Comparison between agent-based modeling and equation-based modeling to study Chemotaxis phenomenon in a bacterium

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Abstract

The single-cell biology study and the behaviors of the cell in an environment have been an interesting topic of research for years. Chemotaxis phenomenon, in particular, has been studied through different approximations such as equation-based modeling (EBM) given a set of differential equations or agent-based modeling simulation (ABMS). Both of the modeling perspectives give different important results to evaluate the model, but those results are not usually considered as a complementary set of information. This research implements an adaptation from the hybrid model "RapidCell" (Nikita Vladimirov & Sourjik, 2008) and the appropriateness of using both of the modeling perspectives is evaluated to gain insight into the overall value of modeling different aspects of cellular behavior using ABMS and EBM.

Keywords: agent-based modeling, equation-based modeling, Chemotaxis, E. coli, hybrid model

1 Introduction

The survival of many organisms, from the largest mammals to microscopic bacteria, is subject to their ability to move within a certain complex environment through the detection, integration, and processing of a set of signals given for whereabouts conditions (Hillen & Painter, 2009). Moving is a crucial aspect of behavior, such as searching for food sources, avoiding predators or bad conditions, and attracting mates. The movement of an organism for the response to external signals in reception to chemical gradients is known as Chemotaxis, a fundamental process in both unicellular and multicellular organisms (Newman & Grima1, 2004).

Extensive research has been carried out for understanding mechanistic and signaling processes regulating in bacteria, specifically *E.coli* (Hillen & Painter, 2009). Even though the biochemical and physiological bases are less well understood, is well known that the Chemotaxis phenomenon is crucial in the navigation of some multicellular organisms, for example, insects like the fruit fly *Drosophila melanogaster* navigate up gradients of attractive odors during food location, and male moths follow pheromone gradients from female during mate location (Hillen & Painter, 2009).

Behavioral variability of molecular interactions of a cell view as an individual could be the result of the stochastic nature of molecular interactions which consequently causes even genetically identical cells could have a different behavior (Emonet *et al.*, 2005). This suggests that stochastic factors play a significant role in single-cell-behavior. The dynamic and stochastic trait besides cell behavior makes Chemotaxis phenomenon to be modeled generally by two common approaches (Guo *et al.*, 2008), Agent-Based Modeling Simulation (ABMS) and Equation-Based Modeling (EBM).

EBM is based on Differential Equations (DE) which include Ordinary Differential Equations (ODE) or Partial Differential Equations (PDE). Theoretical and mathematical modeling of Chemotaxis dates to pioneering works of Patlak in the 1950s and Keller and Segel in the 1970 (Hillen & Painter, 2009), which main property is including spatial pattern formation considering chemical signal as an auto-attractant (Hillen & Painter, 2009). That means that cells produce and migrate up gradients of the chemical signal, giving a treat to biological cells as populations (quantities) and using an approach that disregards the cell's identity(Guo *et al.*, 2008).

ABMS approach allows representing each cell as a unique individual, considering heterogeneous cell behavior that takes place at an individual level, with different state variables and interactions. ABMS has proven to be a powerful tool to model complex biological behavior of each cell type over the variety of environmental topologies and conditions (Guo *et al.*, 2008). Although ABMS captures more realistic behavior, it faces issues related to computation intractability and model

scalability. The main advantage of using ABMS for modeling biological cells biological is the ability to including a wide range of possible states and nonlinearly interacting behaviors (Guo *et al.*, 2008). ABMS and EBM have been widely used to model different aspects of biological phenomenons. However, there is little evidence about how both approaches can be complemented each other from its perspective of the analysis and understanding of the Chemotaxis phenomenon. The main contribution from this paper is an analysis of the connection between different modeling perspectives which consider different modeling assumptions and finally ended no just contributing to a certain field but ended gaining insight with each other. The main analysis of some different aspects such as saturation with different gradients, repercussions of different gradients, and effects of changes in certain enzymes will be considered too in order to reach the main purpose. The process of Chemotaxis occurs generally when extracellular signals are detected by transmembrane receptors which through some intra-cellular mechanisms control the cell's movement in a given substance. This phenomenon is necessary to live as it is known since allows for moving the cell itself, looking for nutrients, and avoiding bad substances. This process is indispensable in events as fertilization (the joining together of sperm and ovum), immune system cell action, or bacteria flagellum movement. To model this phenomenon is important for understanding different aspects of the Chemotaxis, particularly to study the causes and effects of observed cellular behavior (Tindall *et al.*, 2008). It allows the prediction of bacterial behavior in natural environments (Tindall *et al.*, 2008). Also, it allows experimenting by using and to understand from different mathematical and modeling perspectives the microbiological world behavior.

The main weakness of some studies from an agent-based perspective is the failure in modeling cellular behavior, like the information exchange between cells or population growth mechanics. Equation-based modeling otherwise is not able to model individual behavior at all, instead of that, considers quantities contributing to the model dynamic behavior however, sometimes fails to acknowledge the significance of homogeneity among individuals (Van Dyke Parunak *et al.*, 1998). This is supported for what Klimenko *et al.* (2016) writes, where is said that one of the fundamental challenges in today's Chemotaxis modeling is to provide an appropriate description on the macroscale population level while accounting for variation in specific characteristics amongst individual cells.

This model might represent an important tool for those who are studying biological phenomenons to model and experiment with different strategies which allows them to a better understanding of them. Furthermore, it allows us to compare and contrast powerful modeling tools which not only lets approaching the advantages of everyone but it gives the best of each modeling perspective and provides a better understanding of this type of problem. As a research practice, this project is important because it allows us to obtain research skills modeling skills and modeling of real-world problems.

To develop this research confirms the applicability of the four fundamental bases of Mathematical engineering: Statistics, scientific computation, simulation, and theoretical maths, integrating all of those sources and building the mathematical engineering main profile. Statistics are used to analyze the data results from the model, scientific computation is used in the computational implementations of the model, simulation (and modeling) is used in the experiments improve and scenarios understanding, and finally, theoretical maths is used to the development of EBM.

This paper is organized as follows: First of all, a state of the art of different modeling perspectives will be exposed, after that a section with the methodology implemented will be introduced to get into the result and finish with some conclusions.

