Multi-Flagellated bacteria: Stochastic model for run-and-tumble chemotaxis.

by

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Abstract

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Bacterial chemotaxis, as observed for Escherichia coli, in a field of chemoattractant molecules is characterised by a run-and-tumble motion. The motion is effected by the clockwise (CW) or counter-clockwise (CCW) rotation of flagella; filamentous appendages attached to molecular motors on the cell body. Runs appear when all flagella turn in the CCW-direction and are used to maintain a favourable direction. Tumbles emerge as soon as one flagellum starts to turn CW and are used for reorientation. Because of the variation observed between individual bacteria displaying run-and-tumble motion, we choose to model this behaviour within a probabilistic framework.

An important feature of the chemotactic ability of *E.coli* is that the cell increases run while moving in the right direction and shortens it in the opposite case. This underlines that tumbles are used for reorientation. It has been found from experiments that there can be significant variation in the tumble fashion depending on the fraction of CW-rotating motors (Turner *et al.*, 2000). The change in angle produced when fewer flagella are rotating CW was found to be smaller when compared to the case for many CW-rotating flagella. In addition, the change of direction contributed by a small portion of CW-rotating flagella is rarely significant for bacteria with many flagella. Based on these observations, we have distinguished between models for the one-flagellated and the multi-flagellated cases.

Furthermore, since the tumbling angle change increases with the fraction of CW-rotating motors, it would not be impossible to have some cases where the amount of turn produced by the CW-rotating motors induces the bacterium to have a change of direction greater than 2π. But, this feature could

not have been observed because when the bacterium tumbles it can effectuate several revolutions before resuming to a new direction. Therefore, we do not restrict our change of direction to $(0, 2\pi)$ to allow the bacteria to have the possibility to effectuate change of directions of magnitude greater than 2π. To this end, we differentiate between the probability of having directional change of magnitude α and $\alpha + 2\pi$. Thus we do not use angle change distributions that are defined modulo 2π such as the von Mises distribution or the wrapped normal distribution.

The chemotactic ability of the bacterium is modelled by representing the CCW-bias of a single flagellum as a function of the chemoattractant concentration. The model includes the temporal memory of chemoattractant concentration that the bacterium has, which usually spans about 4s. The information about the quality of the current direction of the bacterium is transmitted to the flagellar motor by assuming that this one varies with the chemoattractant concentration level. In addition, the saturation of the bias is incorporated by assuming that the bacterium performs a temporal comparison of the receptor occupancy. The present CCW-bias-Model accounts for the chemotactic ability of the bacterium as well as its adaptation to uniform chemoattractant environment.

The models of one-flagellated and multi-flagellated bacterial motion, are used to investigate two main problems. The first one consists of determining the optimal tumbling angle strategy of the bacteria. The second one consists of looking at the effects of the tumble variation on the chemotactic efficiency of the bacteria. In order to address these questions, the chemotactic efficiency measure is defined in such a way that it reflects the ability of the bacteria to converge and to stay in a near neighbourhood of the source so that they gain more nutrients.

Since its movement is entirely governed by its single flagellum, the one flagellated bacterium is more able to effectuate a run motion. Tumbling events are modelled to be all equivalent because there is not any fraction of flagella to consider.

On the other hand, the tumble variation of the multi-flagellated bacteria is modelled by assuming that the directional change during a tumble is a function of the fraction of CW-rotating motors. By assuming that the number of CW-rotating flagella follows a binomial distribution, we suppose that the multi-flagellated bacteria are less able to effectuate a run motion. This also implies that the change of direction produced by fewer CW-rotating flagella are more likely to happen, and this compensates the lack of run.

The models show that the optimal tumbling angle change for the bacteria is less than 2π and that higher flagellated bacteria have higher chemotacitc efficiency. As the number of flagella of the bacteria increases, there can be more tumble variation, in this case the bacteria are more capable of adjusting their direction. There could be some situation were the bacteria are not moving to the right direction, but do not require a large change of direction.

This ability to adjust their direction accordingly allows them to converge nearer to the source and to gain more nutrients.

In addition, the dependence of the tumbling angle on the fraction of CW-rotating flagella of the mutli-flagellated bacteria, implies that there is a correlation between the tumbling angle deviation and the external environment, because the rotational states CCW-CW of the flagella depends on the external cue. Consequently, it would not be impossible that the average magnitude of tumbling angle change depends on the external environment. To investigate this possibility we analyse the distribution of the tumbling tendency of a single bacterium over time, which is the distribution over time of the average positive tumbling change of the bacterium, within zero-gradient environment and within non-zero-gradient environment. We defined the average of these tumbling tendency over time as the directional persistence.

We observe that the directional persistence within these different non-zero-gradient environment remains the same. However, the difference between the directional persistence within zero-gradient and non-zeros gradient environment gets larger as the number of flagella of the cell increases. There is more correlation between the external environment and the tumbling tendency of the bacterium. Which is the reason why the higher flagellated bacteria responds the best to the external environment by having the higher chemotactic performance.

