A simple cellular multi-agent model of bacterial biofilm sustainability

Tiago Guglielmeti Correale[2†] and Pedro P.B. de Oliveira[1,2‡]

Universidade Presbiteriana Mackenzie
[1]*Faculdade de Computação e Informática &* [2]*Pós-Graduação em Engenharia Elétrica*
São Paulo, SP - Brazil

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A cellular multi-agent system is used to implement a simple and abstract model of bacterial biofilm. Biofilms are social organisations of bacteria that allow them much more adaptive and functional roles than when they are found individually; in fact, contrarily to commonsense knowledge, this is the most common form of bacteria organisation in nature. A series of experiments are reported with the model, addressing the issue of biofilm sustainability, once it has been created. The model is based upon two kinds of agents, representing bacteria and food sources, the former presenting two different roles, according to their ability to sustain the biofilm production. The investigation is focused on the influence of different proportions of bacterial agents with these roles in the system. Some quantitative characterisation to the experiments is given, according to the initial world configuration, its population life span and the energy levels of the system, which allow for explanations of some qualitative observations. The latter clarify the view that biofilm sustainability depends on a balance between the apparently conflicting roles of the bacterial agents involved.

Keywords: Discrete dynamical system; multi-agent system; cellular world; DRIMA; BacDRIMA; biofilm; quorum-sensing; artificial life.

1 Introduction and motivation

Multi-agent systems have been used in a wide range of applications and as conceptual tools (Wooldridge, 2009; Jennings et al., 1998). In particular, in biology several efforts have also been made (Khan et al., 2003; Amigoni and Schiaffonati, 2007), supplementing the more traditional modelling techniques (Endy and Brent, 2001). Among those, cellular multi-agent approaches find its niche in terms of the simplicity and abstraction they naturally support, as well as with prospects to bridging the modelling efforts with the wealth of available knowledge in cellular automata theory and applications (Spicher et al., 2009; Ediger and Hoffmann, 2009).

†Email: tiguco@gmail.com
‡Email: pedrob@mackenzie.br

The problem at issue herein is biofilm formation by bacteria, a very important subject in microbiology. Biofilms are defined as matrix-enclosed bacterial populations adherent to each other and/or to surfaces or interfaces (Costerton et al., 1995). Contrarily to commonsense knowledge, the presence of bacteria in biofilms are much more common in nature than in their individualised (or, planktonic) form (Costerton, 2007). Bacteria produce and release molecules known as auto-inducers, whose concentration may be regarded as information about the density of bacteria in some region of the space. When population density of bacteria increases, the auto-inducer concentration also increases, eventually reaching a point where certain changes in the bacteria phenotype are triggered. This is the moment where bacteria can start producing a certain type of enzyme that allows the effective construction of the biofilm.

In order to explore this theme, we rely upon the current status of the BacDRIMA model, which is aimed at the possibility of addressing a number of issues in the dynamics of formation and sustainability of bacterial biofilm, from the perspective of a cellular, multi-agent system. This model is built upon the simple multi-agent system DRIMA (de Oliveira, 2010), which is totally based on local and simple rules governing the action of agents on a cellular world, much alike cellular automata. Due to space limitation, many aspects of the present conception and implementation of DRIMA are being omitted here.

The model is based upon two kinds of agents, representing bacteria and food sources. Two kinds of bacterial agents are defined, modelling two functional roles of the same kind of bacteria. The first are standard bacteria type organisms, which are the ones directly involved in biofilm formation, and are referred to herein as the *normal* bacteria, for the sake or simplicity. The second functional role defines the so-called *cheaters*, which benefit from the work of normal bacteria without directly contributing to biofilm formation.

BacDRIMA is an abstraction of all these processes. It tries to capture some essential aspects of biofilm development, without specific details related to specific bacteria, therefore aiming at an understanding of the generic dynamics of biofilm development. In order to go about it, the model was built with the following characteristics:

- Multi-agent based;
- Each agent has some kind of energy, that simulates their strength;
- The system has energy (or food) sources;
- Agents can cooperate, by jointly releasing enzymes to maximize energy production, but they can cheat on the work of others;
- Agents can have different properties; and
- The system must support the existence of cheaters(in the sense that they may exist without producing enzymes).

