation of the best fit, which is linear, is: $\log(p/r_0) = a \log(C/C_0) + b$ with $a = -3.0$ and $b = 0.45$. From the values obtained, we can deduce that the relation between the diffusion constant and agar concentration

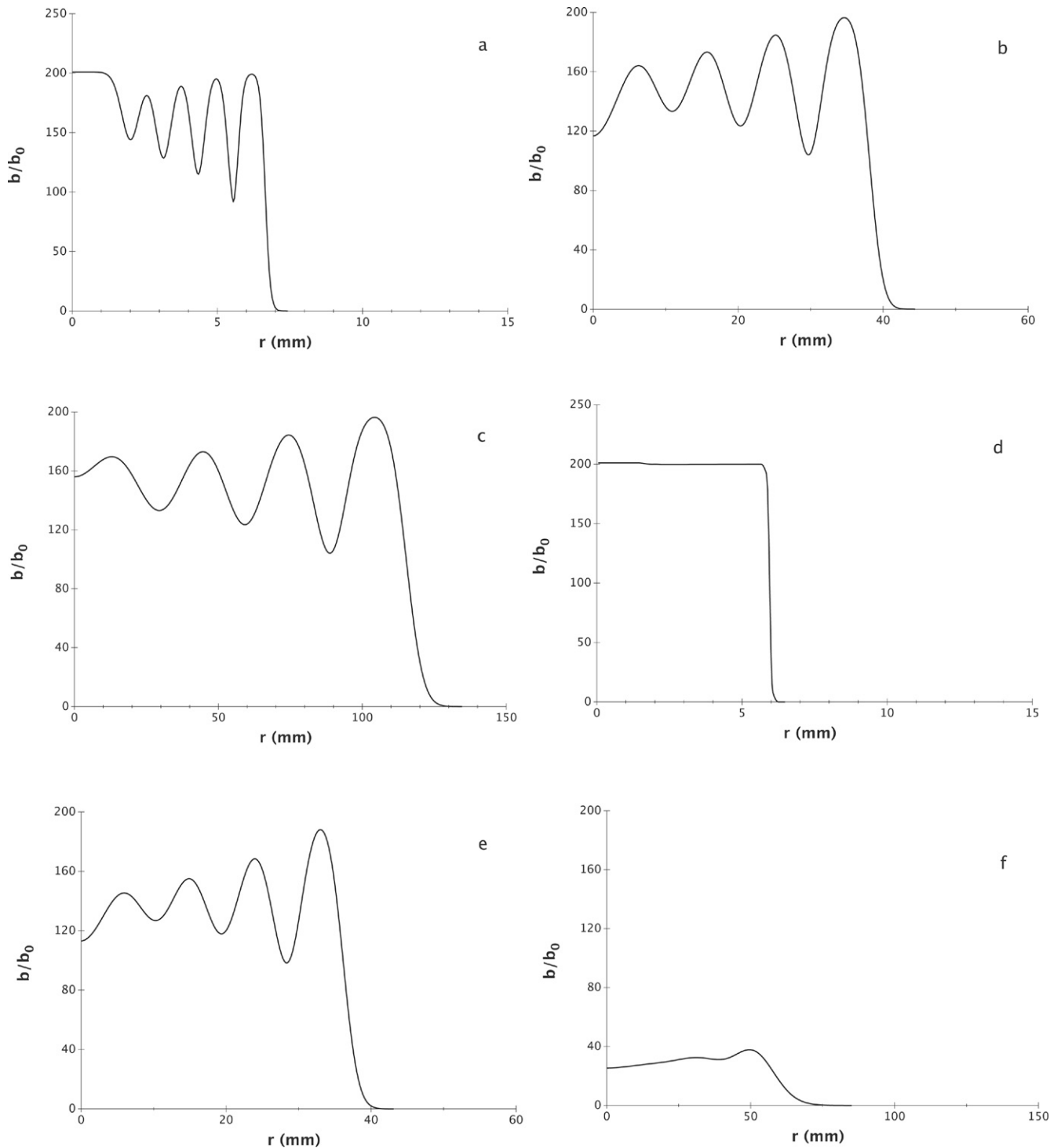


Fig. 1. Concentration profile (obtained from our simulations) of *P. mirabilis* (a, b, and c) and *B. subtilis* (d, e, and f) colonies as a function of r , distance to the centre, for: $D = 2 \times 10^{-5} \text{ mm}^2 \text{ h}^{-1}$ (a and d), $D = 2 \times 10^{-3} \text{ mm}^2 \text{ h}^{-1}$ (b and e), $D = 2 \times 10^{-2} \text{ mm}^2 \text{ h}^{-1}$ (c and f). Notice that, for obvious reasons, the scale is not the same for all the figures.

could be of the form $D \sim 1/C^\nu$, where ν is close to 6. Clearly, this is a result to be taken with a grain of salt since no theory exists allowing us to construct D from a concentration C . For *B. subtilis*, the range of agar concentration for which concentric rings exist (between 0.65% to 0.68%) is too narrow for us to expect to obtain a reliable relation between the period and the agar concentration.