Finally, the total directional persistence generated by the optimal tumbling angle change of the bacteria is the average directional persistence of the bacteria regardless of their number of flagella. Its value, predicted by the model is 1.54 rad within a non-zero-gradient environment and 1.63 rad within a zero-gradient environment.

Uittreksel

Wiskundige modellering van bakteriële hardloop en tuimel chemotakse

("Multi-Flagellated bacteria: Stochastic model for run-and-tumble chemotaxis.")

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Bakteriese chemotakse, soos waargeneem word vir *Escherichia coli*, in 'n veld van chemiese lokmiddel molekules word gekenmerk deur 'n hardloop-en-tuimel beweging. Die beweging word bewerkstellig deur die regsom of linksom rotasie van flagella; filamentagtige aanhangsels geheg aan molekulêre motors op die selliggaam. 'n Hardloop aksie kom voor as al die flagella linksom roteer en word gebruik om 'm voordelige koers te handhaaf. Tuimels kom voor sodra een van die flagella regsom draai en word gebruik vir heroriënteering. Van wee die variasie wat waargeneem word tussen individuele bakterieë wat hardloop-en-tuimel bewegiging vertoon, verkies ons 'n probabilistiese raamwerk om in te werk.

'n Belangrike eienskap van die chemotakse vermoë van *E. coli* is dat die sel meer gereeld hardloop terwyl dit in die regte rigting beweeg en minder gereeld in die teenoorgestelde geval. Dit beklemtoon dat tuimels gebruik word vir heroriënteering. Dit is al eksperimenteel vasgestel dat daar betekenisvolle variasie kan wees in die tuimel wyse, wat afhang van die breukdeel regsom roterende motors (Turner *et al.*, 2000). Die hoekverskil afkomstig van minder regsom roterende flagella was vasgestel om kleiner te wees in vergelyking met die menig regsom roterende geval. Verder word die bydrae tot die hoekverskil van 'n klein breukdeel regsom roterende flagella selde beduidend vir bakterieë met baie flagella. As gevolg van hierdie waarnemings, tref ons onderskeid tussen modelle vir een-flagella en multi-flagella gevalle.

Aangesien die tuimel hoeksverskil vergroot saam met die breukdeel regsom roterende motore, is dit nie onmoontlik om gevalle te hê waar die hoeveelheid draaiaksie gegenereer deur die regsom roterende motore 'n rigtingsverskil groter as 2π kan bewerkstellig nie. Dit was nie moontlik om hierdie eienskap waar te neem nie aangesien die bakterieë 'n paar keer kan tuimel voordat 'n nuwe rigting vasgestel word. Vir hierdie rede beperk ons nie die hoeksverskil tot $(0,2\pi)$ nie om die bakterieë toe te laat om rigtings veranderinge groter as 2π te ondergaan. Vir hierdie doel, onderskei ons tussen die waarskynlikheid van 'n rigtinsverskil met grootte α en $\alpha + 2\pi$. Dus, gebruik ons nie hoekverskil verspreidings wat modulo 2π gedefinieer is nie, soos die von Mises verspreiding of omwinde normaalverdeling.

Die chemotakse vermoë van die bakterium word gemodelleer deur die linksom sydigheid van 'n enkele flagellum as 'n funksie van die chemotakse lokmiddel konsentrasie voor te stel. Die model sluit in die tydelike geheue wat die bakterium besit oor chemotakse lokmiddel konsentrasie, wat gewoonlik oor 4s strek. Die informasie oor die kwaliteit van die huidige rigting van die bakterium word deur gegee na die flagella motor toe deur die aanname te maak dat dit wissel met die chemotakse lokmiddel konsentrasie vlak. Die versadiging van die sydigheid word geinkorporeer deur aan te neem dat die bakterium 'n temporale vergelyking maak tussen reseptor okkupasie. Die huidige linksom sydige model neem die bakterium chemotakse vermoë in ag, as ook aanpassing tot 'n uniforme chemotakse lokmiddel omgewing.

Die modelle van een-flagella en multi-flagella bakteriële beweging word gebruik om twee hoof probleme te bestudeer. Die eerste, bestaan daaruit om vas te stel wat die optimale tuimel hoek strategie van die bakterieë is. Die tweede kyk na die uitwerking van tuimel variasie op chemotakse effektiwiteit. In orde om hierdie vra te adreseer word die chemotakse effektiwiteit op so mannier gedefinieer dat dit die bakteriese vermoë om die buurt om die oorsprong te nader en daar te bly.

Aangesien die beweging heeltemal vasgestel word deur een flagella, in die een-flagella geval, is 'n bakterium meer in staat daartoe om 'n hardloop aksie te bewerkstellig. Tuimel voorvalle word as ekwivalent gemodeleer omdat daar geen breukdeel roterende flagella is om in ag te neem nie.

In teenstelling, word die tuimel variasie van multi-flagella bakterieë gemodeleer deur die aanname te maak dat rigtingsverandering gedurende 'n tuimel 'n funksie is van die breukdeel regsom roterende motore. Deur die aanname te maak dat die getal regsom roterende flagella 'n binomiese verspreiding volg, veronderstel ons dat multi-flagella bakterieë minder in staat daartoe is om 'n hardloop aksie te onderneem. Hierdie impliseer ook dat rigtingverandering wat geproduseer word deur minder regsom roterende flagella meer geneig is om voor te kom en dan kompenseer vir 'n tekortkoming aan hardloop gebeure.