BacDRIMA was developed in *Mathematica*, just like the DRIMA system it was built upon (de Oliveira, 2010). The results reported are preliminary, and refer to the dynamics of cooperation versus cheating. Specifically, although one might imagine that cheaters are always deleterious for the whole system, in terms of always making biofilm development more difficult, the experiments to be reported indicate that this is not always the case. In fact, depending on certain conditions, cheaters help the system as a whole.

The remainder of the paper is organised as follows. After very briefly describing DRIMA in the next section, the basic concepts behind BacDRIMA are presented in the sequence. Then, artificial experimental results are presented, drawn from various experiments, with different initial conditions. Finally, a conclusions section discusses the results obtained, the model itself, and perspectives for the subsequent developments of the work.

2 DRIMA

DRIMA, an acronym for Dynamics of Randomly Interacting Moving Agents, is a discrete dynamical system, created around the idea of a set of reactive agents that interact locally, by changing the way they move (de Oliveira, 2010). It is composed of a regular lattice of cells, with periodic boundary conditions, a set of agents placed on the cells, and parameters that defined the dynamics of the agent's interactions. As a model and a computational system, DRIMA is a tool that may be used in a spectrum of experiments, as long as the problem at issue would rely on the local interaction among the agents resulting in their movement patterns being affected. Agents move on the lattice in a non-deterministic and local way, according to the probabilities defined by their so-called movement pattern; in particular, there is also a probability of their not moving. Each agent has an interaction radius associated with them, and they can interact with all agents within that radius. Interactions will change their movement pattern, by altering the probabilities associated with each direction of movement. The agents follow an interact-first-then-move cycle.

Although various aspects of DRIMA have similarities with cellular automata, a key difference to be noticed is that DRIMA's grid is only a lattice on top of which the agents can roam about.

Agent movement in DRIMA is in general non-deterministic and the lattice is presently either two- or one-dimensional. In the one-dimensional version, each agent can move to the left or right, or simply stay at its current position. In the two-dimensional case, which is our concern herein, each agent has 9 possibilities: East (E), Northeast (NE), North (N), Northwest (NW), West (W), Southwest (SW), South (S), Southeast (SE), and Stop (X). Each agent have a probability associated with each movement possibility. In the case of deterministic agents, only one possibility has probability one, and all others zero; their movement pattern does not change in time, and they are not affected by interactions with other agents. In the case of random agents, each direction has an associated probability (jointly total ling 1), represented as a vector that describes the agent's movement pattern.

The interactions between agents are represented by changes in their movement pattern. Each agent has a radius of influence, within which the interactions occur, including the possibility of an agent interacting with various agents at once (an n-ary interaction). At each interaction, only one agent changes their movement pattern, referred to as the reference agent.

In the case of n-ary interaction, initially the reference agent is identified, together with the neighbouring agents it will interact with.

Since the reference agent will in fact interact with the resulting vector obtained from the movement patterns of the agents in its neighbourhood, this resulting vector is first obtained and normalised (to ensure that its total movement probability remains equal to 1). Only then the actual interaction can occur.

As for the interaction itself, the idea is that the reference agent is 'attracted', so to speak, in the direction of the resulting movement vector of its neighbouring agents. This attraction is implemented in terms of a rotation of the vector representing the reference agent towards the resulting neighbouring vector, and the amount of rotation depends on the angle between the agents.

The actual interaction is governed by Shannon's entropy, associated to each interacting vector, defined as $H = -\sum_{i=1}^{N} p_i log(p_i)$ (Borda, 2011). In our case, $N = 9$ (nine possible movements), p_i is the probability associated with the direction i. The idea here is that entropy indicates the degree of randomness in the movement pattern of an agent.

In order to calculate the approximation angle the reference agent has to undergo as a result of an interaction, a function was defined that gives the angle of approximation, according to the entropies of the

agents involved in the interaction. The details are being omitted here, but the function definition followed the three general conditions below:

1. Movement limits: When an agent with maximum entropy interacts with another with minimum entropy, the agent with minimum entropy should not undergo any changes, while the other should undergo the maximum possible change.
2. Different random agents with minimum entropy should have a minimum (though not null) change in their movement pattern.
3. Agents with the same movement pattern should not change as the result of an interaction.

The 'vectorial' interaction scheme introduced above differs from the one described in (de Oliveira, 2010), and will be presented in detail elsewhere.

3 BacDRIMA and Biofilms

BacDRIMA is a biologically inspired multi-agent model, that relies on DRIMA for its basic dynamics. The reader should be aware that BacDRIMA should be regarded as an abstract model, since it neglects several details of its biological counterpart.

