Modeling bacterial chemotaxis inside a cell

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***Abstract*— This paper describes a bacterial system that reproduces a population of bacteria that behave by simulating the internal reactions of each bacterial cell. The chemotaxis network of a cell is modulated by a hybrid approach that uses an algebraic model for the receptor clusters activity and an ordinary differential equation for the adaptation dynamics. The experiments are defined in order to simulate bacterial growth in an environment where nutrients are regularly added to it. The results show analysis of the motion obtained by some bacteria and their effects on the population behaviors generated by evolution. This evolution allows bacteria to have the ability to adapt themselves to better growth in the available food existed in its environment and to survive.**

Keywords: Virtual bacteria; Chemotaxis network simulation; Evolved behaviors.

I. INTRODUCTION

Simulation models in artificial life have focused metabolic, cellular systems and artificial chemistries. Artificial life research has also made progress in the study of adaptive behavior through computational models of artificial organisms.

Remarkably simple chemical reactions can perform movements toward some attractants, and are therefore capable of modulating the behavior of artificial organisms. The main goal of this work is to test the present knowledge about chemical reactions of a bacterial cell, in order to explain the evolution of organisms with a very simple development process (which is bacterial chemotaxis). We will also demonstrate whether a simple bacterial chemotaxis process of a cell can explain the evolution of more complicated behaviors such as bacterial population dynamics. One of the central questions of modern systems biology is the influence of microscopic parameters of a single cell on the behavior of a cell population. In terms of bacterial chemotaxis, this issue can be formulated as the influence of signaling network parameters on the spatiotemporal dynamics of bacteria that migrate towards chemical attractants and away from repellents. This chemotaxis is one of the simplest behaviors known, and it most likely is one of the first behaviors to have existed in the history of life on earth. Bacteria such as Escherichia coli, is a good candidate organism for chemotaxis modeling, thanks to the rich experimental information collected over years of extensive research. As many other bacteria, *E. coli* can migrate towards high concentrations of attractants and away from repellents [1].

Chemotaxis pathway of *E. Color* changes in attractant or repellent concentrations are sensed by a protein complex consisting of transmembrane receptors, which transduce information about the chemical environment in the cells. The chemoreceptors form complexes inside the cells with the kinase CheA (A) and CheW (W). These receptors are known as methyl-accepting chemotaxis proteins (or MCP, which contain the PAS sensor protein-domain, evolutionarily highly conserved), and are present on the bacterium membrane surface. These proteins act as chemoreceptors and bind with chemicals in the environment. The Autophosphorylation activity of CheA is inhibited by attractant binding and enhanced by repellent binding to receptors. The phosphoryl group is transferred from CheA to the response regulator CheY. The phosphorylated form of CheY interacts with the flagellar motors to induce tumbles. The rate of CheY dephosphorylation is greatly enhanced by CheZ (Z). The binding of attractants to the receptors decreases the rate of CheY phosphorylation and tumbling is reduced. Adaptation is provided by changes in the level of methylation of the chemoreceptors: methylation increases the rate of CheY phosphorylation. A pair of enzymes, CheR (R) and CheB (B), add and remove methyl (m) groups. To adapt to an attractant, methylation of the receptors must rise to overcome the suppression of receptor activity caused by the attractant binding. CheA enhances the demethylating activity of CheB [2-3]. This process is mediated by a protein network, as presented in figure 1.

In the bacterial chemotaxis process, when no attractant or repellant is present, or when the concentration of attractant or repellant is uniform, a bacterium such as E. coli tends to swim in a random walk, with periods of smooth swimming (or runs) interrupted by brief tumbles that changes the swimming direction. In response to attractant gradient, this random walk becomes biased and the bacteria tumble less frequently when encountering increasing concentrations of an attractant (i.e., they swim longer runs), and tumble more frequently when the attractant concentration is decreasing [1, 4].

The motivation for studying such small organisms lies in the belief that elucidating the mechanisms controlling their behavior will help in understanding more complex biological pathways and organisms. We provide here a comprehensive overview of the range of mathematical approaches used for modeling, within a single bacterium, chemotactic processes caused by changes to external gradients in its environment.