2 State of the art

Mathematical modeling applications to understanding the behavior of bacteria under the Chemotaxis phenomenon have been developed over the years. To compile all the needy sources for the research a literature review was made.
As a first instance, a search was carried out on Wednesday, August 12, 2020, with the string "(" chemotaxis "and (agent-based or agent based) and (modeling or modeling or simulation))", through the database of bibliographic data "Web of Science". The search threw 142 results which were filtered through a keyword following the next regular expressions "agent based" and "agent-based". Making such a search on both the title and the abstract. When this filter was carried out, a total of 51 articles were selected, which were subjected to a detailed review through the reading of the abstract, removing the repetitions. This reading leads to a priority classification, high, low, or medium, which was awarded according to the subjective proximity of the abstract with the general objective, the justification, and the output of the work that is being carried out. The number of high priority articles selected is 25, medium priority is 11 and low priority is 14.
This analysis shows as one of the papers closest to the research purpose the one developed by Gavagnin & Yates (2018). In this research, the different approaches, their advantages, disadvantages, and how they can be integrated into each other are discussed. Although the paper integrates different techniques and makes tests to compare the different EBM and ABMS approaches, the phenomenon of chemotaxis is not modeled and although it considers cells as individuals, since there is no direct interaction of these with the environment and so the receptors with the molecule, the possibility of obtaining other types of results is limited. The latter is a direct consequence of the fact that the proposed ABMS approaches are all based on stochastic processes (Markov chains). The paper mentions cellular interaction phenomena, such as adhesion-repulsion and cell growth. The paper offers possible conclusions of the interaction between the different modeling mechanics. The mentioned phenomena of cellular interaction can be implemented in other models. Another big contribution from the research by Gavagnin & Yates (2018) is represented by the figure [1] where the advantages and disadvantages of a Discrete/stochastic and continuum/deterministic approach are discussed.

	Advantages	**Disadvantages**
Discrete/ stochastic	Detailed structure and explicit implementation	High computational cost
	Direct connection to experimental data	Multiple simulations required
	Incorporation of randomness	Relatively inaccessible to mathematical analysis
Continuum/ deterministic	Fast to simulate	Lack of fine detailed structure
	Amenable to mathematical analysis	Difficult to link experimental data
	Suitable for systems of large numbers of cells	Ignore the effects of randomness

Figure 1: Comparison approach table (Gavagnin & Yates, 2018)

Another perspective of ABM modeling is the one gave by Emonet *et al.* (2005), which describes an agent-based model that studies intracellular stochastic behavior including the external behavior of different cells, modeling each one of them as an individual agent with its action against the phenomenon of chemotaxis, motor, and scourge. The model is applied in a 3D environment. Emonet *et al.* (2005) simulated the behavior of *Escherichia coli*, which consider the basic behavior, external signals been converted into molecular intracellular information via a signal transduction network, where each flagellum rotates under the action of a rotatory motor. When most of the motors are rotating counterclockwise (CCW), the flagella form a bundle and the bacteria start swimming, but if most of the motors are rotating counterclockwise the bacterium tumbles erratically (Emonet *et al.*, 2005). As it was said intracellular information is been considered so that the internal concentration of signaling molecules (CheY-P) is the network output, which binds preferentially to the motor, and the CW bias of the flagellar motors, i.e. the fraction to time that a single motor spends rotating in the CW direction increases with the CheY-P concentration (Emonet *et al.*, 2005).
It is important to consider the architecture in which the model AgentCell by Emonet *et al.* (2005) is organized. The key aspects of management can be listed as follows:

- *Cells:* Basic agents whose basic attributes are position, orientation, volume, and motion. Each instance of *Cell* is independent. The ChemotaxisCell class extends Cell with attributes necessary to perform chemotaxis: Receptors, Network, Motor, Flagella. (Emonet *et al.*, 2005)

- *Receptors:* Which provides a method to read the concentration of ligand from the local environment.(Emonet *et al.*, 2005)

- *Motor:* Which keeps track of the binary state of the motors (CW or CCW) and provides a method to switch from one state to the other (Emonet *et al.*, 2005). It also declares an abstract step method to advance the state of the motor in time. The abstract class ThresholdMotor extends Motor with a time step method that switches the motor state from CCW to CW if a threshold condition is satisfied. The threshold condition is defined in subclasses: AveragedCheYpThresholdMotor defines the threshold using the recent history of the intracellular level of CheY-P. (Emonet *et al.*, 2005)

- *Flagella:* Changes in the states of the motors do not always mean changes in the swimming behavior of the cell. The abstract class Flagella handles this discrepancy. The subclasses of Flagella, TetheredFlagellum, and SwimmingFlagella, switch the state of the flagella according to the state of the motor (CW or CCW). (Emonet *et al.*, 2005)

- *Motion:* A package which controls the motions of a cell in the environment. Motion represents cell movements, like a run or a tumble.(Emonet *et al.*, 2005) Another instance, MotionStepper, calls the step routines of the different types of movement.

The algorithms described by Emonet *et al.* (2005) for Motor switch, receptor binding, flagella state, chemotaxis network, motion (run and tumble) result in a useful way to describe this type of behavior. Figure 2 shows the complete architecture of AgentCell:

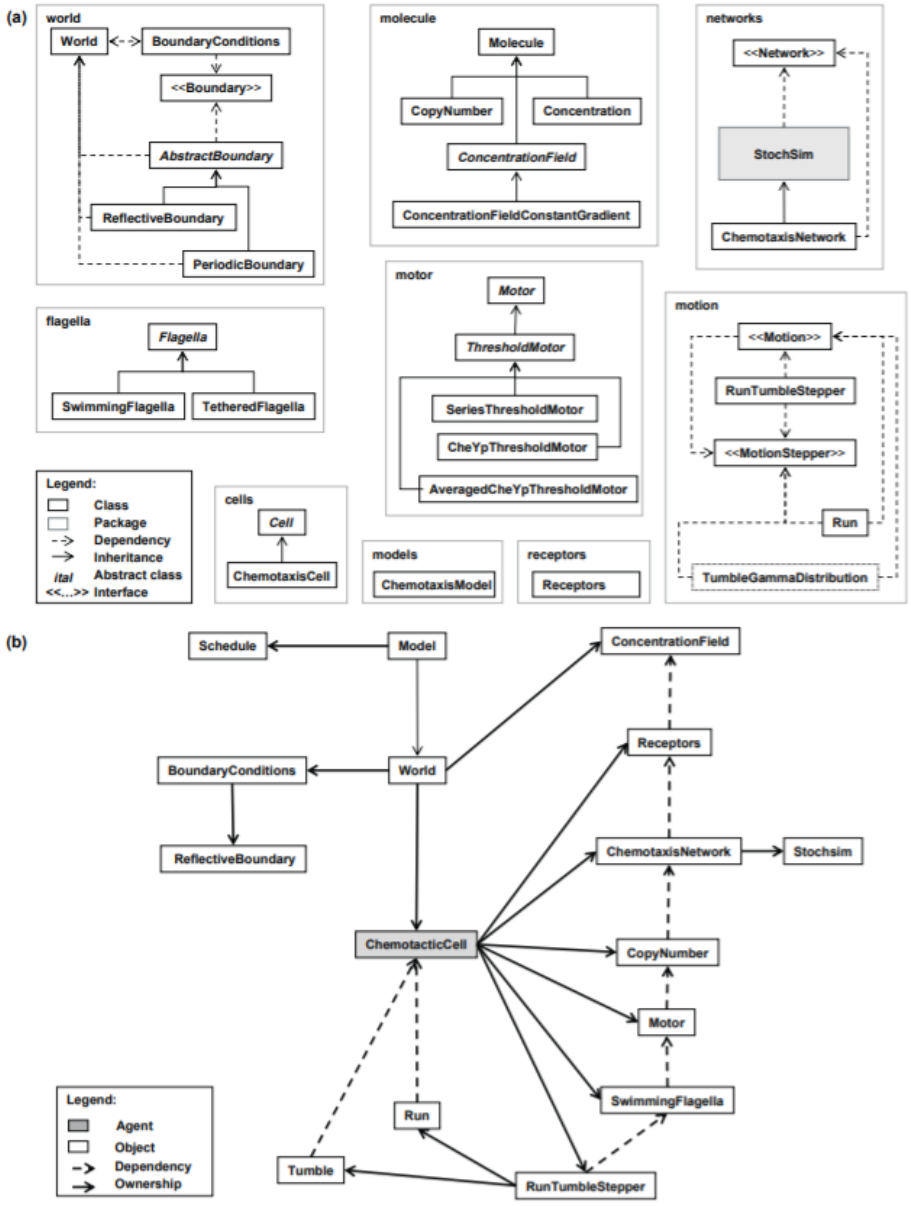

Figure 2: Architecture of AgentCell (Emonet *et al.*, 2005)

Models applied to cellular aggregation under the chemotaxis phenomenon have been already developed. THASNAA FATEHI & FIGGE (2010) implements a model where the cellular aggregation is induced under chemotaxis and phototaxis phenomenon, using an agent-based model to investigate it in response to cell-cell interactions. Cells can secrete soluble chemokines which are detected by other cells through specific receptors, which help to determine the motility of cells given a certain concentration gradient of chemokines. (THASNAA FATEHI & FIGGE, 2010). The model follows a process (Figure 3) and is developed in a bi-dimensional environment.

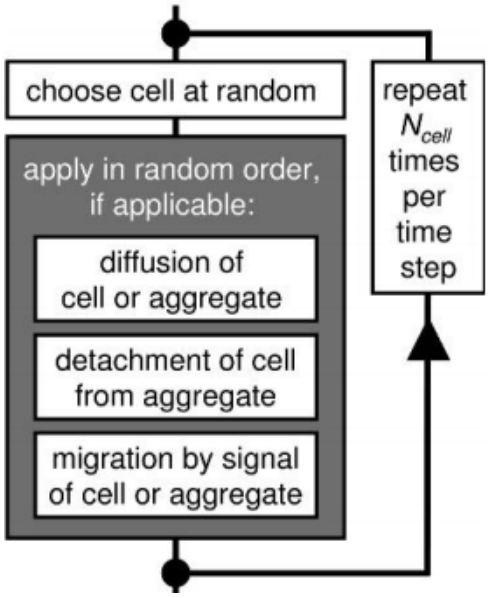

Figure 3: Flow diagram for model by THASNAA FATEHI & FIGGE (2010)

The literature on chemotaxis has highlighted for understanding the link between a single cell and population scales in differing ligand gradients. Matthew P. Edgington (2015) formulate an agent-based population model of *Escherichia coli*, which incorporates a signaling cascade at a single-cell scale, which has the purpose to gain insight into the link between the signaling cascade dynamics and the overall population response to differing chemoattractant gradients.
The algorithm which describes the behavior of the model given by Matthew P. Edgington (2015) is:

1. Calculate the ligand concentration (at the cell location).
2. Update the intracellular signaling pathway.
3. Calculate the flagellar rotational bias.
4. Simulate cell movement — straight swim (run) or turn and swim (tumble).
5. Return to 1.

A graphical summary of the algorithm is given by

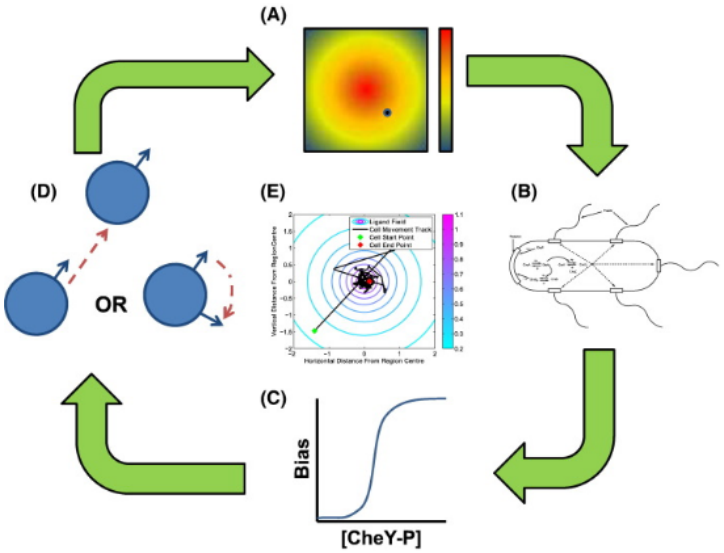

Figure 4: Cartoon diagram of the algorithm by Matthew P. Edgington (2015)