In BacDRIMA, two kind of agents are defined: the bacterial agents, and the energy or food source. Both of them are placed on a two-dimensional grid, presently with periodic boundary. The bacterial agents can move about, in a completely random way, while the food source is randomly placed on the grid, fixed. Each bacterial agent has an active metabolism that consumes energy at each iteration. If the internal energy goes down to 0 the agent dies, so that it must roam around the grid trying to find energy sources to fulfil its energy necessities.

Food sources do not release energy immediately; rather, they require a certain level of enzyme to be released on them, after being produced and secreted by normal bacteria. The enzymes degrade with time, i.e. after some number of iterations they will be destroyed. In order to release more energy, more enzyme must be produced. Each food source has a finite amount of energy to be released, and will eventually cease after some point.

In order to make enzymes, normal bacteria spend energy. Therefore, an energy balance has to be achieved in the system: in order to get energy, an agent must have some energy to produce enzymes, which in turn will be used to liberate energy from the food sources. Since the agents cannot control how much energy will be released by the food source, they must find a good strategy to survive, before their initial energy level becomes too low.

Both normal bacteria and cheaters can secrete another substance, the auto-inducer, that regulates enzyme production. Normal bacteria will produce enzymes only after the auto-inducer concentration becomes greater than a certain value. This is a simple model based on bacteria behaviour. In BacDRIMA, each agent measures its own auto-inducer concentration, as well as those of its neighbours. According to the total auto-inducer production in the neighbourhood of an agent, it may start the enzyme synthesis.

For the sake of energy release, a food source considers the global production of all agents in its neighbourhood, so that the actual release starts when a certain level of enzyme is locally present. But notice that this benefits all agents in its neighbourhood, not only those responsible for the enzyme production that triggered the energy liberation. This is a very important aspect of the model, because it makes it possible the definition of cheaters, i.e., agents that receive the released energy, without having contributed to the enzyme production.

Notice that the energy released by the food source depends on the enzyme production and on the number of agents in its neighbourhood. With higher enzyme levels, more energy is released, but more agents in the neighbourhood ends up sharing it. So, for some enzyme level, more neighbours entail less energy to be accumulated in the food source for each agent. Hence, a trade-off becomes apparent in the model. Since the total amount of energy that each food source can release is set at the start of an experiment, the number of agents around the food source is irrelevant. In fact, what changes is the rate of energy consumption, and not the total amount of energy of the system. So, the rate of energy consumption can be regarded as an efficiency measure of the system. Accordingly, the experiments that we run have shown various degrees of overall efficiency in the system.

Another key point of the model is the way the agents move, which is a slightly modified version from DRIMA, since a simple chemotaxis mechanism has been added. Accordingly, at each iteration, each agent measures its own energy level and, if the energy level keeping decreasing through a certain number of iterations in sequence, the agent starts searching for food in a completely random fashion (this is done by changing the agent's movement pattern to fully random). Nevertheless, if the internal energy of an agent decreases to 0, it eventually dies, being removed from the world.

Now, how does BacDRIMA's characterisation above relate to biofilm production? The way that agents interact in DRIMA entails the deterministic agents to have a huge influence in the system's dynamical stability. In fact, it is typically the case that if all deterministic agents have the same movement pattern, the system eventually converges to this movement pattern. Since all energy sources in BacDRIMA are modelled as deterministic agents (with probability 1 of staying at the same position) all other agents will tend to stop in the neighbourhood of the energy sources. And this tendency can be regarded as a metaphor to biofilm formation.

But since the chemotaxis mechanism may push away from this trend, a question arises about the stability degree of the existing biofilm, in terms of some of the variables involved. This question is the focus of the following section.

4 Experiments

Initially, a series of runs were performed (whose results are being omitted here), just to check whether the model would lead to basic coherent observations. After this successful stage, another set of experiments were run, with the following characteristics:

- Various grid sizes, with the same number of food sources (so as to test the influence of the density of energy sources in the system).
- Fixed population size but varied composition, in terms of different number of normal bacteria and cheaters (so as to test the influence of cheating in the system).
- Each combination of grid size and population composition, is run 10 times, from randomly generated initial conditions, i.e. random initial positions of food sources and bacteria.