Phosphorylation cascade in a chemotaxis network was first simulated by Bray et al [5], using a system of ODEs, and [6], a later version of their model, added adaptation. Spiro et al [7] also incorporated attractant binding, methylation, and phosphorylation and CheYp-motor interaction into their model. A major advance in chemotaxis modeling was achieved in [8].

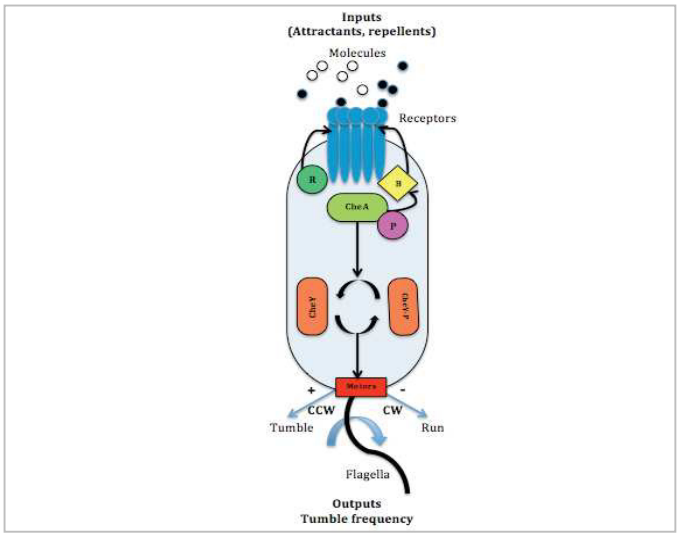

Figure 1. Chemotaxis pathway of E. coli.

Later, in [9], a theoretical analysis of a full ODE system with included phosphorylation cascade are performed.

As deterministic models, Morton-Firth and Bray suggested a fully stochastic model of chemotaxis pathway [10]. Some hybrid models of bacterial chemotaxis simulation were proposed. In [11] the authors describe the chemotactic excitation and adaptation with a simplified model of two ODEs. RapidCell [12] is a hybrid model of chemotactic Escherichia coli that combines the Monod-Wyman-Changeux signal processing by mixed chemoreceptor clusters, the adaptation dynamics described by ODEs, and a detailed model of cell tumbling. In [13], Bray et al used a molecularly detailed reaction kinetic model of the chemotaxis pathway in Escherichia coli that simulates the responses of bacteria to two-dimensional gradients of attractants. Other approaches used their individual model of bacterial chemotaxis to study population behaviors.

Here, we present a simulation of the bacteria chemotaxis network. The chemotactic Escherichia coli bacterium model describes the signal processing by mixed chemoreceptor clusters (MWC 'Monod-Wyman-Changeux signal processing' model), which is a rapid-equilibrium (algebraic) model, adaptation through methylation simulated by ordinary differential equations (ODEs), and the running and tumbling of a cell with a flagella motor [12].

The metabolism of this bacterium is a set of chemical reactions that occur in the cell. These chemical reactions are designed digitally to perform different functions as 'split', 'mutation' and 'death'.

II. Bacterial Modelling

In this part, we aim to describe the proposed model of the bacteria Escherichia coli that combines a model of detailed chemotaxis simulation, a metabolic model, and a genetic process to simulate bacteria evolution in an artificial environment. The chemotactic response is driven by attractants, substances that the bacteria tend to move toward. Metabolism is affected by realizing some functions.

A. Bacterial Chemotaxis

The role of chemotaxis is not only to mobilize bacteria but also to allow them to detect chemical gradients with great sensitivity. The chemotaxis process consists of three stages: chemoreception, signaling, and adaptation [14].

Methyl accepting chemotaxis proteins (MCPs) are located along the cell surface. These proteins act as chemoreceptors and bind with chemicals in the environment. They are simulated in our model with a gene describing the capacity of a bacterium to better detect the nutrients sources. If a nutrient attractant is detected outside of the cell, through MCP, the level of production of protein CheA decreases because the receptors state shifts to the off state. It has been shown that the activity of the receptor cluster depends on the local ligand concentration and the methylation level according to the MWC (Monod-Wyman-Changeux signal processing) model [15-16]. CheA binds with phosphate in the cell (denoted CheA-P). And the phosphate group is transferred from the active CheA to the response regulator CheY. The concentration of CheY-P modulates the motor and its behavior makes the cell run or tumble.

