INDIVIDUAL-BASED MODELLING OF MICROBIAL COLONY DYNAMICS ON FOOD SURFACES IN A PARALLEL SIMULATOR

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ABSTRACT

Throughout the whole food processing and distribution chain, an accurate assessment and control of microbiological food safety is indispensable to avoid large outbreaks of foodborne diseases. For this reason, mathematical models are developed in predictive microbiology to describe the growth and survival of food spoiling and pathogenic microorganisms as a function of the environmental conditions during food processing and distribution.
Traditionally, these models are representative for the planktonic growth of axenic microbial cultures in perfectly mixed liquid media. However, most food products are characterised by a semi-solid structure, where the contaminating cells grow out as colonies. Diffusion limitations emerge in these colonies due to the high local cell density. Hence, it is most appropriate to simulate microbial colonies at a microscopic level, considering the cell as basic modelling unit in an individual-based modelling approach. Within this respect, the MICRODIMS model has been developed at the BioTeC+ research group. However, over the last years, it became clear that the implementation of this individual-based model in the standard Repast Simphony toolkit is rather slow for the simulation of mature colonies containing a large number of cells. For this reason, MICRODIMS has been ported to the TransProg library, which uses modern general-purpose multicore and multiprocessor computers to their fullest potential.
This transfer enables the simulation of mature colony dynamics in three dimensions. In this paper, the branched morphology of colonies growing on the surface of a food substrate is investigated. It is demonstrated that the emergence of this pattern is dependent on the thickness of the food substrate and structural heterogeneities at the food surface.

INTRODUCTION

Over the last decades, significant progress has been achieved in the predictive modelling of microbial pathogen behaviour in food products (McMeekin et al. 2008). These mathematical models are used to quantitatively link microbial hazard levels in food processing companies and the contamination levels to which consumers are exposed, in order to assess the risk of food poisoning.
Traditionally, models in predictive microbiology are based on experiments of axenic microbial populations in homogeneously mixed liquids. In these liquid media, the population dynamics are the result of the corporate behaviour of free-swimming cells that are barely interacting with each other and exposed to more or less the same environmental conditions. For this reason, it is reasonable to consider the integral population as a continuous modelling unit, allowing for a noncomplex description of the population dynamics by means of a limited set of coupled differential and/or algebraic equations – see, e.g., (Baranyi and Roberts 1994).
However, most food products exhibit a semi-solid structure, limiting the mobility of contaminating pathogenic microorganisms. Hence, colonies of related organisms emerge from the initial contaminating cells on the food surface (Wimpenny et al. 1995). In these surface colonies, overconsumption of nutrients/oxygen and secretion of weak acid cell products lead to chemical gradients in the colony environment due to diffusion limitations. Ultimately, this results in nutrient or oxygen depletion and a pH drop in the colony. In other words, the growth of the colony is inhibited through the creation of adverse conditions by the collective behaviour of its constituting cells.
Due to the chemical gradients in and around mature colonies, the colony cells exhibit strongly different metabolic behaviours according to their position along the colony radius. Therefore, the most appropriate modelling unit is the individual microbial cell. This modelling approach is in line with the individual-based modelling (IbM) paradigm, where the dynamics of the considered multiagent system implicitly emerge from the simulated behaviour and interactions of its constituting individuals. The IbM approach facilitates the incorporation of microscopic knowledge about the microbial cells and heterogeneities in the food structure. However, the simulation of the behaviour and interactions of each individual cell leads to long simulation times for mature colonies containing millions of cells.
Over the last two decades, individual-based models have been developed for the simulation of microbial colony behaviour, starting with the BacSim model of Kreft et al. (1998) and the INDISIM simulator of Ginovart et al. (2002a). BacSim is an extension of the Gecko ecosystems simulator which is also used for, e.g., the simulation of spider or tree populations (Booth 1997), implying that BacSim contains a myriad of superfluous functionality compromising its performance and clarity (Dens et al. 2005; Standaert 2007). For this reason, a new individual-based model, MICRODIMS, has been developed in the BioTeC+ research group and implemented in user-friendly software toolkits like NetLogo (Wilensky 1999), Repast Simphony (North et al. 2013), and MASON (Luke et al. 2003). However, it became clear that for mature colonies the simulation time increased heavily due to the large number of spatial interactions between the colony cells. Therefore, the MICRODIMS model has been ported to the TransProg library

in order to make use of modern general-purpose multicore and multiprocessor computers to their fullest potential (Harrouet 2012).
This transfer enables the simulation of mature surface colony dynamics in three dimensions, as elaborated in this paper. More specifically, this paper focuses on the formation of branched colony morphologies in nutrient-limited colonies. The influence of the food substrate thickness and food surface inhomogeneities on the colony morphology are investigated.