Across all experiments, the following parameters are kept the same:

- Each bacteria initial energy: 1000 energy units.
- Each food source's initial energy: 10 times the bacterial value, i.e., 10000 energy units.
- Number of food sources: 5, randomly placed on grid at each execution.
- Enzyme production threshold (i.e., amount of auto-inducer units that must be made in order to activate enzyme production by each bacteria): 10.
- Energy cost to make each enzyme: 10 energy units.

- Amount of energy released by the food source, when enzyme production threshold is attained: 100 energy units.
- Enzyme production rate per bacteria: 1 molecule per iteration.
- Each execution has 2000 iterations.
- Auto-inducer release rate per agent: 1 molecule per iteration for normal bacteria, and 4 for cheaters.
- Waiting period of a bacteria until the chemotaxis mechanism is activated: 10 iterations.
- Energetic need of bacteria for their metabolism: 10 energy units.
- Dying-out criteria for all agents: when their energy level decrease to 0. However, while bacterial agents are removed from the grid, the food sources are not.
- Each enzyme has 20% probability to be degraded at each iteration.

Naturally, cheaters do not produce enzymes, but they produce auto-inducers. We could use the same value of auto-inducer production for both kind of agents, but it will be necessary to use a greater number of agents, making the simulation slow. Although it change the numeric value of simulations, it does not change the qualitative behaviour of the system. In order to test the effect of cheaters, experiments were made with varied percentage of cheaters in the population. All runs have 10 agents simulating bacteria, each one with a different proportion in the number of cheaters and normal bacteria (exception made for the situation with 10 cheaters, because without any bacteria producing enzymes, the system does not obtain energy).

4.1 Results

A key indicator for the successfulness of an organism is its life span. In the present case, in order to have an estimate of the life span of a population of agents, the individual life spans are accumulated, over the entire set of 10 experiments, and the average taken. This measure can be regarded as the total life span of the biofilm; hence, the higher the latter, the larger the sustainability degree of the biofilm.

By varying the proportion of cheaters in the population and the grid size, while preserving the same amount of food source, some aspects become apparent. The smaller the grid size, the larger the energy density available in the world; this is clearly the case for the 4×4 grid, as shown in Figure 1, that refers to normal bacteria alone. Notice that they live less, as the proportion of cheaters grows. Also, they can live relatively longer for small grid sizes than for larger ones. On a very large grid (100×100), their life span becomes the same as in the situation with no food sources, indicating they would be living just with the energy they started with.

Depending on the type of bacterial agent at issue (normal bacteria, cheaters, or both of them together), different kinds of observations can be made, as the grid size grows. So, for cheaters, the situation is the opposite to that of the normal bacteria, as shown in Figure 2. Cheaters cannot produce enzymes, so that, in order to survive for longer, they must find normal bacteria that secrete enzymes. Since in the experiments each agent has 1000 energy points at the beginning, but needs 10 points at each iteration to fulfil its own internal metabolism, a cheater can survive for 100 iterations, without any additional energy source (analogously, n cheaters have a total life span of $100n$). In Figure 2 this corresponds to the two lower curves (grid sizes larger than 25). For these sizes, cheaters simply do not take any advantage. However, for small grid sizes (and, consequently, larger energy densities) cheaters benefit much more than normal bacteria. But the benefits depend on the proportion of cheaters in the population. Notice in Figure 2 that the cheaters' total life span can grow until the proportion of 0.7; after this point, their total life span starts diminishing, as there are just too many cheaters for few normal bacteria, and the system collapses.