Die modelle wys dat die optimale tuimelhoek verandering minder as 2π

is en dat bakterieë met meer flagella meer chemotaksies effektief is. Soos die getal flagella vermeder, kan daar meer tuimel variasie wees, en in die geval is die bakterieë meer in staat om hul rigting te verander. Daar kan omstandighede wees waar die bakterieë nie in die regtige rigting beweeg nie, maar nie 'n groot rigtingsverskil nodig het nie. Hierdie vermoë om hul rigting byvolglik te verander stel hul in staat om nader aan die oorsprong te konvergeer en dus meer voedingstowwe op te neem.

Die afhanklikheid van die tuimel hoek op die breukdeel regsom roterende flagella van multi-flagella bakterieë dui daarop dat daar 'n korrelasie is tussen die tuimel hoek afwyking en die eksterne omgewing, omdat die roterings toestand, regs- of linksom, van die flagella afhanklik is van die eksterne sein. As 'n gevolg, is dit nie onmoontlik dat die gemiddelde grootte van die tuimel hoek verandering van die eksterne omgewing afhang nie. Om hierdie moontlikheid te bestudeer, analiseer ons die verspreiding van die tuimel neiging van 'n enkele bakterium oor tyd, wat die verspreiding oor tyd van die gemiddelde positiewe tuimel verandering is, in 'n nul-gradient en nie-nul-gradient omgewing. Ons het hierdie gemiddelde tuimel neigings oor tyd gedefinieer as die rigtings volharding.

Ons het waargeneem dat die rigtings volharding binne verskillende nie-nul-gradient omgewings dieselfde bly. Nogtans is die verskil tussen die rigtings volharding binne nul-gradient en nie-nul-gradient omgewings groter soos die getal flagella vermeder. Daar is meer korrelasie tussen die eksterne omgewing en tuimel neiging van die bakterium. Dit is die rede hoekom bakterieë met meer flagella die beste reageer op die eksterne omgewing deur beter chemotakse effektiwiteit.

Ten slotte, die totale rigtings volharding gegenereer deur die optimale tuimel hoek verandering is die gemiddelde rigtings volharding ongeag van die getal flagella. Die waarde wat deur die model voorspel word is 1.54 rad binne 'n nie-nul-gradient omgewing en 1.63 rad binne 'n nul-gradient omgewing.

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Nomenclature

Constants

$b_0 =$ 0.64 the probability of CCW-motion of a single flagellum in a uniform environment.

D_{rot} 0.15 Rotational diffusion (Nicolau *et al.*, 2009). . . . . [$\mathrm{rad}^2\,\mathrm{s}^{-1}$]

$\mathrm{e} \sim$ 2.718 281 828

$g =$ 50 amplification parameter (used in the simulations). [ ]

$\epsilon =$ 0.3 the standard deviation of the tumbling angle distribution of the one-flagellated bacteria (used in the simulations). . . [rad]

$\epsilon_0 =$ 0.7 the maximal standard deviation of the tumbling angle distribution in the case of a F-flagellated bacteria (used in the simulations). [rad]

$\nu =$ 25 The mean bacterial velocity (Nicolau *et al.*, 2009). . [$\mu\mathrm{m.s}^{-1}$]

$\pi \sim$ 3.141 592 654

$\Delta t =$ 1 time step.

Parameter

c_{max} The peak of chemical substance concentration. . . . . [$\mathrm{Mol}.\mu\mathrm{m}^{-2}$]

k_D Dissociation constant of the receptor. . . . . [$\mathrm{Mol}.\mu\mathrm{m}^{-2}$]

F Number of flagella on the cell body.

σ Concentration parameter. . . . . [$\mu\mathrm{m}$]

ϕ_F Reference angle for the positive modes of the tumbling angle distribution of a F-flagellated bacterium. . . . . [rad]

φ_F The directional persistence of a F-flagellated bacterium. [rad]

Notations

B The binomial distribution.

N The normal distribution.

$\mathcal{N}$ Tumbling angle distribution.

U The uniform distribution.

$C(a, b)$ The circle of center a and radius b.

Variables

b_{ccw} Probability of a CCW-rotation of a single flagellum. [ ]

b_{cw} Probability of a CW-rotation of a single flagellum. [ ]

b_{run} Probability of a run motion. [ ]

b_{tumble} Probability of a tumble motion. [ ]

c Concentration of chemical substance. [$\mathrm{Mol}.\mu\mathrm{m}^{-2}$]

n_{cw} The number of CW-rotating flagella.

$p = (x, y)$ Coordinates of the bacterium. [$(\mu\mathrm{m}, \mu\mathrm{m})$]

r Random variable drawn from $U(0, 1)$. [ ]

s Normalised concentration of chemical. [ ]

A Receptor occupancy to which the cell is adapted. [ ]

F_{cw} The fraction of CW-rotating motor on the cell body. [ ]

I The signal added to b_0 to get the saturated impulse response. [ ]

N_{tumble} The estimated number of tumble effectuated by the bacterium.