1) MWC model: We applied the MWC model for a mixed receptor cluster [15, 16, 17]; were each receptor homodimer is described by a two-state model. The inactive state of a receptor has a higher affinity to the attractant than the active state. The entire complex exists with all of its receptor homodimers either active or inactive.

The probability A that receptor cluster is active is dependent on ligand concentration and the methylation state of the receptors.

$$A = 1/(1+e^{F}) \quad \text{.....(1)}$$

Where $F=F^{on} - F^{off}$, and where $F^{on/off}$ is the free energy of the cluster to be on/off as a whole. Hence, the average activity per receptor in the cluster is A. The total free-energy difference in the mean-field approximation is $F=n_r f_r(m)$, which is just the sum of the individual free-energy differences between the receptor 'on' and 'off' states:

$$f_r(m) = f_r^{on} - f_r^{off} = \varepsilon_r(m) + \log\left[\frac{1+\frac{[S]}{K_r^{on}}}{1+\frac{[S]}{K_r^{off}}}\right] \quad \text{.....(2)}$$

Where [S] is the ligand concentration, and $K_r^{on/off}$ is, the dissociation constant for the ligand in the 'on' and 'off' states, respectively. The methylation state of the receptor enters via the 'offset energy' $\varepsilon_r(m)$.

2) Adaptation model: Adaptation is modeled according to the mean-field approximation of the assistance-neighborhood (AN) model [15, 18]. Adaptation in chemotaxis is mediated by two enzymes, methyltransferase CheR and methylesterase CheB. It is assuming that the demethylating enzyme CheB works only on active receptors and that the methylating enzyme CheR works only on inactive receptors within the AN.

Each bound CheR adds methyl groups at a rate a(1-A), and each bound CheB removes methyl groups at a rate bA. It is assumed that both enzymes work at saturation:

$$dm/dt = a(1-A)[CheR] - bA[CheB] \text{.....(3)}$$

The average methylation level evolves in time as:

$$m(t+\Delta t) = m(t) + kV\Delta t \text{.....(4)}$$

The parameter k indicates the adaptation rate relative to the wild type adaptation rate V that is the rate of receptor methylation (see equation 3) [12].

3) Kinase activity: Both ligand binding and receptor methylation affect the activity of CheA. For example, the increase of an attractant inhibits CheA activity, but subsequently methylates a specific receptor. CheA kinase activity [12] is calculated as:

$$CheA = CheA_{tot} AK_A / (AK_A + K_Y CheY_{tot}) \text{.....(5)}$$

where A is the probability that receptor cluster is active, $CheY_{tot}$ is the total CheY concentration, K_A=5 and K_Y=100 are the rate constants according to [12].

4) CheY phosphorylation: The concentration of CheYp is obtained as a function of active CheA from the steady-state equation [19].

$$CheY = CheY_{tot} K_Y A / (K_Y CheA + K_Z CheZ + g_y) \text{...(6)}$$

Where, $CheY_{tot}$ is the total CheY concentration, CheZ is the total CheZ concentration, CheA is the active [CheA], and K_y=100μM-1s-1, K_Z = 30/[CheZ]s-1, Y = 0.1 are the rate constants according to [19, 20, 21].

Receptor modification increases CheA activity and decreases sensitivity to attractants.

5) The CCW motor bias: The CCW motor bias depends on CheYp concentration in the following form [22, 23].

$$mb = \frac{mb_0}{CheY(1-mb_0) + mb_0} \text{.....(7)}$$

where, mb_0 is the steady-state motor bias.