Another question that can be naturally asked concerns the effect of nutrient concentration on the colony's formation. In Fig. 6, we present our results for the colony radius as well as the biomass on the initial nutrient concentration, after a 50 h evolution. We remark that while the total biomass grows strongly with the nutrient concentration, the radius is practically constant, in agreement with experimental findings [23].

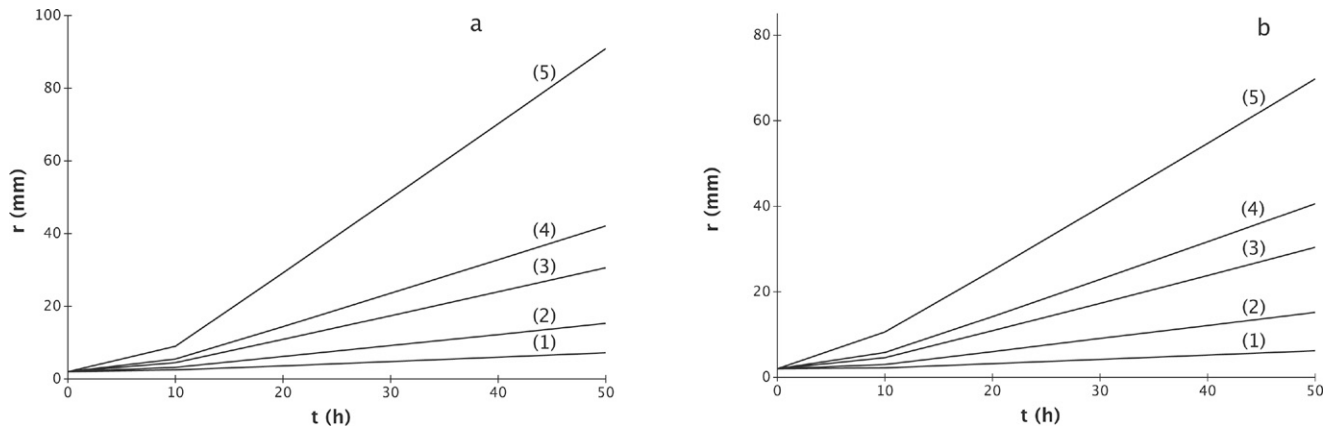


Fig. 2. Radius of *P. mirabilis* (a) and *B. subtilis* (b) colonies as a function of time (obtained from our simulations). (1): $D = 2 \times 10^{-5} \text{ mm}^2 \text{ h}^{-1}$, (2): $D = 2 \times 10^{-4} \text{ mm}^2 \text{ h}^{-1}$, (3): $D = 10^{-3} \text{ mm}^2 \text{ h}^{-1}$, (4): $D = 2 \times 10^{-3} \text{ mm}^2 \text{ h}^{-1}$, (5): $D = 10^{-2} \text{ mm}^2 \text{ h}^{-1}$.