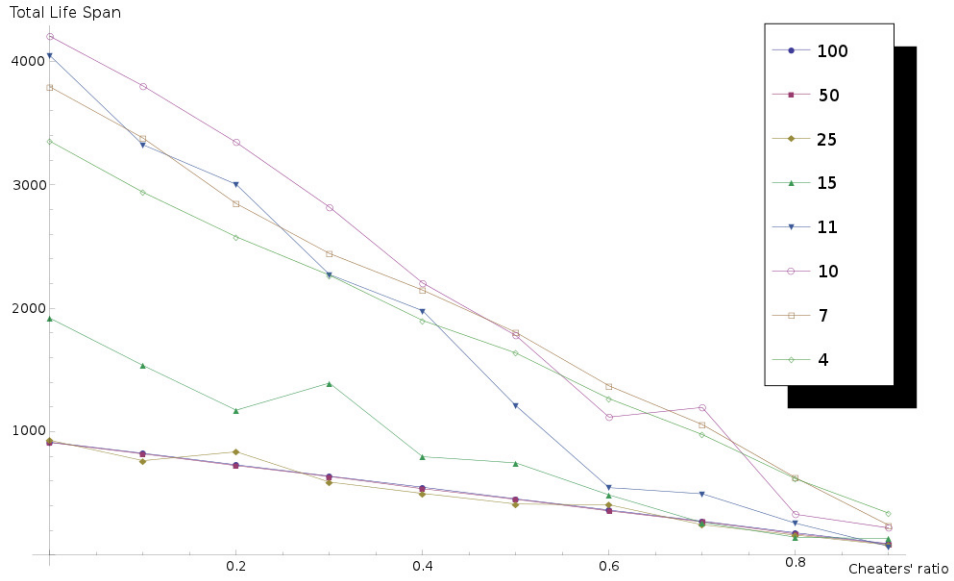

Fig. 1: Total life span for normal bacteria, with different grid sizes.

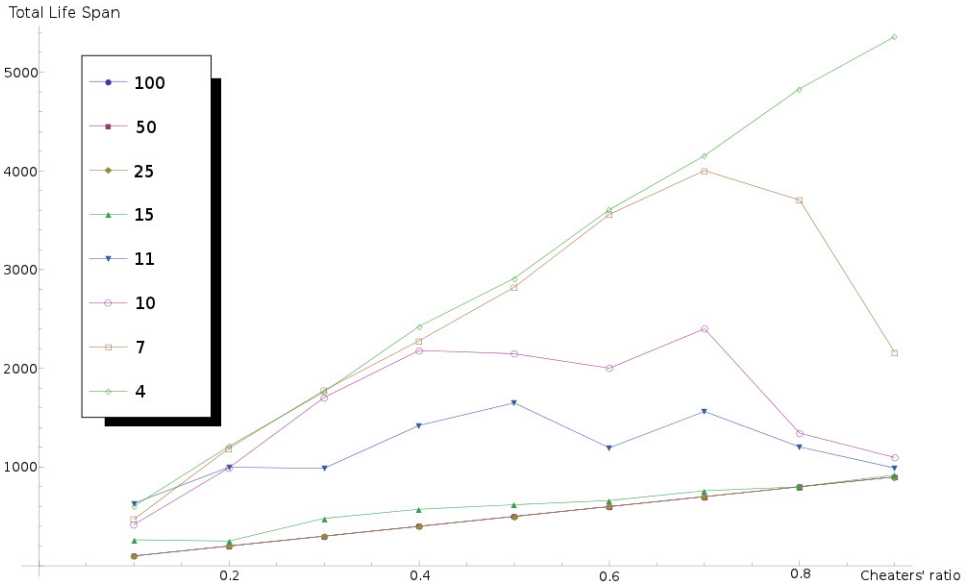

Fig. 2: Total life span for cheaters, with different grid sizes.

Figure 3 shows the situation for all bacterial agents, normal and cheaters, that is, a characterisation of the biofilm as a whole. For grid sizes smaller than 10×10, the system has always a tendency to grow their total life span, until the proportion of cheaters becomes 0.7. So, as a whole, cheaters can make the total life span grow, up to a critical point. For grid sizes larger than 25×25, the overall total life span becomes the same, so that the good influence of the cheaters to the biofilm sustainability can no longer be observed. In other words, the interesting good effect of the cheaters on the biofilm happens for high energy densities of the world.