P Chemoreceptor occupancy. [ ]

P_{binom} The probability mass function of the binomial distribution. [ ]

$STD(t)$ The standard deviation of the population of bacteria at time t, with respect to the source of chemoattractant. [$\mu\mathrm{m}$]

STD_0 The steady state standard deviation of the population of bacteria, with respect to the source of chemoattractant. [$\mu\mathrm{m}$]

$\Delta\theta(t)$ Angle deviation at time t. [rad]

$\epsilon_F(F_{cw})$ The standard deviation of the tumbling angle distribution associated to the fraction of CW-rotating flagella F_{cw} of a F-flagellated bacterium. [rad]

λ Tumbling angle deviation. . . . . [rad]

η Random variable drawn from $N(0,1)$. . . . . [ ]

θ Angle of direction. . . . . [rad]

ϱ The minimal normalized steady state standard deviation of the population of bacteria. . . . . [rad]

Θ The positive mode of the tumbling angle distribution. [ ]

$\bar{\Theta}$ The tumbling tendency of the bacterium. . . . . [rad]

$\Theta_F(F_{cw})$ The positive mode of the tumbling angle related to the fraction of CW-rotating flagella F_{cw} of a F-flagellated bacterium. [rad]

Function

cos: The cosine function

sin: The sine function

mod: The modulo operation

$||\,\mathbf{.}\,||$: The euclidean distance

Glossary

Chemotactic efficiency: The survival ability of the bacterium using chemotaxis

Directional persistence: The average positive tumbling angle change over time.

Run: A less or more smooth and straight movement in the forward direction.

Tumble: A rapid somersaulting driving to a particular change of direction.

Tumbling angle: The change of direction during a tumble.

Tumbling strategy: The configuration of angles changes that the bacteria uses for tumble.

Tumbling tendency: The average positive tumbling angle of the bacterium at a given time.

Chapter 1

Introduction

The aim of this thesis is to build mathematical models that describe bacterial motility in a field of chemical attractant. Particularly, the motion of the cells toward a source of chemical attractant molecules which they need for their survival. We specifically study the movement of *Escherichia coli* (*E. coli*) bacteria in a two dimensional space. Furthermore, we differentiate between one-flagellated and multi-flagellated bacteria, since these two kinds of bacteria display different tumbling behaviour. Features of this bacterial behaviour is investigated using the models. Notably, the optimal tumbling orientation strategy and the effect of the number of cellular flagella on their chemotactic efficiency. Before outlining the details of our models, we will provide some context for the study of bacteria.

1.1 The history of bacteriology and chemotaxis

Bacteria are single celled micro-organisms that have existed on our planet for billions of years. They can be found everywhere, in soil, in water, in, and on our body (Fredrickson *et al.*, 2004; Sears, 2005). They play an important role in our lives because they protect our bodies from external danger. However, some of them are very pathogenic, causing serious diseases like gastrointestinal infections and tuberculosis. Therefore, it is important for us to understand their behaviour.

Bacteriology started in 1676 when Antony van Leeuwenhoek discovered bacteria (Berg, 2006). He did so with a microscope of his own design. Even though van Leeuwenhoek and others observed bacteria moving, this phenomenon was not adequately described till the work of Julius Adler in the twentieth century in a paper called "Chemotaxis in *Escherichia coli*" (Berg, 2006).

Chemotaxis is a mechanism that allows organisms to sense and direct their movement toward or away from a source of chemical substances (see Fig 1.1 and Blair (1995); Lengeler *et al.* (1999)). There are similar mecha-

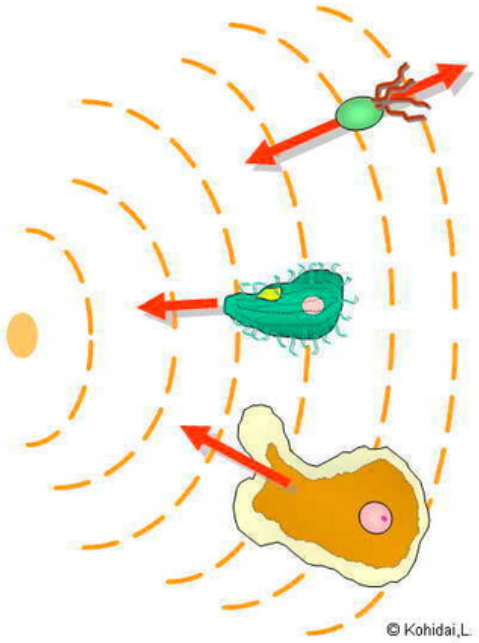


Figure 1.1: An illustration of chemotaxis of prokaryotic and eukaryotic cells, created by Laszlo Kohidai. The cells detect change of the chemical substance concentration in their surrounding and are able to direct their directions toward the source of attractant or away from a source of repellent. Each organisms uses their proper movements, for example by gliding, or like *E. coli*, by running and tumbling, but they are all using their chemotactic ability to sense their external environment and to migrate in a better region.

nisms that motile organisms use, for example: aerotaxis, for sensing oxygen; phototaxis, for detecting light; magnetotaxis, for orientating themselves in a magnetic field; and, thermotaxis, for detecting temperature changes (Lengeler *et al.*, 1999). A movement toward a source of chemical attractant is called "positive taxis" and conversely a movement away from a chemical repellent is called "negative taxis" (Lengeler *et al.*, 1999).