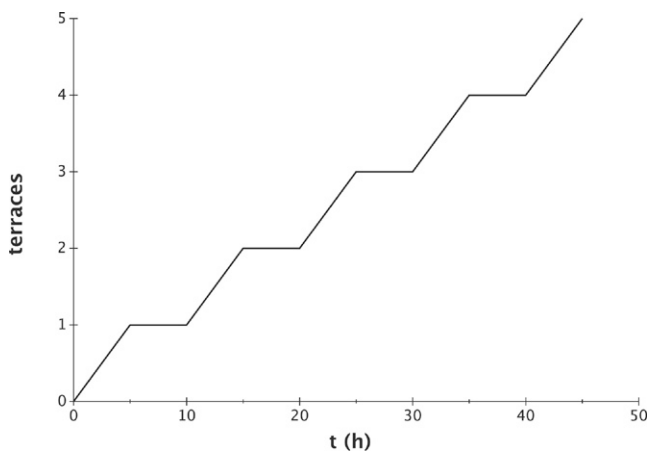


Fig. 3. Terracing of *P. mirabilis* and *B. subtilis* colonies (for diffusion constant values corresponding to oscillations), as a function of time (obtained from our simulations).

Finally in Fig. 7a and b, we give the dependence of the mean colony density on the expansion velocity of the colony (which can be assessed from the slope of Fig. 2a and b) for *B. subtilis* and *P. mirabilis* respectively. We notice a hyperbolic dependence in both cases, which is in agreement with experimental findings [23].

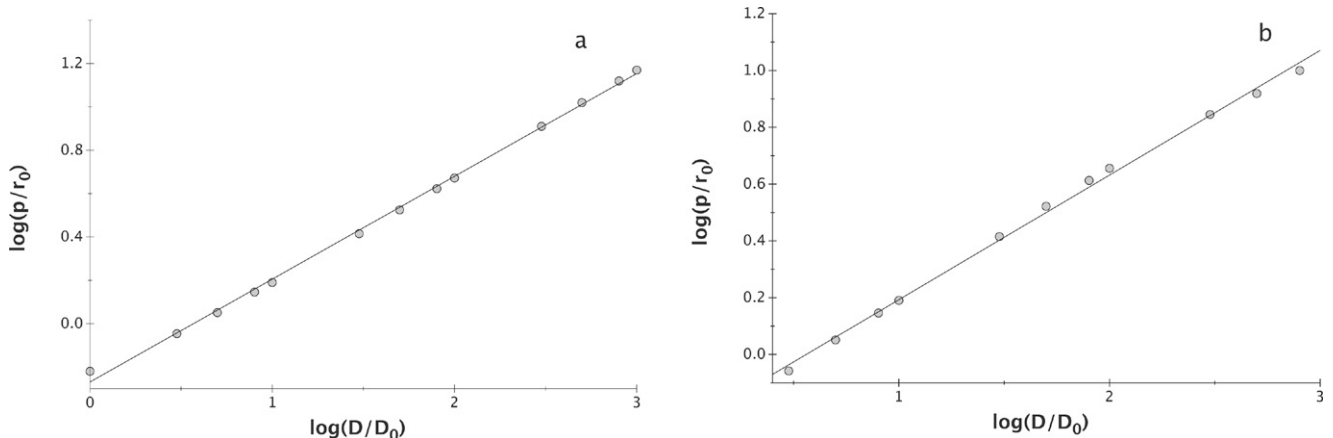


Fig. 4. Period of the rings of *P. mirabilis* (a) and *B. subtilis* (b) colonies as a function of the diffusion constant in a log–log graph (obtained from our simulations).

4. Discussion

In this article, we presented a very simple model for the description and the comparison of the concentric ring patterns observed in two bacterial species colonies, *P. mirabilis* and *B. subtilis*. To our knowledge, it is the first model that compares both types of bacterial species colonies and explains the differences in their morphological diagrams in the case of a rich-nutrient medium. We are convinced that the same principles govern the existence of the same pattern in different bacterial species, and the differences between them should lie in slight changes of parameters.