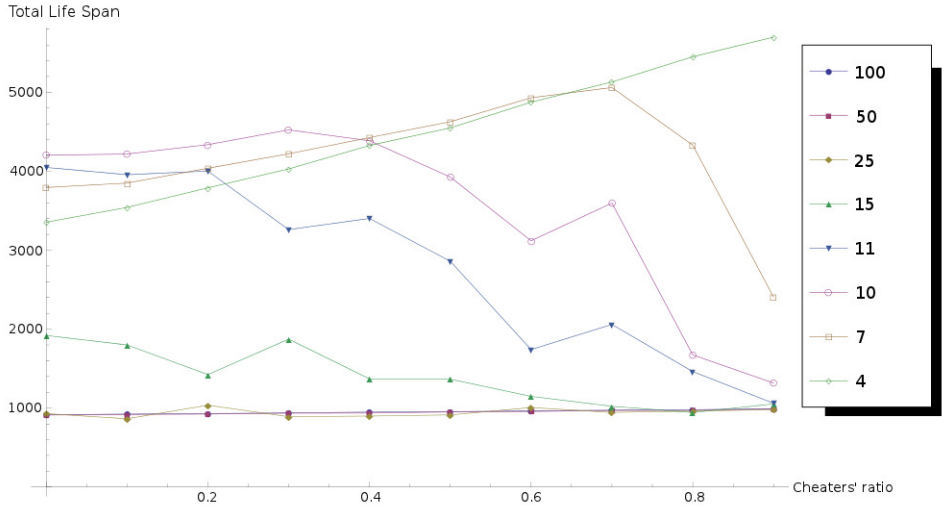

Fig. 3: Total life span for all agents, with different grid sizes.

Figure 4 refers to 10 simulations, with a 7×7 grid, without any food source. The overall system (i.e., the biofilm as a whole) has a small increase in its total life span, as the proportion of cheaters increases. The increase is a consequence of the fact that cheaters do not spend energy at enzyme production, but normal agents do, even though with unfruitful effects. But notice that the maximum life span in all three cases depicted in the figure falls below 1000 iterations, which is the maximum life span of the agents in the situation where they would rely only upon their initial energy levels, without any energy consumption (due to enzyme production).

Figure 5 depicts two plots of the total internal energy of all agents of the system on a 7×7 grid. Each time an agent obtains energy from a food source, its internal energy increases. But, at each iteration, each agent spends energy with its own metabolism, and on enzyme production. The total energy of the system is the sum of the internal energy of all agents. The peak in the solid line plot of Figure 5 corresponds to the moment at which most agents are getting the largest amount of energy from all sources.

Notice that in the solid line of Figure 5, a peak occurs for 125 iterations. And a similar peak was also observed for an ensemble of 60 executions (with the very tight standard deviation of less than 10), with varying proportions of cheaters, up to 60%. For progressively larger proportions, the peak gets displaced more and more to the left-hand side, eventually reaching the situation depicted in the dashed

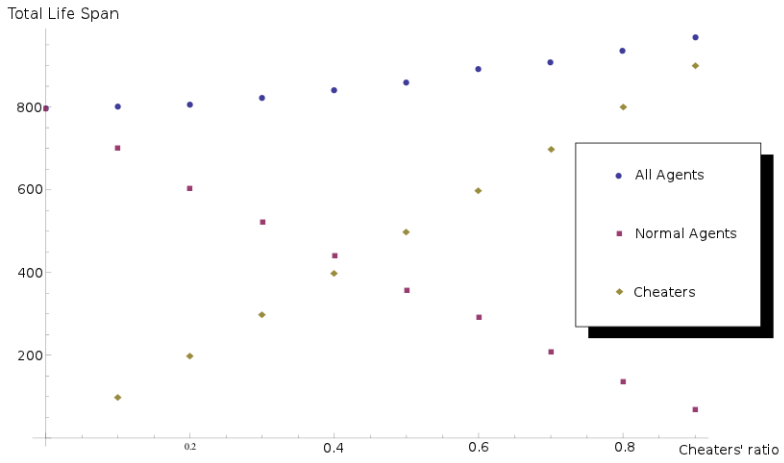

Fig. 4: Total life span for a system without food, grid size 7×7, with different agent types.

line, that corresponds to 90% of cheaters. The intensity of the peak becomes smaller as the concentration of cheaters increases; so, in the case displayed in the dashed line, the maximum value is the very first point, indicates that the energy of the system only gets smaller at each iteration. This dynamics is a consequence of the energy balance of the system. So, with very few (or no) cheaters, normal agents can get more energy from the food sources, therefore living longer. Consequently, they are able to produce more enzymes which, in turn, entail they can get more energy, and the cycle restarts. When the proportion of cheaters becomes higher than 60%, the normal agents tend to live less, thus producing less enzymes, therefore leading the peaks to happen earlier and, since the system has produced less energy, the peaks are progressively smaller.

5 Concluding remarks

A cellular multi-agent model is used to address the problem of bacterial biofilm sustainability. In spite of its biological motivation, this work can also be clearly regarded as aligned with artificial life type efforts (Langton, 1997). The study is a direct application of the current status of the BacDRIMA model, which is aimed at the possibility of addressing a number of issues in the dynamics of formation and sustainability of bacterial biofilm, from the perspective of a cellular, multi-agent system. Key in the present study is the premise that the biofilm formation is a direct consequence of the inherent dynamics of DRIMA, on which the model is implemented. Aspects of the present conception and implementation of DRIMA are being omitted here.