MATERIALS AND METHODS

The relevance of the considered microorganism is explained in this section. In addition, the MICRODIMS model and its TransProg-based revision are described in more detail.

Considered Model Organism

In this work, *Escherichia coli* K-12 MG1655 is used as the simulated microorganism. This nonvirulent *E. coli* substrain is frequently applied in experimental studies as a model organism for pathogenic strains of *E. coli* and *Shigella* (Hayashi et al. 2001; Jin et al. 2002). Infection with these pathogenic strains can result in severe gastrointestinal disorders, kidney failure, and even death. Pathogenic *E. coli* strains are particularly dangerous for young, elderly, and immunity-compromised people. Moreover, treatment with antibiotics increases the risk of haemolytic uraemic syndrome (HUS) and renal failure (Wong et al. 2000; Tarr et al. 2005). In the US, the annual cost of Shiga toxin-producing *E. coli* (STEC) infections amounts to hundreds of millions of dollars (Frenzen et al. 2005; Economic Research Service, USDA 2014).
As a facultative anaerobic organism, *E. coli* can survive on a wide variety of nutrition sources both in the presence and absence of oxygen, increasing the risk of proliferation in food products. In this paper, only aerobic colony dynamics are considered, as described in Tack et al. (2015a), eliminating the possibility that weak acid cell products are secreted into the environment as a result of the mixed acid fermentation metabolism of *E. coli*.

Model Description of MICRODIMS

The MICRODIMS model has been described in full detail in previous publications (Tack et al. 2014; Tack et al. 2015a). It considers two kinds of agents: the microbial cells and the food substrate. This food substrate is divided in discrete units to simulate diffusion processes of glucose through the food system. The implementation of this diffusion process is explained in the next section.
Diffusion of glucose through the environment is caused by glucose uptake of the colony cells from their local environment. This glucose uptake is used for cell growth and maintenance purposes, and is modelled by means of the Monod kinetic model (Monod 1942):

$$v_{k,(i,j)} = v_{k,\max} \cdot \frac{C_{S,(i,j)}}{K_S + C_{S,(i,j)}} = \frac{\mu_{k,\max}}{Y_{X/S}} \cdot \frac{C_{S,(i,j)}}{K_S + C_{S,(i,j)}} \cdot X_k. \quad (1)$$

In this formula, $C_{S,(i,j)}$ [fg/fL] is the glucose concentration of the environmental unit in which the microbial cell is situated, $v_{k,(i,j)}$ [fg/min] is the glucose uptake of cell k, $v_{k,max}$ [fg/min] is the maximum glucose uptake rate, K_S [fg/fL] the Monod half-saturation constant, $\mu_{k,max}$ [min^{-1}] the maximum specific cellular growth rate, $Y_{X/S}$ [fgDW/fg] the cellular yield coefficient of biomass on glucose, and X_k [fgDW] the mass of cell k. The cellular growth and maintenance behaviour are implemented as an exponential growth law, containing contributions of the Monod-type glucose uptake, and biomass degradation according to the Herbert model (Herbert 1958):

$$\frac{dX_k}{dt} = \mu_k \cdot X_k = v_{k,(i,j)} \cdot Y_{X/S} - m_S \cdot X_k \cdot Y_{X/S}, \quad (2)$$

with μ_k [min^{-1}] the specific cellular growth rate of microbial cell k, and m_S [fg/(fgDW·min)] the specific maintenance coefficient.
A microbial cell starves when its maintenance requirement is not met and, consequently, its specific growth rate is negative. In a starving cell, the DNA replication and cell division processes stop progressing. These processes are modelled by means of an adapted version of the Donachie model (Donachie 1968), elaborated in Tack et al. (2015). In this model, the DNA replication (*C*-phase) and chromosomal segregation (*D*-phase) take a fixed period of time as a function of the specific cellular growth rate:

$$C + D = 3.50 \cdot \mu_k^{-0.658} \text{ for } \mu_k < 0.011 \text{ min}, \quad (3a)$$
$$C + D = 67.92 \text{ min} \text{ for } \mu_k \geq 0.011 \text{ min} \quad (3b).$$