Where,

- A. Initial location for a simulated cell within a static ligand field
- B. Cells detect the external ligand concentration and responds via ODE model of intracellular pathway
- C. The rational bias of the simulated cells flagella is calculated and running or tumbling behavior is selected
- D. A new location is defined if the cell "runs" or a new direction of travel and new location is chose if the cell "tumbles".
- The new ligand concentration is calculated and the process repeated for the desired number of time steps,

It is important to know literature about flagellum movement and interaction/reaction over the Chemotaxis phenomenon in agent-based modeling. That is what Bray *et al.* (2007) improves, where a model based on differential equations of signaling reactions is developed to recognize the patterns and movement parameters of a bacterium to simulate its behavior to attraction gradients (Chemotaxis phenomenon). It is marked the importance of a visual interface to understand bacterium behavior and trajectory.
Approximations between two different perspectives are also improved by hybrid models. Guo *et al.* (2008) describes a hybrid agent-based approach for modeling microbiological systems, where an implementation based on differential equations is proposed inside an ABMS, experimenting with immune systems cells Chemotaxis behavior, finding certain patterns, and comparing them to laboratory experiments.
Another approach to model Chemotaxis Phenomenon has been developed by The Keller-Segel model of Chemotaxis, one of the pioneering works of Theoretical and mathematical modeling of Chemotaxis (Hillen & Painter, 2009), where the original form consists of four coupled reaction-advection-diffusion

equations, which can be reduced under quasi-steady-state assumptions to a model for two unknown functions u and v which denotes the cell (or organism) density and the concentration of the chemical signal respectively (Hillen & Painter, 2009).
Under this approach, some other variations have been developed, such as signal-dependent sensitivity models, density-dependent sensitivity models,non-local model, nonlinear-diffusion model, nonlinear signal kinetics model, nonlinear gradient model, and cell kinetics model (Hillen & Painter, 2009).
Many of the rupture points (lacks some of the mentioned articles) of these papers allows us to develop different things for this research, such as sensitivity, uncertainty, and robustness analysis, the joining of cellular behavior, population's cellular growth behavior, and visual interfaces for some experiments, as equal as a comparison between models and the way how they can integrate each other

3 Solution method / Methodology

To present a clear Methodology a ODD protocol (Overview, Design concepts, and Details) protocol (Railsback & Grimm, 2012) of the model was applied.

3.1 Overview, Design concepts, and Details

3.1.1 Purpose

The purpose of this model is to represent different cellular behavior of bacteria such as intracellular and extracellular behavior, run-and-tumble movement and macroscopic cellular aggregation and movement patterns in response to chemotaxis phenomenon been carried out by a substance or ligand to gain insight the value of modeling with and EBM support.

3.1.2 Entities, state, variables, and scales

- **Entities:**
  - *Bacteria:* Represented as individuals, which a certain behavior to interact with a gradient acting under a certain intracellular signaling pathway
- **State variables:**
  - *(X, Y) position*: Dynamic,discrete value
  - *Cell orientation*:Dynamic,discrete value
  - *CheA-P*:Dynamic,discrete value,proportion
  - *CheY-P*:Dynamic,discrete value, proportion
  - *Receptor methylation*: Dynamic,discrete value
  - *CCW motor bias*:Dynamic,discrete value
  - *Frequency of change for CCW to CW*:Dynamic,discrete value
  - *Number of motor CW*:Constant,discrete value
  - *Running or tumbling*:Dynamic, binary value
  - *Attractor sensed by cell*:Dynamic,discrete value

- **Scales:**
  - Model runs every 0.01 seconds time-setp. Due to that it is possible to measure the molecular noise in individual bacteria. Even thought some parts of the cell involve on every different timescales, which means when a cell execute one step, some sub-steps should be executed too. Another way to do this is via causal relationships between events, in order to implement a complex scheduling mechanic which represent better this behavior.
  - The model will be implemented in a 2D limited space grind.

3.1.3 Process overview and scheduling

The state variables are updated every 0.01 seconds, discrete-time. Model is keeping a global clock, updating the clock to the next event, and maintaining a sorted list of events. Each agent inserts its future events inside the scheduler's list of events. The model's final step in every time step is to move the cell. To do that, in every time step a list of events must happen (even if they are sub-steps time scale or causal relationship between events), those events are:

- To manage the activity of the receptor cluster, which depend on the local ligand
- To calculate the ligand concentration given by receptors in every cell.
- Update the intracellular signaling pathway
- To calculate the flagellar rotational bias
- Methylation and demethylation kinetics
- Motor switching
- Cell movement -straight swim (run) or turn and swim(tumble)-

Those actions must be executed in that order, just because this is the order described by experimental behavior and is usually how literature model this phenomenon

3.1.4 Design concepts

- **Basic principles:**
  This model represents the Chemotaxis phenomenon, which is a process where organisms can move toward or away from certain chemical gradients in their environment to migrate in the direction of nutrients and favorable conditions and away from toxins and unfavorable conditions. This process occurs generally when extracellular signals are detected by transmembrane receptors which through some intra-cellular mechanisms control the cell's movement in a given substance. Those intra-cellular mechanisms are carried out by a certain set of proteins, which react given a receptor signal and change the cellular motion given the current state of the flagellum and the cell.
- **Emergence:**
  The key outcome of the model is the bacteria concentration intracellular signaling pathway (proteins concentration), ligand concentration, cell trajectory, cell motion (run and tumble

changes toward the time). Those outcomes are given by intra-cellular reactions and cellular motion.

- **Adaptation:**
  The run and tumble action in motion might be thought of as adaptive behavior. This behavior depends on receptor signaling which carries to intracellular mechanics carried out by stochastic events. Molecule's movement behavior depends on the gradient and the flow of the environment.

- **Objectives:**
  The objective measure used is to decide where the bacterium is moving is given the receptors signaling due to a molecule, which carries to how close (or far if is a toxin) is the cell from the maximum chemotactic gradient.

- **Learning:**
  Every movement of the agent depends on the last position and the action given by all of the behavior mentioned. The agent does not learn from the actions he did.

- **Prediction:**
  The agents do not have an explicit prediction at decision making, the model is not designed to represent how agents make predictions. But the model includes an implicit prediction, as well as a bacterium, is following a gradient increasing (or decreasing) scent.