Some quantitative characterisation to the experiments was given, according to the initial world configuration, its population life span and the energy levels of the system, which allowed for explanations of some qualitative observations. The latter clarified the view that biofilm sustainability depends on a balance between the apparently conflicting roles of normal bacterial agents and cheaters.

Indeed, on a certain proportion of those agents in the system there is a degree of cooperation among them, so as to support the biofilm sustainability as a whole. Depending on the grid size and the proportions

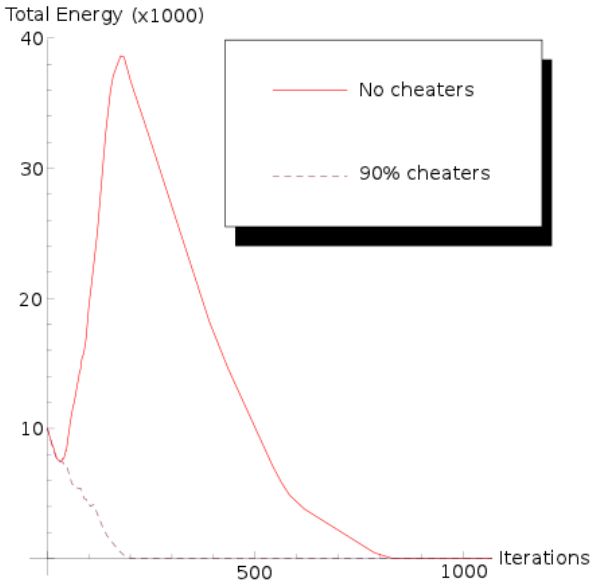

Fig. 5: Total internal energy of all agents in the system, on a 7×7 grid. Solid line: energy level at each iteration, with no cheaters. Dashed line: energy level for a single execution, with 90% of cheaters.

of bacterial agents, cheaters are not bad for the biofilm sustainability, as one might preconceive. This is a direct consequence of the fact that auto-inducers are important for the regulation of enzyme production of the normal bacterial agents. But if the proportion of cheaters becomes too high, the system collapses. This is in agreement with results in (Sandoz et al., 2007), (Travisano and Velicer, 2004) and (Allison, 2005). Consequently, in spite of its simplicity and high level of abstraction, BacDRIMA displays consistent outcomes.

Viweing the present results under the light of (West et al., 2006), the normal bacteria are "actors" (using that paper's notion) that must secrete enzymes to get energy, and they benefit from their own enzyme release; but cheaters (therein referred to as "recipients") benefit too. So, both types of organisms benefit from enzyme production, in clearly mutual benefit. The problem is that, as the proportion of cheaters grows, the same amount of energy must be shared by the entire population, thus entailing that the benefit of enzyme production becomes lower. At some point, normal bacteria become unable to get enough energy to survive, and eventually die out; but since cheaters cannot produce enzymes, they cannot get energy by they own, and eventually die out as well. At this point, the phenomenon dubbed in (West et al., 2006) as "tragedy of the commons" comes about: if all bacteria would cooperate and produce enzymes, all the population would benefit, but, with too many individuals not cooperating, the system breaks, and everyone dies. So, depending on the proportion of cheaters, three types of system can be observed: with low proportion, mutual benefit; with the selfish behaviour of cheaters, the benefits of enzyme production for normal bacteria declines, down to the point where the latter's behaviour becomes altruistic (as they spent more energy to produce enzymes than to get energy from food); finally, after the death of all normal bacteria, the tragedy of the commons becomes apparent, leading to the extinction of the population, in a

clearly spiteful behaviour.

Since BacDRIMA is yet an ongoing development, forthcoming improvements in the work include:

- Reproduction: The main focus of the current effort to expand the BacDRIMA model is the introduction of an asexual reproduction scheme for the agents, based upon their genome, which encodes the agent's enzyme production and auto-inducer production.
- Diffusion of chemical elements: Since in the present model the chemical elements (enzymes and auto-inducers) do not diffuse on the grid, the addition of some kind of diffusion would make the overall behaviour more natural.
- Addition of energy cost to auto-inducer production: This is meant to allow the study of the relation between the metabolism energy cost, enzyme production and auto-inducer production.

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