This equation has been derived as a fit on data of Helmstetter (1996) and Michelsen et al. (2003).
According to Donachie (1968), DNA replication cycles are initiated at a critical ratio X_c [fgDW] of the cell mass to the number of ongoing DNA replications:

$$\frac{X_i}{n_i} = X_c \Rightarrow X_i = X_c \cdot n_i = X_c \cdot 2^j \text{ with } j = 0,1,2,\ldots \quad (4)$$

For exponentially growing cultures, the critical initiation ratio can be derived from the mean cell mass at division X_D^{m} [fgDW] (Dens et al. 2005):

$$X_D^{\mathrm{m}}(\mu_{\max}^{\mathrm{m}}) = X_c \cdot \exp\left(\mu_{\max}^{\mathrm{m}} \cdot (C + D)\right). \quad (5)$$

Although Donachie (1968) postulated that the critical ratio was a constant, Wold et al. (1994) observed a linear decrease of X_c as a function of the specific cellular growth rate:

$$X_c = A - B \cdot \mu_{\max}^{\mathrm{m}}. \quad (6)$$

The mathematical constants *A* and *B* can be estimated from experimental data of Volkmer and Heinemann (2011) on the mean cell mass at division as a function of the specific growth rate, after the substitution of the critical initiation ratio in Equation (5) by the expression in Equation (6).
Finally, cells avoid spatial overlap by shoving over the surface and forming layers on top of each other, as explained in the next section.
All parameter values in the previous equations can be found in Tack et al. (2015a).

Porting the Model to TransProg

The TransProg library is not by itself a simulation engine dedicated to bacteria. It is rather a set of facilities (multiplatform and written in C language) for a programmer to harness the full potential of modern general-purpose computers. However, it was designed with individual-based simulations in mind, and consequently makes use of multiple cores and processors (CPU) as well as graphical processing units (GPU) for both rendering and computing.

The simulation of the aforementioned MICRODIMS model involves many bacterial individuals and a food substrate containing glucose as the carbon nutrient source. Because the simulation of glucose diffusion through the substrate implies computing Fick's second law with a discrete Laplacian on a spatial grid, these computations are identical in each spatial cell and use a regular pattern; therefore they are suitable to GPU computing (with the Nvidia Cuda toolkit). On the other hand, each individual takes its own decisions (consume glucose, grow, start a new DNA replication cycle, divide, separate from neighbours…); CPUs can easily deal with this kind of irregular computations and we dedicate all of them in the computer to the behaviour of the bacteria. The workloads on these CPUs are dynamically balanced according to their cache memory hierarchy in order to preserve data locality and then maximise computing efficiency. For the same purpose, alignment, cache blocking, and vectorisation techniques, as summarised in Jeffers and Reinders (2013), are used where suitable.

In this model, bacteria stay on the surface of the food substrate, thus the only interface between these two distinct computations is the top plane of the substrate. Bacteria get to know the local concentration of glucose (computed on the GPU) by reading a bidimensional spatial grid describing local glucose concentrations in this plane. In a similar way, they express (on the CPUs) their local glucose consumption in another bidimensional spatial grid that will be provided to the substrate to be considered in the next diffusion computation. This is a synchronous approach in which, at each time step, every computation refers to a previous immutable global state to produce the next one. Because, on a hardware point of view, GPU and CPU computations are asynchronous, they can run simultaneously. For this opportunity to be fully exploited, the back and forth data transfer of the two previous bidimensional spatial grids must also overlap with the computations; this is achieved with a triple-buffer scheme as described in Hrabcak and Masserann (2012).