B. Bacterial Metabolism

The metabolism is responsible for essential cycles of growth, development and reproduction. Genes and movement of a bacterium affect the majority of these cycles. In this model, every bacterium is represented by a genome from which it extracts its basic properties describing how it moves, gains energy, and expels toxins. These properties are updated in the genome at each time step, and mutation is applied after each "split" operation. The absorption of nutrient may invoke the production of a matter, (but it is not applied here). Each bacterium must survive while maintaining its energy level, which is calculated from its metabolism. Energy is accumulated by the absorption of nutrients from the environment and is decreased by the cost of movement; this cost depends on tumble frequency. This metabolic model encourages bacteria to stabilize their energy consumption in order to reach splitting threshold. Upon reaching its splitting threshold, the bacteria split into two daughter cells. The amount of energy in the bacterium is exposed to various changes during its lifespan; the following table lists the various modifications applied to the metabolism of a bacterium. First, the energy of each bacterium at birth is E_0. The energy level of each bacterium is then increased by E, which is the rate of energy gained from the absorbed nutrient, and decreased by -T, -F, -S, or -P; which are, the toxin consumption rate, and the costs of movement, and splitting, respectively.

C. Genetic representation

In the bacterial chemotaxis, there is a processing system of moderate complexity within the cell, triggered by its inputs and producing an output response. In *E.Coli* bacterium, this response corresponds to a change in the flagella rotation. The bacterial chemotaxis shows properties of receptor function, adaptation, memory and motor bias.

To control these properties in order to simulate bacterial population behaviors, we use a genome that encodes the activities of each level in the chemotaxis network. By updating some of its parameters, we can control the response of a bacterium and evolve its behaviors in a virtual environment.

D. Mutation and split

When biological life-forms (such as bacteria) clone themselves asexually, the clones are not exact copies of their parents [24]. The biological 'copy operation' does not work perfectly. Biology would not be improved by a perfect copy operation. Imperfect copying in biology causes the mutations and novelty that allow evolution to happen. In our work, an individual of the evolved population of bacteria will be divided; once a bacterium manages to accumulate enough energy to reach the division state, it divides immediately into two identical daughter cells, except that, the new bacterium copy will be mutated, in order to enable bacteria to evolve. This ensures that the parent's genetic material is preserved, and that simultaneously, new genetic material is introduced in the population. A small probability pm of mutation is proposed to be applied to the genome, by adding noise to a selected gene. It must be emphasized at this point that, after the division process, the amount of energy of the parent's cell will be distributed equally between the two copies. This will guarantee that the parent cell continues to exist, and it can create many different offsprings during its lifetime and does not 'die' after division. In general, the survival probability of an individual is directly related to its relative effectiveness in the population.

III. EXPERIMENTAL SETUP

The experiments in this paper address the simulation of a bacterial system that reproduces a population of bacteria that behave from simulating the internal reaction of each bacterium cell. The model describes bacterial properties including MCP capacities, metabolism, cell division, and death. The environment of simulation is a two-dimensional space subdivided into discrete grid squares in which the bacteria exist as individual entities. This environment additionally to bacteria, it contains resources that are an important element of the simulation, as they provide the energy that is required to sustain life.

Figure 2. The bacterium's genome

The artificial bacteria are represented by their genomes as described above. The genetic materials of each bacterium consist of a set of reactions that transfers the inputs (i.e. detected molecules) to its outputs (i.e. tumble frequency). This reactions modeled by the ODEs (see section II) determines the behavior of the bacterium when subjected to different types of stimuli. The objective of the genetic algorithm is to modify the set of the concentration inside a cell in such a way that a desired behavior is obtained. The choice of the interval of MCP capacity is important in the overall behavior of the system. If it is chosen too small, the bacteria may not be able to detect sufficient energy to function, and may quickly become inactive. On the other hand, if it is chosen too large, the resources may be depleted very rapidly before the system has time to explore the environment and evolve new and interesting behavioral patterns (or capacities). The simulated environment is defined by a 200 by 150 grid, consisting of 30,000 sites. The initial population size is 10 bacteria, the initial nutrient count is 10 and their concentrations are 1000. The simulation ends when the population biomass reaches zero. The most important parameters are listed in Table 1. The parameters presented at the top of this table are fixed over time while the others are variables.

IV. Experimental Results

In this section we present a collection of simulation results and some tests that demonstrate how the bacterial system that simulates a bacterium cell, can be used in the context of evolution to obtain the desired behavior, that is one that maximizes the lifespan and reproductive success of a bacterium. We have conducted our experiments with the same initial conditions that were carefully chosen (after many of trials). The runs are obtained with a set of randomized genotypes.