Given the abundance of bacterial species, it is hard to study all these organisms separately. It is easier to study a particular species and extend the resulting model to others. These particular type of organisms are called "model organisms". *E. coli* is the model organism for bacteria. Nowadays, more is known about this bacteria than all other existing organisms (Berg, 2006). For this reason, we also focus on *E. coli* and it would be useful to give some description.

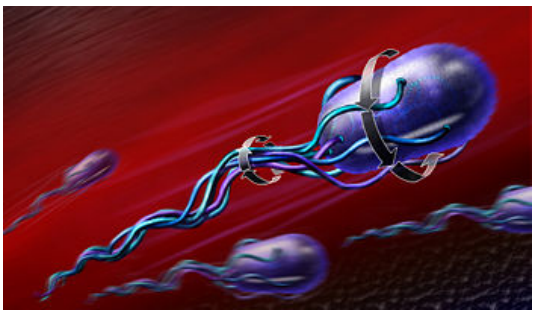


Figure 1.2: All the flagella of the bacterium turn in the CCW-direction. They join in a bundle behind the cell which serves as propeller and induces straight swim through the medium. Figure from at `http://www.thefullwiki.org/Flagellum`.

1.2 Run and tumble chemotaxis is "*E. coli*"

E. coli is a rod-shaped bacteria which can have up to about six flagella. Flagella are thin filaments located on the surface of the cell body (Blair, 1995).

Depending on the rotation of the flagella, which can be either in the counter-clockwise (CCW) or the clockwise (CW) direction, the cell can display two kinds of movements, namely a "run" and a "tumble", and under some circumstances it is able to combine these two movements.

When all the flagella are rotating in the CCW-direction, they form a bundle that propels the cell in a particular direction (Fig 1.2). The bacterium performs a more or less smooth and straight trajectory called a "run". If one of the flagella in the bundle reverses its rotation, the bundle becomes dis-coordinated causing the cell to somersault rapidly and reorientate itself into a new direction (Blair, 1995; Lengeler *et al.*, 1999). However, it can happen that the fraction of CW-rotating flagella is not big enough to sufficiently disturb the bundle (Turner *et al.*, 2000). In this case the cell keeps running and tumbling, and its trajectory more closely resembles a stumble or as will be seen in Chap. 4, a partial tumble.

It has been observed that in a region of uniform concentration of chemical attractant molecules, the movement of *E. coli* is similar to the random walk of a particle. Its trajectory is composed of a series of successive runs interrupted by random tumbles (Blair, 1995; Lengeler *et al.*, 1999). The average run duration is about $1s$ and the average tumble duration is $0.1s$ (Blair, 1995; Berg and Brown, 1972; Lengeler *et al.*, 1999). However, this random walk becomes biased when the bacterium is moving in a non-zero gradient environment (Blair, 1995; Lengeler *et al.*, 1999). *E. coli* cells increase the run duration while moving toward a source of chemical attractant, and increase tumble while drifting away from the source (Berg and Brown, 1972; Blair, 1995; Lengeler *et al.*, 1999). These observations underline that run motions

are used to maintain a favourable direction whereas tumble motions are used to reorient the cells in the right direction. This biased random walk is achieved through an internal mechanism called a "chemosensory pathway", that acts on the rotational states of the flagella. It allows the cells to memorise and compare the concentration of chemicals that they experience during the past few second and this short-term memory spans about 4s (Blair, 1995; Lengeler *et al.*, 1999).

Specific works had been looking at *E. coli* in the cellular levels, to observe how the bacteria display their chemotactic ability. Experimental investigations such as Block *et al.* (1982, 1983) focused on how the bacteria respond to stimuli, by looking at the rotational states of the bacterial flagella.

There are also some other important experimental works that investigated the tumbling change of direction of the bacteria within a ligand free environment. Some of these works are the tracking experiments of Berg and Brown (1972), and the experiments of Turner *et al.* (2000).

The tracking experiment of Berg and Brown (1972) was looking at the overall trajectory of the bacteria. It was not possible to observe the rotational states of the flagella, thus, tumbles were defined to be the changes of directions of magnitude greater than 0.7 rad (Turner *et al.*, 2000).

Later on, Turner *et al.* (2000) had developed a novel way of looking at the multi-flagellated bacterial tumbling fashion. They observed that the tumbling angle was correlated to the fraction of CW-rotating flagella. Consequently, there could have been tumbling angle changes less than 0.7 rad, and even smaller. These small changes were usually the results of a few number of CW-rotating flagella. It has also been found that the change of direction produced by fewer CW-rotating motors becomes less significant for highly-flagellated bacteria.

These biological experiment has been the basis of several mathematical investigations. The next section provides a broad overview of some mathematical modelling of chemotaxis.