- **Sensing:**
  Agents can feel the gradient of the ligand through certain receptors, which activate all of the intra-cellular mechanics. This is a sensing method. Some other variables as the flow direction, temperature, concentration of proteins inside, and flagellum action are implicitly known for agents.

- **Interaction:**
  There is a direct interaction between molecules and bacterium as well as molecules are located by bacteria receptors given a gradient of the ones mentioned. The basis of the chemotaxis phenomenon occurs due to the interaction between a certain molecule and bacterium receptor.

- **Stochasticity:**
  One of the most important events in the simulation is a stochastic process. The motor switching is simulated stochastically.

- **Collectives:**
  The initial conditions of the model pretend to be an aggregation of bacteria. Bacteria aggregation is also a studied phenomenon of this model. The model pretends to study different lineage of a bacterium, which means, that's another model's collective. The collectives in the last case pretend to have a special behavior given by competition between different lineages called antagonistic communication.

- **Observation:**
  Summary statistics of agent density (molecules and bacteria), proteins density, tumble-running time interval, average speed, molecules gradient concentration, and the average distance from max gradient are provided via plot on the interface and output files. Graphical output of the cells and molecules trajectory show their behavior in every time step.

3.1.5 Initialization:

The initial parameters of the model are based on "RapidCell" which is a hybrid model of chemotactic *Escherichia coli* presented by Nikita Vladimirov & Sourjik (2008).(Figure 5)

Parameter	Value
K_a^{on}	12 μM
K_a^{off}	1.7 μM
$K^*(K_D)$	4.52 μM
K_s^{on}	10^6 μM
K_s^{off}	100 μM
n_a	6
n_s	12
$[CheR]$	0.16 μM
$[CheB]$	0.28 μM
a	0.0625
b	0.0714
$[CheY]_{tot}$	9.7 μM
A^*	1/3
CCW mb_0	0.65
H	10.3
v	20 $\mu m\, s^{-1}$
D_r	0.062 $rad^2\, s^{-1}$
Δt	0.01 s

Figure 5: Initial parameters used in the model (Nikita Vladimirov & Sourjik, 2008)

3.1.6 Input data:

The model does not use input data.

3.1.7 Submodels:

As the model which is been used is an adaptation from Nikita Vladimirov & Sourjik (2008) it is necessary to define the models which "RapidCell" model is been used, due to those are the corresponding submodels.

- *Monod-Wyman-Changeux or MWC model*:
  The MWC used by Nikita Vladimirov & Sourjik (2008) takes a individual receptor which is described as a two-state receptor, being either 'on' or 'off'(Cite). Then the the probability that a cluster will be active is:

$$A = \frac{1}{1 + e^F}$$

  where $F = F^{on} - F^{off}$, and F^{on}/F^{off} is the free energy of the cluster to be on/off as a whole.(Nikita Vladimirov & Sourjik, 2008) Now, cluster free energy, in the mean-field approximation for a cluster which is composed of n_a Tar and n_s Tsr receptors, the total free diference is given by

$$F = n_a f_a(m) + n_s f_s(m)$$

  which is the sum of individual free-energy between both receptor states:

$$f_r(m) = f_r^{on}(m) - f_r^{off}(m) = \epsilon_r(m) + log(\frac{1 + [S]/K_r^{off}}{1 + [S]/K_r^{on}})$$

  where [S] is the logand concentration, and $K_r^{off/on}$ is the dissociation constant for the ligand.(Nikita Vladimiro & Sourjik, 2008).

- *Adaptation model*:
  Considering CheR and CheB to be bind receptors independent of their activity. A bound CheR (CheB) can (de-)methylate any inactive (active) receptor within the AN. Each bound CheR adds methyl groups at a rate $a(1A)$ (Nikita Vladimirov & Sourjik, 2008). Assuming both enzymes work at saturation:

$$\frac{dm}{dt} = a(1 - A)[CheR] - bA[CheB]$$

  which means that a enzyme can only act if the receptor cluster is inactive or active with a (1-A) probability. (Nikita Vladimirov & Sourjik, 2008)

- *Kinase activity* Considering activity of CheA as constant, then, according to Nikita Vladimirov & Sourjik (2008) the concentration of CheY-P is given for:

$$Y_p = \frac{k_y A_p Y^t}{K_y A_p + K_z Z + \gamma_Y}$$

- *CheB phosphorylation* The kinase-dependet CheB phosphorylation follows the steady-state equation:

$$[CheB] = [CheB]_{tot} \frac{A}{A + k_{0.5}}$$

- *Motor switching* Given a motor bias resulted of the converted concentration of the response regulator [CheY-P] using a Hill function, the rotation time for a motor is:

$$mb = \frac{T_{CCW}}{T_{CCW} + T_{CW}}$$

  where T_{CCW} and T_{CW} are the means of exponentially distributed CCW and CW intervals.(Nikita Vladimirov & Sourjik, 2008).

- *Runs and tumbles* The cell has N motors, if the majority of the motors rotate CW the cell switches from "Run" to "Tumble", but if the majority of the motors rotate CCW the cell switches from "Tumble" to "Run".

- *Tumbling angle* The tumbling angle is distributed to the probability density function

$$f(\Theta) = 0.5(1 + \cos\Theta)\sin\Theta \quad 0 < \Theta < \Pi$$

(Nikita Vladimirov & Sourjik, 2008)

3.2 Implementation:

The model is an adaptation from the model "RapidCell" by Nikita Vladimirov & Sourjik (2008) which was implemented using Java classes, considering a discrete-time Monte Carlo scheme with a time step of 0.01. The output of the model where analyzed with MATLAB(The MathWorks,MA)

4 Results

4.1 Chemotaxis in different gradients

To test the behaviour of the model is important to see the possible routes that the bacteria have in different gradients.The Figures((6)(7)(8)(9)(10)(11)) shows the behavior of the cell under certain conditions.