Our model is based on realistic biological hypotheses. The first one is the definition of two phases of growth: the consolidation phase, where bacteria only reproduce without diffusion, and the migration phase, where the bacteria only diffuse but do not reproduce. These phases have specific durations, T_C and T_M respectively, that can vary with the agar concentration. However the total time cycle $T_C + T_M$ is taken as constant for both *B. subtilis* and *P. mirabilis*, in agreement with experiments [23,26] (cf. Figs. 1 and 3).

Our main assumption is that it is possible to model the differences between *B. subtilis* and *P. mirabilis* by using a different dependence of the duration of the consolidation phase (and therefore of migration phase) on the concentration of agar.

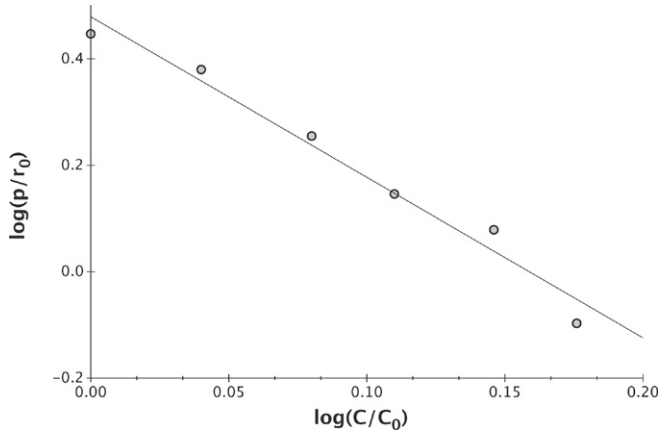


Fig. 5. Experimental period of the rings of *P. mirabilis* colonies as a function of the concentration of agar in a log–log graph.

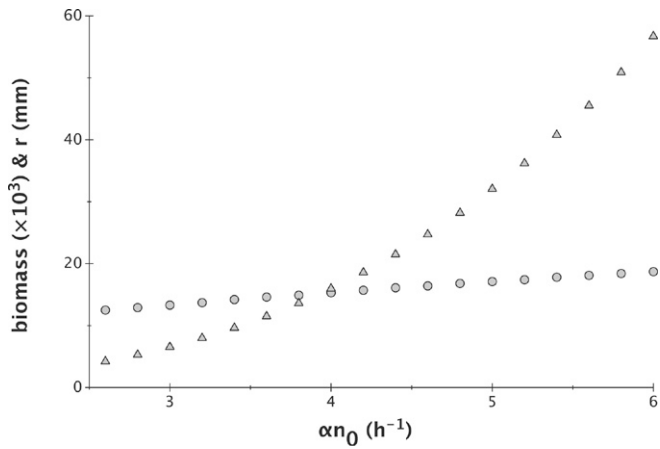


Fig. 6. Biomass (triangles) and radius (circles) of *P. mirabilis* colonies as a function of nutrient concentration (obtained from our simulations), after 5 cycles of migration–consolidation.

We assume that T_C depends far more strongly on the diffusion constant (and the concentration of agar) for *B. subtilis* than for *P. mirabilis*. This hypothesis is based on the comparison of the variation of consolidation time with the concentration of agar

in experiments, for *B. subtilis* [26] and *P. mirabilis* [23]. The difficulty is that *B. subtilis* forms concentric rings on a very narrow area, so the range of agar concentration is not the same in both cases. From the experimental data, we estimated that the consolidation time for *B. subtilis* varies roughly linearly with agar concentration as $61C_a$, whereas for *P. mirabilis* the variation of the consolidation time is much smaller, $2.8C_a$. Since the relation between the concentration of agar and the diffusion constant of the bacteria is unknown, the relation between the diffusion constant and the consolidation time can only be phenomenological. Thus, we considered two extreme cases: one with a strong variation of the consolidation time with the diffusion constant, which would be suitable for *B. subtilis*, and the other where the consolidation time does not depend on the diffusion constant, in the case of *P. mirabilis*.