1.3 Review of mathematical models of bacterial chemotaxis

The motion displayed by micro-organisms has been modelled using the theory of random walk (Codling *et al.*, 2008). The theory of random walk associates an appropriate model for each kind of behaviour. The simplest random walk that one could think of is known as "the Brownian motion", in which the location of the particle at each time step is totally independent from the previous ones, and there is not any preferred direction (Codling *et al.*, 2008). It has been shown that the Brownian motion can lead to the standard diffusion equation (Codling *et al.*, 2008). However, in the case

of a particle that displays tendency in moving in a particular direction, the Brownian motion is no longer sufficient. Having a preferred direction means that some direction are likelier to be taken, and this behaviour is modelled by the drift-diffusion or advection-diffusion equation, and it is often called " a correlated random walk"(Codling *et al.*, 2008). There can also be some particular case where there is not any preferred direction but rather a preferred target region, this behaviour is called "a biased random walk" (Codling *et al.*, 2008). This later case is the motion displayed by *E. coli* while moving within a chemical gradient.

One of the most a general representation of a biased random walk is the model for population chemotactic behaviour. This approach is used to model the bacterial population motion toward or away from a source of chemical substances is represented in (Eq. 1.3.1). This model plays an important role in understanding the population behaviour. The population of bacteria is considered as a global mass rather than an assembly of single particle. The movement of the bacteria is then represented by the basic reaction diffusion-chemotaxis equation which is

$$\frac{\partial u}{\partial t} = f(u) + \varepsilon \nabla u \chi(c) \nabla c + \nabla D \nabla u, \tag{1.3.1}$$

where u represents the number of bacteria or the bacterial density, f is the function representing the growth of the population. D is the diffusion coefficient of the bacteria, c is the concentration of chemical substance. $\chi(c)$ is the chemotactic term and $\varepsilon = -1$ if it is a positive chemotaxis (chemical attractant, motion up the gradient) and $\varepsilon = +1$ if it is a negative chemotaxis (chemical repellent, motion down the gradient). Furthermore, the chemical concentration varies with the position and the time ($c = c(x, t)$), it also needs a special equation to describe its diffusion, its production by the source and its degradation due to bacterial consumption and other phenomena (for further details see the book by Murray (2004)).

The chemotactic term $\chi(c) > 0$ is often the term that makes the difference between one population of micro-organism to another. It represents the strength of the chemotactic flux of bacteria which is induced by the surrounding environment, and due to the chemotactic ability of the bacteria.

There are also some mathematical investigations that had been modulated upon the experimental works described in Sec. 1.2. Amongst them we cite the models by Clark and Grant (2005); Nicolau *et al.* (2009); Vladimirov *et al.* (2010).

Clark and Grant (2005) mainly investigated the cell's response function or the CCW-bias of a single flagellum, which is the probability of a CCW-rotation of the flagellum. This chemotactic response function was represented as the temporal comparison of chemical substances that *E. coli* performs in order to find its direction. The work consists of optimizing two independent chemotactic performance criteria in order to find the optimal

response function for the cell. The first performance criterion represents the ability of the bacteria to reach the source of food in the non-steady state regime, and it is the measure of the early time transient velocity of the bacteria. The second performance criterion represents bacterial aggregation in the steady state regime and this reflects the ability of the bacteria to stay in a region of high nutrients. By simulation of bacterial movement in one dimension, the authors observed that when one criterion is optimized, the other is not. To remedy to this situation, they included both criteria in a composite optimization. They obtained an optimal response function the closely reflected experimental measurement for some particular fitting parameters.

The above approach of Clark and Grant (2005) was used by Nicolau *et al.* (2009) to model the tumbling probability of a bacterium. They focused on the effect of the directional persistence (the mean-tumbling angle) on chemotactic efficiency of the bacteria. To this end, they used a spatial Monte Carlo model of bacteria swimming in a gradient of chemical attractant and simulations of natural selection based on chemotactic efficiency. The model consists of simulating the bacteria within a linear gradient environment. The effect of the natural selection was introduced after some simulation time. It consisted on removing 50% of the bacteria that reflected a poor chemotactic performance assuming that they were not surviving. The rest of the bacteria were allowed to divide once in order to preserve the population size. The chemotactic performance was taken as the measure of the percentage of attractant that the bacteria acquired up to the current time. By direct simulation and simulation in *silico* Evolution, the authors concluded that the sensitivity of the chemotactic efficiency to the directional persistence appears only in a high-gradient regime. The directional persistence improves the chemotactic efficiency of the bacteria in the case they are climbing a sharp gradient. They also found a beneficial directional persistence interval that contains the experimental measurement 1.1rad (Berg and Brown, 1972).

