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Abstract

Bacteria growth, detachment and surface-associated motility are recongnized to play an important role in microbial biofilm formation. In this paper we we investigate using an individual-based model how these processes interplay to yield complex biofilm spatial patterns.

1 Introduction

Bacteria attach to hydrated surfaces and develop biofilms. Biofilms development is a complex and sequential process often initiated by a small number of cells on a hydrated surface. Through binary fission and a number of other mechanisms including surface migration, exopolymer production and biofilm detachment, the initial colonizers develop progressively complex and sophisticated structures. In many applications where biofilms are envolved, it is important to understand how such complex structure develop. This can be performed through microscopic observation of the biofilm development, in particular using Confocal Laser Scanning Microscopy, and individual-based modeling, a convinient tool to develop a comprehensive understanding of how different individual level processes interplay yielding the emergence of complex biofilm structures.

In this work we propose a minimal individual-based model capable of reproducing a large number of observed biofilms spatial structures. Many powerful individual-based models (IBMs) have been proposed in the litterature for the study of biofilm development [2] [3] [5][**?**]. These IBMs often explicitily include the substrate diffuson, exopolymer production and other processes like the shoving process. Such IBMs have proven their capacity to reproduce realistic spatial pattern and significantly contributed to our understanding of the biofilm development mechanisms. Our aim here is to derive a much simpler IBM by considering only three main processes: birth (binary fission), death (or detachment) and surface migration. The main question adressed in this work is wether these three processes are sufficient to reproduce the large diversity of biofilm spatial patterns observed using confocal laser microscopy techniques.

Model description

1.0.1 Overview

State variables and scales We consider a two-dimensional space containing discrete individuals (bacteria)characterized by there coordinates within the domain. The vectors $p = (x_i), i = 1..N$ formed with the locations of all the bacteria at a time t define the spatial pattern at that time.

Process overview We assume that the spatial pattern changes in time due to three stochastic events acting on the individuals:

- birth of a new bacterium
- detachment (death) of a bacterium
- migration of a bacterium to a new location

Birth is a process by which a parent individual produces an offspring individual which location is selected randomly in the neighborhood of the parent individual. Detachment is the process by which an individual is removed from the system. Migration is a process by which an individual changes moves to a new location within the spatial domain.

Scheduling The temporal behavior of the IBM is governed solely by the three stochastic processes. They are scheduled according to a discrete event scheme by adapting the Gillespie's algorithm [1]. The algorithm iterates over the following steps:

1. Set time to $t = 0$
2. Calculate the sums $r_b = \sum_{i=1}^{N(t)} b_i = bN(t)$ and $r_d = \sum_{i=1}^{N(t)} d_i = dN(t)$. The total rate at which events occur (births or deaths) is given by $r(t) = r_b(t) + r_d(t)$
3. Choose a waiting time τ for the next event to occur according to $\tau = -\frac{1}{r} ln\lambda$, where $0 < \lambda \leq 1$ is a uniformly distributed random number
4. Choose a birth or death event with a probability r_b/r and r_d/r respectively
5. Choose an individual k with a probability b_k/r_b (if the event is a birth) or d_k/r_d if the event is a death, where $b_k = b$ and $d_k = d$ are respectively the birth and death rates of the individual k
6. Perform the selected event on the individual k
7. Update time according to $t = t + \tau$
8. Update the number of the individuals $N(t)$
9. Continue from step 2 until $t < t_{end}$

1.0.2 Details

Initialization The model is initialized with $N(t = 0)$ bacterial cells distributed uniformly over the domain.

Submodels

- Birth process:

We suppose that the probability per unit of time that a bacterium particle i in position x_i produces a new bacterium located in position x_i' is given by:

$$B(x_i, x_i') = (b_1 + b_1' \sum_{j=1, j\neq i}^{N} w_{bv}(x_i - x_j)) w_b(x_i - x_i') \tag{1}$$

The parameters b_1 and b_1' are the density independent and the density-dependent birth rates respectively. $w_{bv}(x_i - x_j)$ is an interaction kernel that measure the contibution of the individual in x_j to the birth rate of the individual in x_i and $w_b(x_i - x_i')$ is a birth kernel measuring the probability that the newly formed individual will be located in x_j'.