All the care taken to optimise the computer efficiency enables us to address larger simulations than those run with the original version of MICRODIMS. If the number of simulated bacteria increases, the thickness of the food substrate should also be considered in the simulation. For this purpose, a three-dimensional grid is used for the discrete Laplacian computation; it is solved (on the GPU) by Jacobi iterations around the backward Euler method (or alternatively Crank-Nicolson). The top layer, which is actually the only layer accessible to the bacteria, is fine grained and has the same thickness as its horizontal grid step. As layers stand deeper, they can get coarser without influencing the bacteria that much. Hence, the diffusion equations are adapted to a geometric progression of the layer thickness, as illustrated in Figure 1. This three-dimensional cut view is an informal example that shows a bacterial colony standing on top of a multi-layered substrate. The red to blue gradient depicts the glucose concentration from its initial value to zero (totally consumed). The discrete steps of this colour gradient highlights the various thicknesses amongst the substrate layers. The food substrate acts as a thick glucose buffer without using too many layers that would harm computing efficiency. However, a thick substrate is likely to facilitate the bacterial access to nutrient since glucose does not only diffuse from beside, where it is already partially consumed by other bacteria, but also from below, where there is no consumption. In these conditions, bacterial growth is sped up (glucose is the only limiting factor in this model), and mechanical repulsion between the cells in a monolayer is not fast enough to separate individuals.

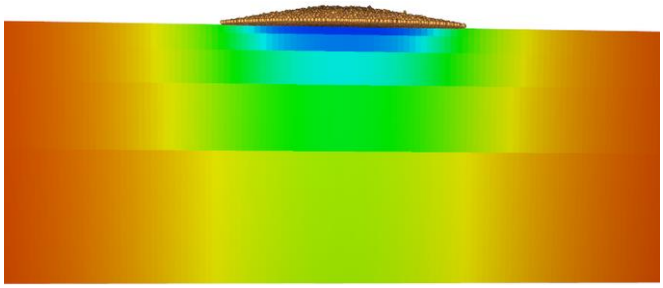

Figure 1: Cut View Under a Colony of Bacteria

Therefore, we introduced a stacking algorithm for the bacteria that produces multi-layered colony shapes as visible on Figure 1; it simply depends on their local density. As placement at a stacking level relies on a discrete spatial grid (to ease inter-individual detection for neighbour repulsions), each spatial cell keeps track of its remaining space. When a bacterium does not fit in a full spatial cell, it is then placed in the spatial cell on the above stacking level. Although some bacteria appear on top of some others, they all still interact with the substrate through its top layer. The main goal of this stacking algorithm is not to make the simulated colony look like a real one but it prevents a computational overload of the mechanical repulsion between bacteria. Actually, these repulsions are computed independently at each stacking level, then, as the density is contained, each bacteria has only a few neighbours to consider during the repulsion.

RESULTS

The aim of the experiments described here is to investigate branched colony shapes, as observed in Fujikawa and Matsushita (1989) and simulated by Ginovart et al. (2002b) and Tack et al. (2015a). Although the main model parameters directly come from Tack et al. (2015a), a peculiar care was taken when choosing some of them in order to achieve a satisfying trade-off between numerical stability and simulation duration. We retained 4 μm as horizontal grid step for the substrate and 0.1 min for the time step. It was checked that a factor 2 in the geometric progression of the thickness of the substrate layers gave results similar to those obtained with regular layers. We also checked whether the application of the backward Euler method with the selected time step to simulate glucose diffusion was similar to using the Crank-Nicolson method with a much smaller time step respecting the Courant-

Friedrichs-Lewy (CFL) constraint. The substrate is a square with a side dimension of 4096 µm; its thickness changes over the various experiments. Its initial glucose concentration is 0.1 g/L; it is maintained constant at the square boundaries. The usual glucose diffusivity inside this substrate is $6.7925 \cdot 10^{-10}$ m^2/s, but a tenfold lower value has been used in some simulations. These experiments were run on a dual Intel E5-2697 computer (24 cores, 48 threads) with a Nvidia Titan GPU.

Figure 2 contains some views of the patterns obtained when running such simulations with various conditions of substrate thickness and glucose diffusivity. Figure 2-*a1* shows the whole 4096 µm wide substrate, while Figures 2-*a2* to 2-*g* give a closer view (Figures 2-*a1* and 2-*a2* both depict the same experiment in the exact same state). The simulation experiments are stopped before the colony (1.5 mm diameter) gets near to the constant borders (4 mm wide). The red to blue gradient depicts the glucose concentration varying from its initial value to zero.