In our simulations, the appearance of maxima in the bacterial concentration comes from the maxima in the growing rate, which is the product of the bacteria and the nutrient concentrations. No chemical factor, which would influence the colony growth, is needed to explain the terraces. This is compatible with experiments where colonies are partially cut and removed without any change in the width of terraces [10].

The range of parameters we chose is also realistic. Let us consider the diffusion constant values: if the theoretical diffusion coefficient of a particle of diameter $1\ \mu\text{m}$ in water is of the order of $10^{-4}\ \text{mm}^2\ \text{h}^{-1}$, the diffusion coefficient of bacteria like *Bacillus circulans* [7] or *E. Coli* [4] in water is between 0.1 and $1\ \text{mm}^2\ \text{h}^{-1}$. In agar, Eiha estimated a diffusion coefficient for *B. circulans* between 1 and $10^{-4}\ \text{mm}^2\ \text{h}^{-1}$ for agar concentrations between 0.3% and 0.9% [7]. We did not find analogous measurements for *B. subtilis* or for *P. mirabilis*. Still, our diffusion constant varies from 10^{-5} to $10^{-2}\ \text{mm}^2\ \text{h}^{-1}$ for higher concentrations of agar (between 2% and 3%), which is compatible with the experimental results. We took a total cycle time of 10 h, which is compatible with experimental results, for both types of bacteria [23,26]. For the set of parameters we chose, the concentration of bacteria does not exceed $200b_0 \approx 2^8 b_0$. This means that the number of reproduction cycles is around 8 during a 5 h-period (consolidation phase). Thus, the

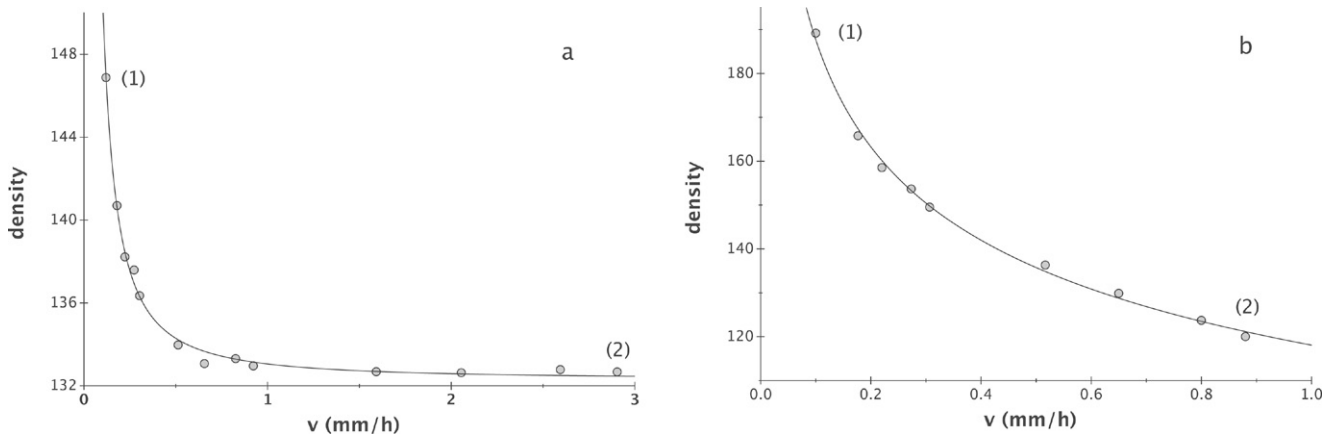


Fig. 7. Mean density of *P. mirabilis* (a) and *B. subtilis* (b) colonies as a function of the expansion velocity of the colonies (obtained from our simulations). The data points correspond to different values of the diffusion constant, from (1): $D = 2 \times 10^{-5}\ \text{mm}^2\ \text{h}^{-1}$ to (2): $D = 2 \times 10^{-2}\ \text{mm}^2\ \text{h}^{-1}$ for *P. mirabilis* and from (1): $D = 2 \times 10^{-5}\ \text{mm}^2\ \text{h}^{-1}$ to (2): $D = 2 \times 10^{-3}\ \text{mm}^2\ \text{h}^{-1}$ for *B. subtilis*.

doubling time of the bacteria is close to 40 min, which is compatible with the experimental measurements [23,26].