- Bacteria detachment process

An individual in location x_i detachs with a probability $D(x_i)$ given by:

$$D(x_i) = d_1 + d_1' \sum_{j=1, j\neq i}^{N} w_{dv}(x_i - x_j) \tag{2}$$

d_1 and d_1' are the density-independent and the density-dependent detachment rates. $\sum_{j=1, j\neq i}^{N} w_{dv}(x_i - x_j)$ is the density of individuals evaluated in x_i using an interaction kernel $w_{dv}(x_i - x_j)$

- Bacteria motility

An individual in location x_i moves to new location x_i' with a probability $M(x_i, x_i')$ given by:

$$M(x_i, x_i') = (m_1 + m_1' \sum_{j=1, j\neq i}^{N} w_{mv}(x_i - x_j)) w_m(x_i - x_i') \tag{3}$$

with m_1 and m_1' are the density independent and the density-dependent motility rates respectively. $\sum_{j=1, j\neq i}^{N} w_{mv}(x_i - x_j)$ is the individuals density in x_i measured using and interaction kernel $w_m(x_i - x_i')$ and $w_m(x_i - x_i')$ is the motility kernel.

Parameters The model parameters are summarized in table 1.

Different kernel types can be used. In this model we use a uniform kernel given by:

$$w(x - x') = \begin{cases} 1/w & if \quad ||x - x'|| < w \\ 0 & else \end{cases} \tag{4}$$

Implementation We implement the model using the Mason framework, an open-source java-based library for implementing agent-based models [4]. The individual-based simulator outputs are the timeseries of the population size and the pair correlation function $C(\xi)$. Snapshots of the spatial pattern can also be taken at a fixed period. The simulator allows the replication of an individual-based simulation and the calculation of the average and variance of $N(t)$ and $C(\xi)$.

	Description
b_1	Bacteria density-independent birth rate
b'_1	Bacteria density-dependent birth rate
d_1	Density-independent bacteria detachment rate
d'_1	Density-dependent bacteria detachment rate
m_1	Density-independent bacteria motility rate
m'_1	Density-dependent bacteria motility rate
w_b	birth kernel
w_{bv}	birth interaction kernels
w_{dv}	detachment interaction kernels
w_m	motility kernel
w_{mv}	motility interaction kernels

Table 1: Model parameters

2 Results

Though very simple, this IBM has 11 parameters which potentially can have an impact on the processes and the simulated biofilm patterns. In order to analyse this IBM we start with aunderstanding the patterns that arise in a birth-death IBM by switching the migration terms off (in practice this is performed by setting the parameter, m_1 and m'_1 to zero) and then in a second step introduce switch on the migration process and attempt to analyse how bacteria motility impacts the simulated biofilm structures.

2.1 Birth-death IBM

2.1.1 The density-independant case

In the case where birth and death are density-independent processes (b'_1, d'_1) a (quasi) stationnary state can be obtained only for $b_1 = d_1$ as if $b_1 > d_1$ the population grows exponontially and when $b_1 < d_1$ the population goes to extinction. In the case where $b_1 = d_1$ the spatial pattern is sensitive to the size of the birth kernel w_b. The individuals form colonies (aggregates) if w_b is smaller than the domain size as illustrated in figure 1.

2.1.2 The density-dependant case

There are three means of introducing the effect of neighboring individuals:

- the neighbors can have an influence on the birth process but not on the death process
- the neighbors can have an influence on the death process but not on the birth process
- the neighbors can have an influence on both birth and death process

In each of these situation the effect of the neighbors can be positive or negative. In the positive interaction the presence of neighbors increase the intensity of the process. For example one can assume that the presence of

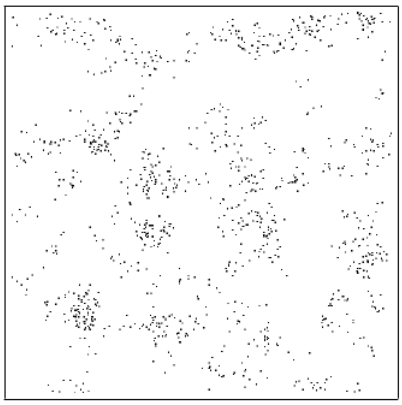

Figure 1: Snapshots of the quasi stationary spatial pattern for $b_1 = d_1 = 0.1$ and $w_b = 5$ for a domain size of 101×101

neighbours increases the death probability of a focal individual. The negative interaction refers to the situation where the presence of neighbors reduces the intensity of the process. For instance, the presence of neighbors can reduce the birth probability of a focal individual. Taking into consideration the three types of density-dependent configurations and the sign of the interactions we end with 8 possibilities summarized as follows: B+, B-, D+, D-, B+D+, B-D-, B+D- and B-D+, where for B+ refer to the case where only birth is density dependent and the dependance towards the density is positive (the increase of local density increases the birth probability of a focal individual).