And finally we cite the work by Vladimirov *et al.* (2010) who presented an anisotropic model of bacterial run-and-tumble chemotaxis. This model consisted of considering the cell's tumbling angle as a function of the fraction of CW-rotating flagella as shown by experimental data (Turner *et al.*, 2000). The authors introduced this dependence in their previous model published in 2008 (Vladimirov *et al.*, 2008), where they suggested an isotropic model in which the cell's tumbling angle was chosen stochastically. The main purpose of the work was to study the effect of such a dependence of the tumbling angle on the chemotactic efficiency of the bacteria. The frequency of tumbles produced by each porting of CW-rotating motors was determined by using a chemosensory pathway model. The bacterium was simulated within a ligand free environment and the resulting frequencies were reused in the anisotropic model. The tumbling angle corresponding

to a particular fraction of CW-rotating flagella was chosen to be close to the experimental data found by Turner *et al.* (2000). As a result, the authors observed a great enhancement on chemotactic efficiency of the bacteria for those simulated from the anisotropic model compared to those simulated from isotropic model. Therefore, they suggested that in addition to increasing the mean run length toward the source, *E. coli* uses a new level of optimization of chemotactic ability that consists of fine-tuning the tumbling angle according to the swimming direction.

Most of these methods focused on the particularity of *E. coli* bacterium as had been used to investigate some specific questions. The specific questions that we are going to investigate are described in the next section.

1.4 Motivations and addressed questions

For bacteria, it is crucial to find food, which usually diffuses chemical attractant molecules that are also called chemoattractant. The bacteria use these chemoattractant molecules to direct their movement toward a zone of high density nutrient around the source. A good chemotactic performance that the bacteria should have is being able to converge as near to the source of food as possible whatever the chemoattractant gradient is. This study can help us to predict the behaviour of the cell subjected to different kind chemical attractant gradient, and this might allow us to control the development of the population of bacteria. Nowadays, bacteria are used for various purposes, comprising pharmaceutical manufacturing. For instance, with the advancement of biotechnological research, it has been found that *E. coli* bacteria can be used in the production of human insulin. Since chemotaxis is one of the key factors of the bacterial survival, it is important to study every aspect of it. We may need to detect any possible failure of this system or to improve it in order to enhance the life of the bacteria.

Although Eq 1.3.1 captures the chemotactic behaviour of the population of bacteria toward the source of attractant, including bacterial growth and interaction, it fails to emphasise the run-and-tumble movement that distinguishes *E. coli* bacteria from many other organisms and which is one of the aims of our work. Therefore we rather investigate an individual-centred model than a population level model. Bacterial growth and interaction are omitted to simplify our work.

In addition, the experimental results of Turner *et al.* (2000) shows an evidence of flagellar dependence on the tumbling fashion of the bacteria. Turner *et al.* (2000) discovered that the tumbling angle varies with the fraction of CW-rotating motor on the cell body. In consequence, although flagellated bacteria share a common ability such as chemotaxis, their behaviour depends as well on the number of flagella that they possess. And it is known that under some circumstances, the bacterium modulates its number of flag-

ella in order to have a better survival strategy. Therefore, we model the bacterial behaviour depending on their number of flagella and differentiate between the one-flagellated and the multi-flagellated bacteria. The behaviour of the one-flagellated bacteria is modelled separately from the other due to the fact that its motion depends entirely on its single flagellar motor and it can only effectuate one kind of tumble motion. Whereas, for the multi-flagellated bacteria there are many ways from which tumble can be generated, because any fraction of CW-rotating flagella generates a tumble.

Moreover, the possibility that the tumbling angle of the bacteria depends on the fraction of CW-rotating flagella, arises the fact that the reorientations effectuated during a tumble might be further biased. Particularly, within a chemical gradient environment, the rotational states of the bacterial flagella depends on the external environment. Therefore the fraction of CW-rotating flagella depends as well on the external gradient. The tumbling angle change of the bacterium could vary with the position of the bacteria. Thus, we speculate that within a non-zero gradient environment, the tumbling change distribution of the multi-flagellated bacterium is different from its tumbling change distribution within a ligand free environment. Therefore, we will compare the tumbling change distribution of the multi-flagellated bacteria within these two environment.

The models are used to address some particular question, such as the effect of tumbling angle strategy which is the tumble variation of the bacteria, and flagellar number (Vladimirov *et al.*, 2010) on the chemotactic efficiency. We also investigate the value of the directional persistence generated by the optimal tumble variation of the bacteria, which is the average positive tumbling change of direction. The chemotactic performance measure that we take is the ability of the bacterium to converge and to stay in a near neighbourhood of the source of food.

1.5 Thesis outlines

Working within a stochastic framework, omitting the "chemosensory pathway", we build an individual-centred model that consists of simulating random runs and tumbles of *E. coli*. The direction of the bacterium is entirely determined by its angle of direction, so that a very small variation of the angle of direction models runs whereas significant directional change are often needed to model tumbles. The work is organised as follows. In Chap. 2, we begin by defining the basic elements and assumptions used in the models. Both Chap. 3 and Chap. 4 focus on model-formulation of the bacterial motion, starting from the one-flagellated bacteria model to the multi-flagellated bacteria case. In, Chap. 5, we discuss some possible ways of investigating the models, by addressing some particular problem using numerical simulation. Finally Chap. 6 will be about discussion and conclusion.