In Figures 2-*a1*/*a2* to 2-*d*, the same tenfold lower diffusivity is used, but the substrate thickness is varied from 4 µm to 60 µm. Despite the fact that very sharp branched patterns resembling a diffusion-limited aggregation pattern appear quite easily on a very thin substrate – as in Tack et al. (2015a) – they get smoother and involve more bacteria on a thicker one. Figure 2-*a1*/*a2* contains $2 \cdot 10^5$ bacteria (97% starving after 34 simulated days) and took 57 minutes to obtain (nutrient depletion implies slow growth rate), while Figure 2-*d* contains $1 \cdot 10^6$ bacteria (92% starving after 9 simulated days) and took 27 minutes to obtain.

Figures 2-*e* and 2-*f* show the effect of a substrate with a usual diffusivity value and a thickness of respectively 4 µm and 12 µm. It is clear that when the diffusivity rises, branched patterns are much more difficult to obtain even with larger colonies: they hardly start to appear with $3.2 \cdot 10^6$ bacteria forming a 2 mm wide colony on Figure 2-*f*.

For all of these simulations, the main part of the colony contains starving (dark) bacteria; the colony only continues growing at its border (light bacteria). This makes the branches appear where the colony border becomes irregular. Actually, when some bacteria are accidentally placed slightly apart from the colony due to inter-individual repulsions, they get an easier access to glucose, thus they grow faster than the other cells which are enclosed into the colony. Consequently, they are likely to produce an offspring which would stand even farther from the colony center, and this self-maintained process goes on, leading to branches.

In Figure 2-*g*, the same settings are used as in Figure 2-*f* except that some irregularities are introduced in the glucose diffusivity by placing some 64 µm wide random plots with a tenfold lower value. Our intent was to alter the regular border of the colony in order to induce some early branch starts. The obtained Figure 2-*g* shows that when branches actually start, they tend to persist because the glucose depletion between them prevents the cells at the colony border from growing towards this gap.