Among these 8 cases we can drop the configurations B+ as in this situation the formation of colonies will be accelerated yielding an exponontial growth of the size of the population. The configuration D- should also yield to the exponontial growth of the population. These two trivial results are independent of the values of the parameters b_1, d_1 and d_1' b_1'.

We propose to analyse the case D+, namely the increase of the local density increases the death probability of a focal individual. We analyze the case where $d_1 < b_1$ (and $d_1' > 0$ for the positive interaction) The case $b_1 <= d_1$ is trivial and yields to the extinction of the population as the death rate of an individual is always high or equal to its birth rate. Figure 2 shows two examples of spatial pattern obtained for two different sizes of the death interaction kernel and a comparable spatial pattern observed in a real biofilm experiment.

The patterns shows the formation of colonies separated with a quasi regular distance that depends on the size of the death interaction kernel (w_{dv}).

2.2 Birth-death-motility IBM

2.2.1 Case of density-independent motility

Density-independent motility tend to disperse the individuals. Hence, increasing the rate of the density independent motility (m_1) is comparable to increasing

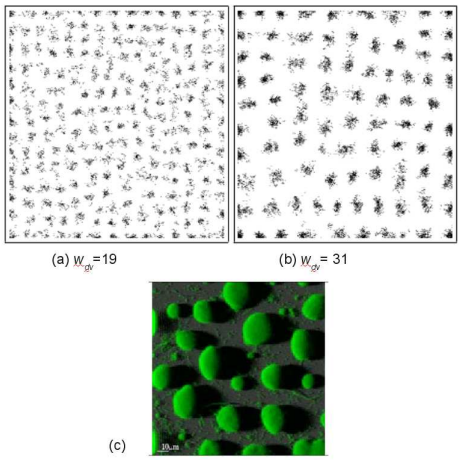

Figure 2: Snapshots of simulated patterns (a, b) and CLSM biofilm image for *Pseudomonas aeruginosa* (c)

the size of the birth kernel. The motile newborn individual disperse over larger distances preventing local accumulation and the formation of colonies.

2.2.2 Case of density-dependent motility

The density-dependent motility implies that the motility rate of an individual depends on the local density of neighbors measured with an the interaction kernel w_{mv}. This interaction can be positive $m_1' > 0$ or negative $m_1' < 0$. This adds a further complexity to the configurations identified in the case of the pure birth-death model.

We investigated the spatial patterns that arise in the case D+M- : the birth process is density-indepedent, the death rate increases with the increase of the local density while the motility is reduced by the increase of the local density. In this situation the spatial pattern shows the development of labyrinth comparable to the labyrinths observed in real biofilm experiments as illustrated in figure 3.

3 Concluding remarks

During the last two decades individual-based modelling has been used for investigating how complex biofilm spatial patterns emerge from local interaction between the individuals. Our model is an attempt to develop a minimalistic IBM that is able to reproduce a diversity of observed patterns. Our work shows that by considering only three density-denpendent processes (birth, death and migration) it is possible to reproduce complex spatial patterns observed in rela biofilms.

Though simple our model has 11 parameters that can potentially influence the spatial pattern. Hence additional exploration of the effect of these parameters

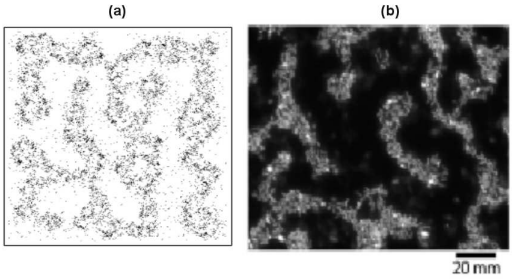

Figure 3: (a) Snapshots of simulated patterns (b) and CLSM biofilm image for *Pseudomonas aeruginosa*

is required in order to cover all the potential patterns that can be represented by this IBM.

Acknowledgement

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