A typical simulation run of the bacterial system is illustrated in the figure 3, which shows six snapshots of the environment in different stages of the simulation. The followed graph presented in figure 4 shows paths realized by the initial 10 bacteria, they are very sensitive to initial conditions, especially in the case where the resources are present in the environment knowing that the genomes are randomly initialized. The simulation has to been repeated many times with different conditions, until the population contained bacteria that are sufficiently fit, as they evolve faster and utilize the resources more efficiently.

TABLE I. THE SIMULATION PARAMETERS

Parameters	Values	References	Parameters	Values	Ref
K_{on}^{a}	12	[10]	[CheB]	0.28	[26]
K_{off}^{a}	1.7	[10]	[CheYtot]	9.7	[26]
K_{on}^{s}	106	[15]	[CheR]	0.16	[26]
K_{off}^{s}	100	[15]	a	0.0625	[12]
n_a	6	[15]	b	0.0714	[12]
n_s	12	[15]	E0	25	TW*
A	1/3	[15]	ST**	50	TW*
mb_0	0.65	[21]	Energy	10	TW*
P_m	0.1	TW*	A	[0-0164]	[12]
CheA	[0-1]	[12]	meth	[1.9-2.8]	[12]
Motor Bias	[0-1]	[12]	CheYP	[0-2.6]	[12]

*This Work **Splitting Threshold

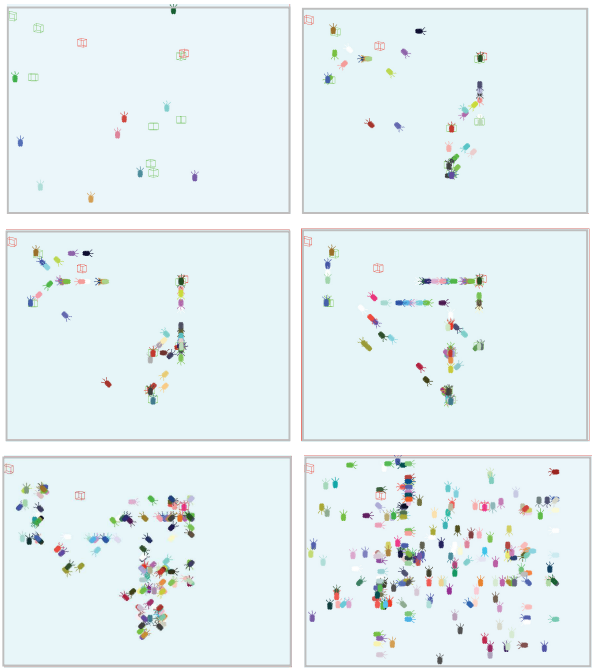

Figure 3. Snapshots of the bacterial system at different stages of the experiment.

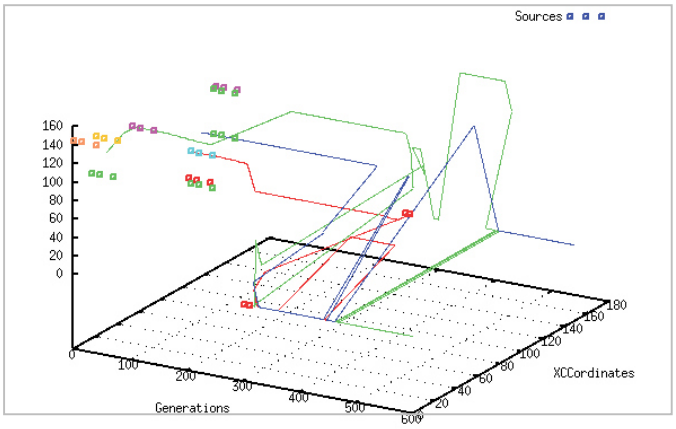

Figure 4. Path realized by the initial 10 bacteria in 2D space for the first 300 cycles.

The figure 4 shows the path of (x,y) coordinates of the 10 initial bacteria bacteria borrowed from the simulation in the first 300 generations, when a bacterium follow nutrients existed in the environment.