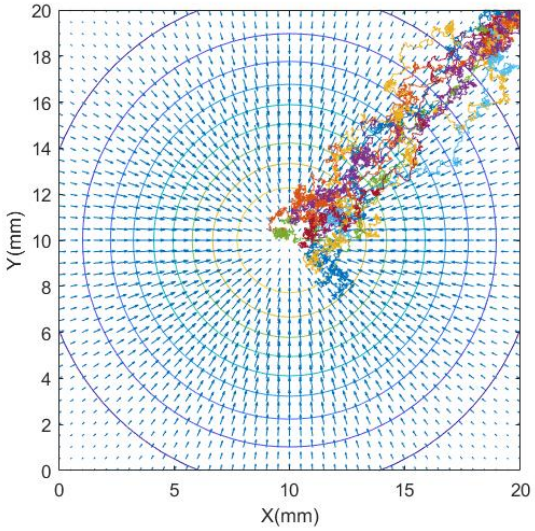

Figure 6: Chemotaxis under bi-dimensional Gaussian gradient with 10 cells and a simulation time of 10000s

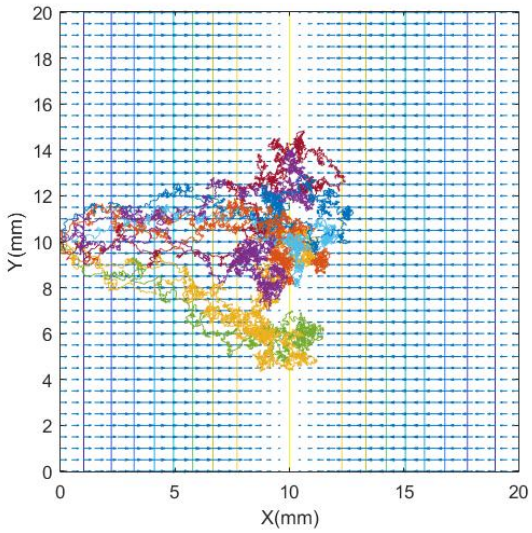

Figure 7: Chemotaxis under one-dimensional Gaussian gradient with 10 cells and a simulation time of 15000s

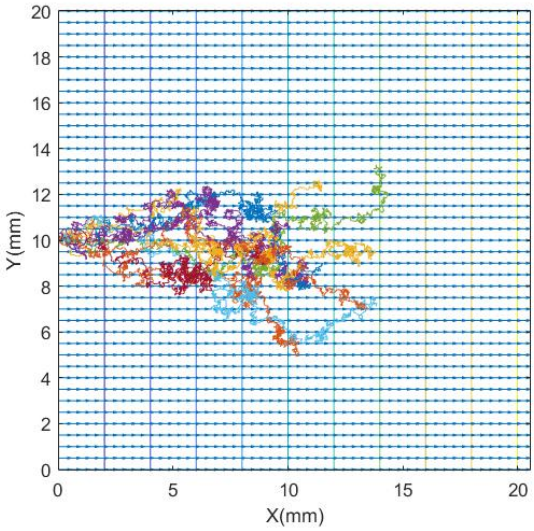

Figure 8: Chemotaxis under one-dimensional linear gradient with 10 cells and a simulation time of 10000s

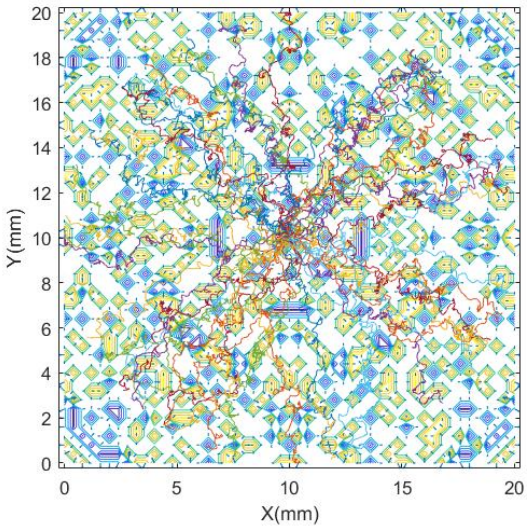

Figure 9: Chemotaxis under bi-dimensional Constant-activity gradient with 50 cells and a simulation time of 10000s

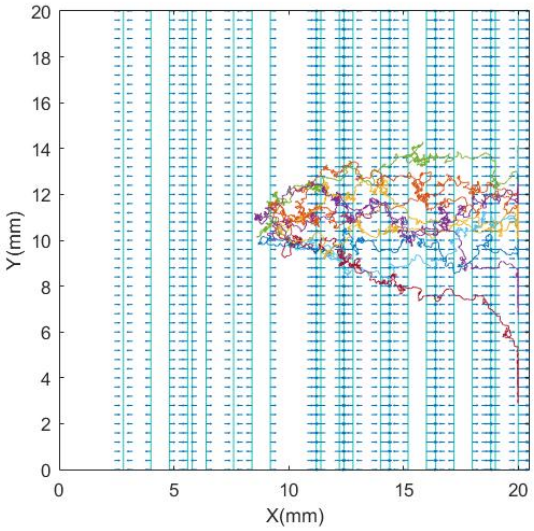

Figure 10: Chemotaxis under one-dimensional Constant-activity gradient with 10 cells and a simulation time of 5000s

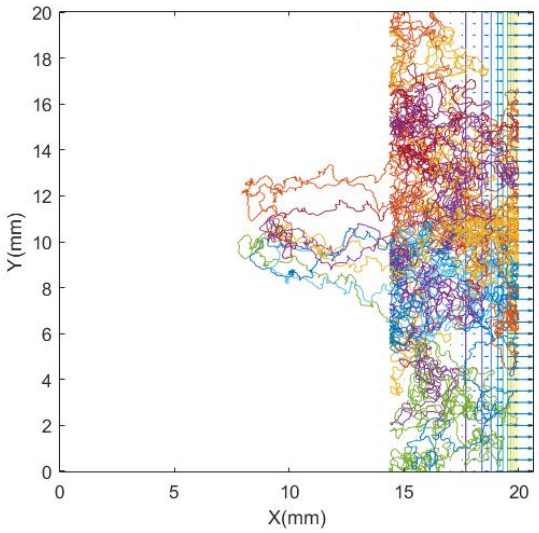

Figure 11: Chemotaxis under one-dimensional Exponential gradient with 10 cells and a simulation time of 10000s

Where the gradients implemented can be described as follows:

- **Figure 6**

$$G(x,y) = Max * e^{\frac{-(x-x_s)^2 + (y-y_s)^2}{2\sigma^2}}$$

- **Figure 7**

$$G(x) = Max * e^{\frac{-(x-x_s)^2}{2\sigma^2}}$$

- **Figure 8**

$$L(x) = \frac{(Max - min)x}{Lx}$$

- **Figure 9**

$$C(x,y) = Kd * Csignal * \frac{R}{\frac{(Ka_{on} - Ka_{off})}{Kd - Csignal * R}}$$

where

$$Csignal = \frac{0.999}{\frac{R * (Ka_{on} - Ka_{off})}{Kd}}$$

$$R = \sqrt{(\frac{x - Lx}{2})^2 + (\frac{y - Ly}{2})^2}$$

- **Figure 10**

$$C(x) = \frac{\frac{Kd * Csignal * x}{(Ka_{on} - Ka_{off})}}{(Kd - Csignal)x}$$

where

$$Csignal = \frac{0.999}{\frac{R * (Ka_{on} - Ka_{off})}{Kd}}$$

- **Figure 11**

$$E(x) = Rate * e^{x}$$

The parameters for simulating the gradients were:

Parameter	Value
Lx	20
Ly	20
Xs	10
Ys	10
sigma	5
Min	0.1
Max	0
Rate	0.001
Ka_{on}	0.5
Ka_{off}	0.02
Kd	0.1

Gradients as the constant-activity gradient represent an important application of Chemotaxis motion, due to indicates that receptors are not been saturated in a certain amount of time, so as saturation usually happen in normal or linear gradients. Constant-activity gradient gives a better behavior of the real cell and represent a better behavior of an application in real world experiments.

4.2 CW and CWW intervals

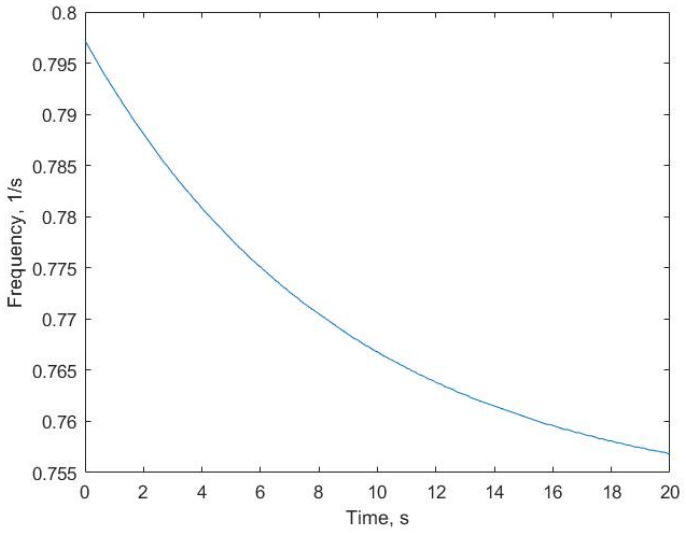

Figure 12: Frecuency of CCW to CW

As it is showed in Figure 12, the frequency of a single cell to CW and CCW in a medium without attractant tend to follow the curve described by Emonet *et al.* (2005), where it is showed that intervals of individual flagellar motors have that behaviour.(Figure 13)

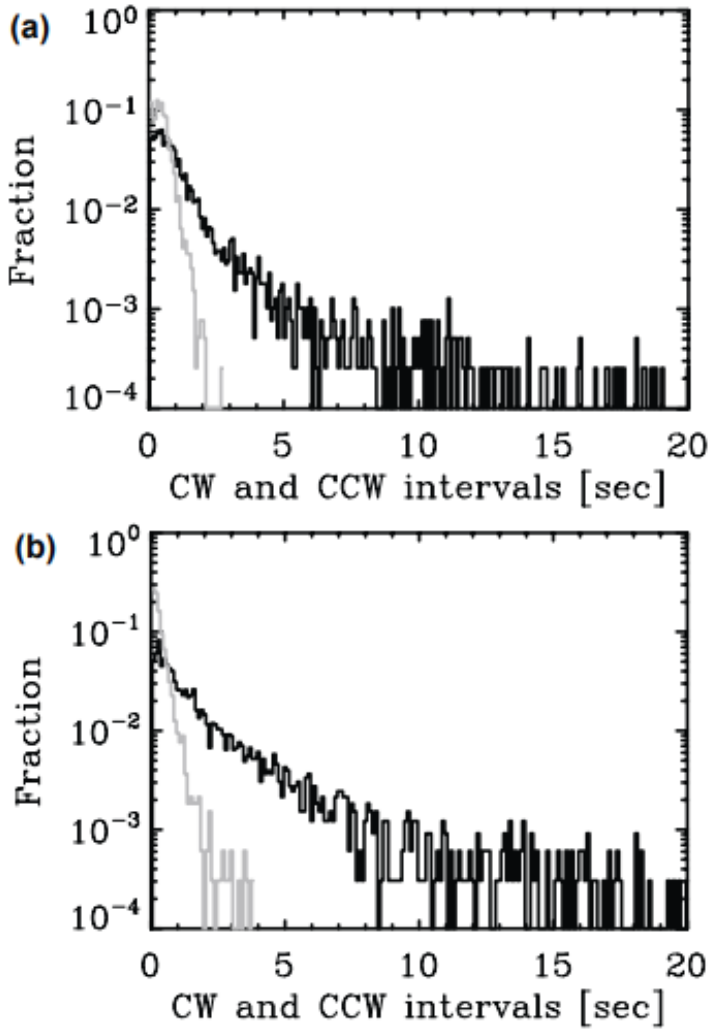

Figure 13: Fraction of CW and CCW intervals of individual flagellar motors from non-stimulated wild-type cells in a medium without attractant. (a) Real cell and (b) simulation. (Emonet *et al.*, 2005)

The curve given by Emonet *et al.* (2005) is not clearly the same that it is been simulated, but it refers to the same thing that is been indexed as so AgentCell is plotting a fraction of the change in CW and CCW actions. Also the parameters of the models are not the same given the stochastic nature of AgentCell .

The probability of the motor to rotate CW is very sensitive to the concentration of CheY-P inside the cell. As it is showed in Figure 14, AgentCell runs a chemotatic response of a single cell to a constant gradient of aspartate, where intracellular number of Chey-P molecules as function of time

(black) and the vertical grey stripes indicate tumbling events (Emonet *et al.*, 2005). The motor switches when CheY-P molecules crosses the threshold 1422.