Although minimal, our model can reproduce several qualitative and quantitative characteristics of bacterial colonies. If the common pattern (rings) in the bacterial concentration profiles is present (Fig. 1a, b, c, e), the differences between *B. subtilis* and *P. mirabilis* colonies are clearly visible on the concentration profiles. For *P. mirabilis*, oscillations exist over a large range of diffusion constant values, as can be seen in experiments [19] (Fig. 1a, b, c). Since for *B. subtilis*, for very small diffusion constant, the migration time is also very small, the oscillations are not visible any more (Fig. 1d). This corresponds to the “B” region in the morphological diagrams of [9,20,25] (usually associated to Eden-type structures). For very large diffusion constants, the oscillations are washed out by diffusion and disappear, just as they do in experiments (region “D”, disk-like morphology) (Fig. 1f). The evolution of the radius of the colonies as a function of time (with a lag-time at the beginning of the evolution) and the range of values of radii (between 0 and 80 mm for a 50 h evolution) are close to experimental results for *P. mirabilis* [23]. As seen in experiments, the colonies on a hard agar expand more slowly and are characterized by a higher bacterial density, as reflected by the hyperbola-like shape of the variation of the density as a function of the velocity of expansion [23] (Fig. 7a and b). The expansion velocities of colonies are in the same range as the experimental ones (around 1 mm/h). Finally, the evolution of the biomass and the radius as a function of nutrient concentration (Fig. 6) is equally close to the corresponding profiles presented in [23].

From the model, we were able to make the phenomenological assessment that the diffusion constant could vary as the inverse of the agar concentration to the power 6 for *P. mirabilis* for agar concentrations between 2% and 3%. The relation between the diffusion constant and the agar concentration is different for *P. mirabilis* and *B. subtilis*, and is difficult to deduce from experiments in the latter case. However, if we keep the same expression for the period as a function of the agar concentration as for *P. mirabilis*, we obtain a value of ν close to 7. This means that the power does not critically depend on the variation of the consolidation time with the diffusion constant. The only available data we could compare our results with were those on *B. circulans*, on soft agar. From [7], we estimated that the diffusion constant varies as the agar concentration to the power -5 , which is compatible with our findings. It would be interesting to have some similar experimental results for *B. subtilis* and *P. mirabilis*. There does not exist (to our knowledge) any theoretical relation between the diffusion constant and the agar concentration. Indeed, the system is quite complicated and does not resemble the diffusion of particles of the same size in water: the bacteria move actively, and not only by diffusion. Moreover, they do not move in the main bulk of the agar solution but rather on its surface, in a thin water layer, the thickness of which depends on the agar concentration. Finally, the bacterial strains *B. subtilis* and *P. mirabilis* utilize the cooperative intercellular interaction to differentiate, changing their phenotype to form motile swarmer cells. A model which would describe the rela-

tion between the concentration of agar and the motion of the bacteria, and express the dependence of the diffusion constant on the agar concentration, is still missing for the moment.

Of course, our model has limitations. It does not reproduce the dependence of the lag-time on the initial density of bacteria [23,10] for *P. mirabilis*. Our lag-time corresponds to the first consolidation phase, and its duration is constant by construction. Moreover, our model is based on phases with fixed duration, whereas it seems that the different phases are rather defined by density thresholds [23,10]. Our next step will be to improve our model in order to introduce such density thresholds, so as to be closer to experiments and to the biological reality, while insisting on the comparison of the two bacterial species *B. subtilis* and *P. mirabilis*, just as we did here. We shall return to this problem in some future work.

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