Figure 5 presents the 'Growth rate' runs, where all experiments (i.e. runs) show a fast population increase in the twenty first simulation cycles (or generations). This increase lead to a population reproduction (or split), and then the population stays relatively constant for about 200 generations. From this level to the generation 300, the population decreases rapidly. This is a consequence of two facts. First a high number of bacteria die due to the depletion of food resources. Secondly, the speed of decrease is due to the bad MCP and toxin avoidance capacities. From generation 300, and every 300 cycles, the growth rate is often increased according to the capacities defined in the genome of each bacterium, which are

also advanced. The number of species varies great during an experiment, which means that bacteria frequently split and die over time. It is important simply not relate this to food in the environment and to their own biomass, it is rather related to MCP and toxin avoidance capacities that are evolved after each split (i.e. over time).

In the simulation runs, where the sources of nutrient are regularly added each 300 generations, all the bacteria change oscillation degrees and move toward new detected sources with MCP and toxin avoidance capacities corresponding to each bacterium. This costs them energy, as explained above in the metabolism model.

In Figure 6 we observe that the metabolizable resources are consumed, while the population's collective energy decreases in the beginning of the run (as new cells are created), at the division process's maximum speed, division process the biomass is exponentially decreased. Knowing that all sources are depleted. Within thirty generations, while many bacteria die because they did not have enough energy for movement, but fortunately not all the population, as, all simulation will stop in this case (but this has been tested before choosing the environment parameters).

In iteration 300, when new nutrients resources are added to the environment, the bacteria consume nutrients, split, and when no more nutrient are present in the environment, their biomass decreases again but avidly than before. This means that the bacteria obtained after thousand of time steps are more stabilized and more effective in their use of energy. This effectiveness is due to the evolved capacities of detection (MCP capacities) of nutrients.

The figure 7 shows the path of (x,y) coordinates of some bacteria borrowed from the simulation, when a bacterium applies long runs and short tumbles in the presence of nutrient sources (as response to the nutrient). A tumble presents a reorientation of the bacterium, which is seen in the figure as the angles formed between two runs. The 'random walk' is a movement applied by bacteria that is presented with short runs and many tumbles, as observed in the graph when no nutrient sources are present from the twentieth generations. Some bacteria don't move because, they are not fit enough to exploit the available resources (they are not present in the graph).

V. DISCUSSION

The results show that a single simulation model of single-celled creatures and biological mechanisms and simple chemical reactions allow us to model more complicated behaviors of a population of these bacteria. Therefore, the results have managed to answer the question posed at the beginning of this paper. Results show that the growth rate and biomass of the whole population in all runs tend to evolve over time; some are increased and others are stabilized.

We summarize that the growth rate continues to increase for several hundred epochs, until the resources are eventually present in the environment, and the population's collective lifespan is ameliorated because the evolved bacteria consume less energy with their optimal capacities and gather more sources.

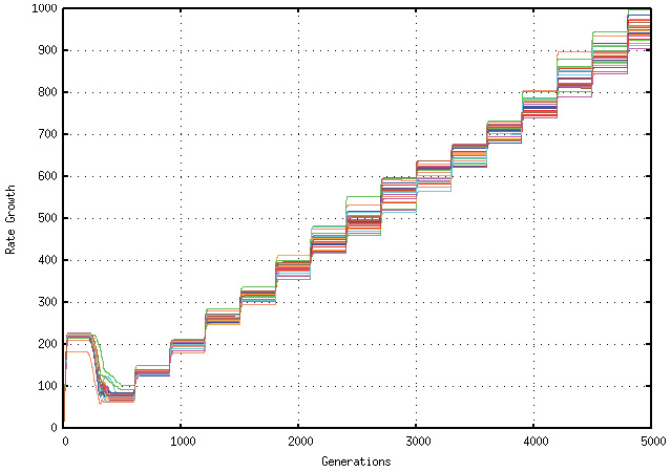

Figure 5. The 'Growth rate' runs, which we have replicated 30 times with quantitatively the same results, representing the optimal values of the whole of the bacteria for 5000 generations.