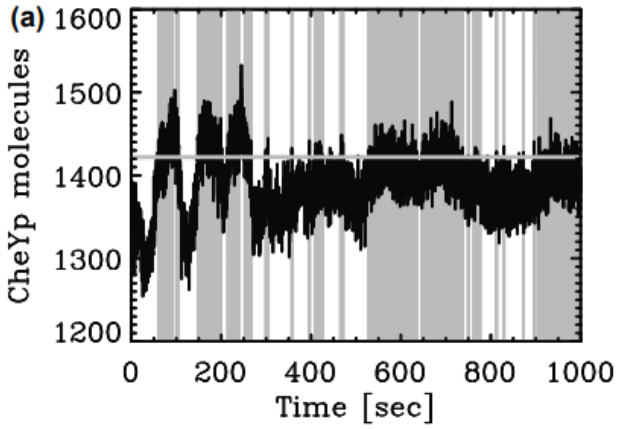

Figure 14: Chemotatic response of CheY-P molecules in every time step(Emonet *et al.*, 2005)

This concept is valid for the model which is been implemented, due to the time which the motor spends rotating in CW direction increases with the Chey-P concentration(Figure 15 and Figure 16) . The model was run with 1 cell for 1000 seconds in a Constant-activity gradient in a liquid medium with a center initial position.

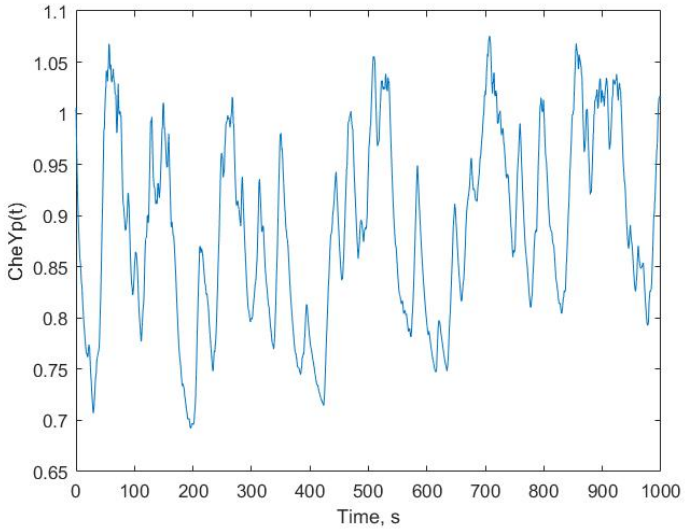

Figure 15: Chemotatic response of CheY-P molecules in every time step

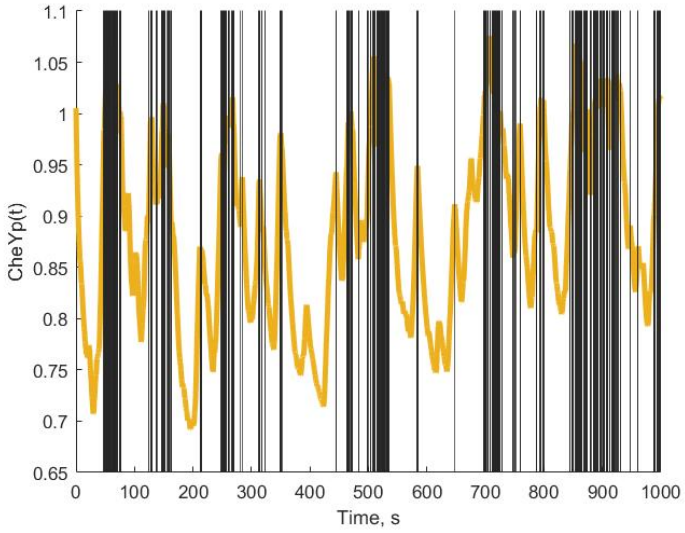

Figure 16: Chemotatic response of CheY-P molecules in every time step where the vertical black stripes indicate tumbling events

In addition to this, an analysis related to CW and CCW motor motion threw an relation which is opposite to the one showed before. Figure 17

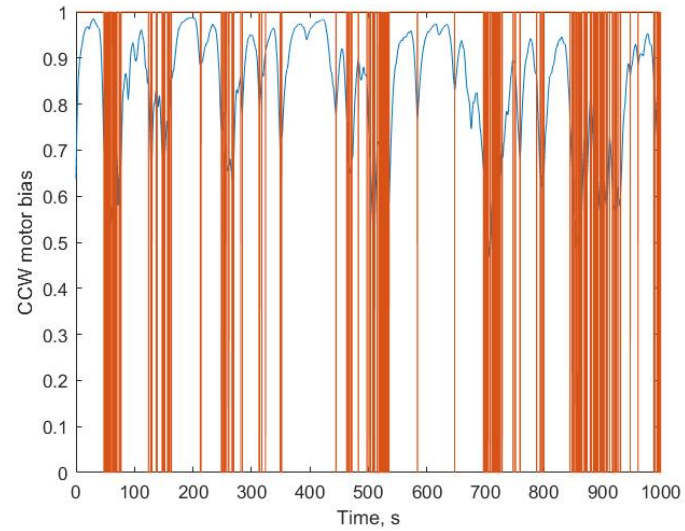

Figure 17: Chemotatic response of CCW motor bias every time step where the vertical orange stripes indicate tumbling events

5 Conclusions and future research

The effect of using one of the other modeling perspectives to model the Chemotaxis phenomenon is so evident. ABM is a good approach to high degree localization and distribution dominated by

discrete decisions, applied to systems that depend on certain physical laws rather than information processing, or estimation of parameters. ABM supports more direct experimentation and gives a better visualization of the system itself. This can be evidenced in the comparing outputs with the literature. EBM gives a bigger quantity of quality general information and it is needy at estimating good parameters. Then, when such a complex system as chemotaxis is presented, a better option is to form, if it is possible, a hybrid with both of the modeling perspectives, or select what it is advisable: to know the individual or to know the population. With the results showed it is possible to see then the direct relation between different modeling perspectives, and how they can contribute to better results. Future works can include a possible application of the chemotaxis phenomenon to other environments, such as agriculture or biotechnology. Also, another future contribution can be represented for the improvement of the interface which was implemented such as the searching of complex population behaviors on the cells.

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