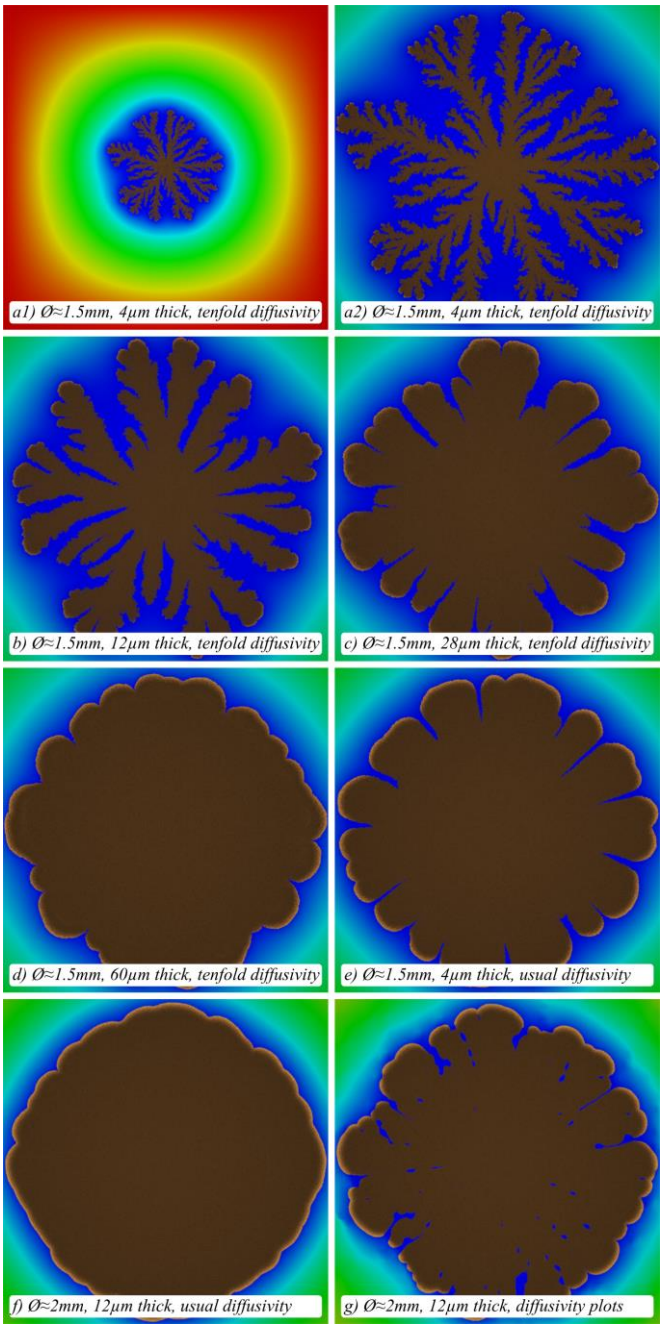

Figure 2: Colonies of Bacteria Labelled with their Diameter, the Substrate Thickness and Glucose Diffusivity

DISCUSSION

Optimising the computing efficiency of the simulation was an important step in this work. While several days where necessary in Tack et al. (2015a) to produce a 165 µm wide pattern involving around ten thousand bacteria, we now spend several dozens of minutes to a few hours to obtain colonies of many millions bacteria forming millimetre scale patterns. This enabled us to try and compare various sets of parameters in a decent time and to extend the simulation in the third dimension.

Actually, although it has been shown in Tack et al. (2015a) that nutrient depletion has a significant influence on the formation of branched colony shapes, this new version of the simulation helped to investigate this hypothesis further. These new results highlight that both the thickness of the substrate

and the diffusivity of glucose have a decisive impact on the ability to obtain such patterns. With no more new hypothesis than glucose depletion, it seems that millimetre scale branched colony shapes cannot be obtained with the usual diffusivity in a thick substrate. (This would probably require a much larger scale).
An alteration of the substrate with lower diffusivity plots was intended to reflect its natural heterogeneity. This led to early branch patterns on a thin substrate, but it is presumed that it would not be sufficient on a thick one. A new hypothesis to explain these patterns at the millimetre scale would be to consider the influence of oxygen diffusion in the colony. The inclusion of information from phenotypic phase plane analysis (Edwards et al. 2001) would enable the modelling of the whole spectrum from aerobic respiration to anaerobic fermentation, as described in a forthcoming publication (Tack et al. 2015b).
From a more technical point of view, we realised that the computing time was mainly spent to the calculation of the bacterial behaviours on the CPUs, while the GPU stays idle once the substrate is updated. It should be possible to assign the straightforward parts of these behaviours (consumption and growth) to the GPU and only use the CPUs for the division and spatial repulsion of the bacterial cells.

CONCLUSIONS

The previously implemented MICRODIMS individual-based model, dedicated to bacteria colony simulations, was rewritten on top of the TransProg library in order to maximise the computing efficiency. This speedup enables us to run larger simulations (several millions of individuals) and to extend the model in the third spatial dimension.
This new simulator helped investigate further the formation of branched colony shapes in relation with the role of the substrate in nutrient depletion. This led towards a new hypothesis implying both aerobic respiration and anaerobic fermentation.
Future efforts will both tend to further investigate this new hypothesis and to increase the GPU workload in order to raise the global computing efficiency.

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NOTE

This paper is the result of a collaboration between the BioTeC+ research group and the European Center for Virtual Reality (CERV). In fact, this collaboration started at the previous FOODSIM conference in Brest, where I. Tack and G. Desmeulles discovered common research interests. At that time, both researchers were involved in projects on the simulation of microbial colony dynamics. During a first research visit of I. Tack at CERV, G. Desmeulles introduced him to F. Harrouet to reimplement the BioTeC+ MICRODIMS model with the TransProg library. The idea to write a common paper came at a second meeting at BioTeC+ in Ghent.

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The TransProg Library.
http://www.enib.fr/~harrouet/transprog.html
(provides simulation source code and data).

BIOGRAPHY

IGNACE TACK was born in Turnhout, Belgium. He graduated as Master of Chemical Engineering at the University of Leuven (KU Leuven) in 2011. After his graduation, he has been working on multiscale modelling techniques in predictive microbiology as a PhD researcher at the BioTeC+ division of KU Leuven.

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