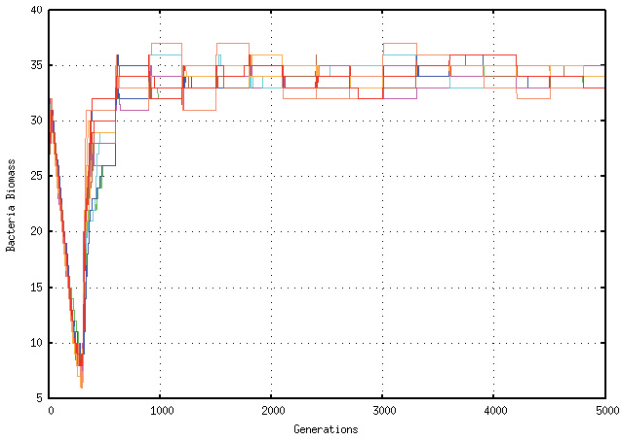

Figure 6. The 'Biomass' of the evolved population of bacteria for 30 runs at 5000 generations.

The evolution leads to a population composed of individuals well adapted to their environment. When environmental difficulties appear (food consumed, toxins present), results show a decrease in population number. The behavior of the system is thus to favor emergence of best capacities to detect food and avoid toxins, therefore to avoid death and to better reproduce and to survive longer. Concerning the chemoaxis network, when bacteria are moving, consuming and splitting? The different genes of a bacterium vary in intervals as presented in table 1. In the figure 8 we present the two states of a bacterium; an inactive state when bacteria are consuming sources (from generation 0 to 50) and an active state when bacteria are applying a 'random walk'.

VI. CONCLUSUION AND FUTURE WORK

Our model has been designed to simulate growth and behavior of bacterial system; it controls a group of bacteria cells at each time step.

To analyze the obtained behaviors, we present data that characterizes bacteria positions in space, biomass, and, state in the cellular reproduction cycle.

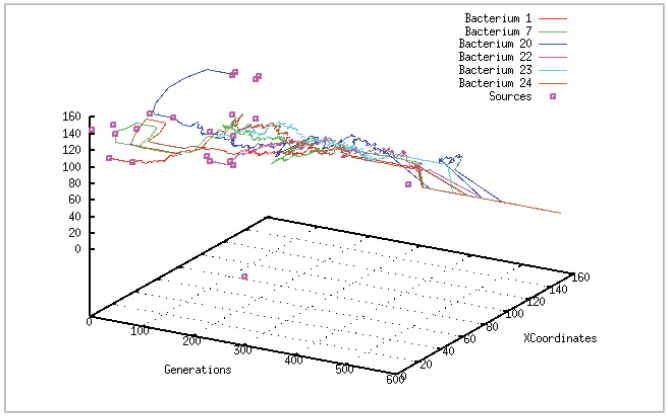

Figure 7. Path realized by some bacteria in 2D space for the first 600 cycles.

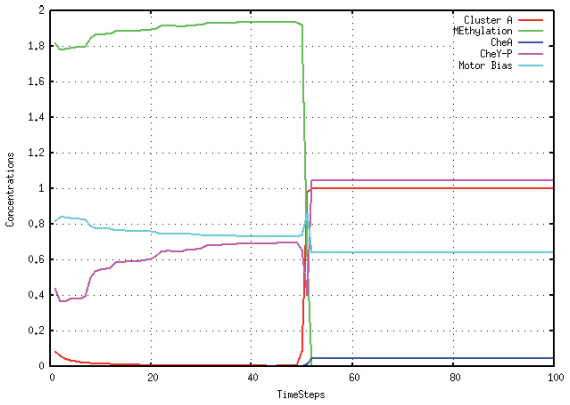

Figure 8. Graph of variations in concentrations of proteins and enzymes used inside bacteria during the chemotaxis process.

These results demonstrate that bacteria are still able to evolve through mutation and adapt rapidly according to their changing environment. It was shown that a simple chemotaxis network of simulated bacteria could result in a set of highly fit bacteria with strong MCP capacities that can be used to evolve more interesting behaviors in bacteria colonies. In future work, we aim to improve the effect of the chemotaxis network to obtain more powerful bacteria that can emerge as new species which behaves differently from others, via the concept of colonies, and also to test this model on different environmental conditions and various changes. Finally, we plan to include this detailed system of simulating bacterial chemotaxis in an ecosystem with creatures of different natures such as foragers [27].

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