Chapter 2

Basic elements of the models

The main purpose of this chapter is to familiarise ourselves with the basic elements and assumptions that will be used in our modelling of bacterial run-and-tumble chemotaxis. The bacterial movement toward a source of chemoattractant is our model focus. The flagellar dependence of tumble motion is included in the multi-flagellated bacteria model. Therefore, some elements such as bacterial environment and bacterial flagella behaviour are fundamental for our approach. Firstly, it is necessary to define an anisotropic bacterial environment, and this is illustrated in the following section.

2.1 Anisotropic bacterial environment

Our real world is a three-dimensional space, and so is the bacteria environment. However, the directions of the bacterium is often quantified by the angle between run-to-run, which is often defined as the difference between the polar angles (Berg and Brown, 1972; Turner *et al.*, 2000) without taking the azimuth angle into account. For this reason, it is sufficient to consider a two dimensional bacterial environment. This assumption also simplifies our work.

The source of food diffuses chemical attractant molecules into the bacterial environment following to the diffusion law. This creates an anisotropic environment that the bacteria perceive and use to find nutrients. The source of food could be degraded by other physical phenomena such as temperature or humidity, or even by the bacteria themselves as they feed on it. However, for the purpose of our study we assume that the degradation of the source and the chemical attractants occurs at a much more slower timescale than the bacterial lifetime. Thus, the distribution of chemical attractant can be defined to be fixed.

A Gaussian function is more appropriate to represent the anisotropic bacterial environment, since it is a particular solution of the diffusion equation. The source of chemical attractant is placed at the origin of the plane

where the chemical concentration peaks at its maximal value, c_{max}. Thus, the chemical density at a position $p = (x, y)$, in the space, is given by

$$c(p) = c_{max} e^{-\frac{||p||^2}{2\sigma^2}} = c_{max} e^{-\frac{x^2+y^2}{2\sigma^2}},$$

where σ is the standard deviation of the Gaussian distribution; which will be termed as "concentration parameter" throughout this work.

The choice of the concentration parameter σ is also crucial in defining an anisotropic bacterial environment. If the concentration parameter is too small, the chemoattractant concentration will be negligible almost everywhere. If it is too big, the chemoattractant molecules will be too spread, and the chemical distribution will tend to a uniform one. In either cases, the bacterial behaviour is not the scoop of this work. Thus, we restrict our investigations to $\sigma = 20\nu\Delta t$, $30\nu\Delta t$, and $40\nu\Delta t$ where $\nu = 25\mu m.s^{-1}$ is the average velocity of the bacterium (Nicolau *et al.*, 2009) and Δt is the time step of our simulations, so $\nu\Delta t$ represents one bacterial step.

We define the time step Δt to be only the mean run duration which is $1s$. In reality the Δt, at which the bacterium updates its position depends on the motions that it is effectuating. In the absence of a tumble, the position is updated after $\Delta t = 1$. The same holds in the case of a mixture of run-and-tumble because the tumble duration is included into the run duration. Whereas, in the case of a run succeeded by a fixed tumble the bacterium updates its position after $\Delta t = 1 + 0.1$ the sum of average run-and-tumble duration found by Berg and Brown (1972)($1s$ run and $0.1s$ tumble). However, incorporating this later case into the model would induce computational difficulties. Considering that we are using a fixed chemoattractant distribution profile, the ambient environment will not change during a tumble. In addition, the distance travelled by the bacterium in $0.1s$ is only $\nu \times 0.1 = 2.5\mu m$, thus the change in the chemical substance measurement can be neglected. Therefore, we may neglect the duration of a fixed tumble and then assume that $\Delta t = 1$.

Far away from the source the concentration of chemical is almost zero. The study therefore resumes to the uniform concentration case which is not of our interest. The problem is avoided by assuming a bounded domain for our study.

2.2 Boundary conditions

The bacterial environment is assumed to be bounded and we use a reflexive boundary. Whenever the bacterium encounters the boundary, the new position is the reflection of the previous one.

The shape of the distribution of chemical changes for any concentration parameter σ. Consequently, the concentration of chemical that the bacterium senses at any given position changes according to σ and it is not

appropriate to define a common boundary domain for all chemoattractant distribution. We find the magnitude of the concentration of chemical, only relevant within $C(0, 3\sigma)$, which is the circle of center $(0, 0)$ and radius 3σ.

Using this circular boundary, we can express the reflection angle as follows.

If $\theta(t)$ denotes the angle of direction of the bacterium at a given time t, and the bacterium is at position $p(t) = (x(t), y(t))$ at the boundary then the next angle of direction is given by

$$\theta(t + \Delta t) = 2\beta(t) - \theta(t) + \pi,$$

where $\beta(t)$ is an additional expression that is defined as follows

$$\beta(t) = \begin{cases} \arctan\left(\frac{y(t)}{x(t)}\right) & \text{if } x(t) \neq 0 \\ \frac{\pi}{2} & \text{if } x(t) = 0 \text{ and } y(t) > 0 \\ \frac{3\pi}{2} & \text{if } x(t) = 0 \text{ and } y(t) \leq 0. \end{cases} \tag{2.2.1}$$

The idea of the reflexive circular boundary domain is illustrated in Fig. 2.1.

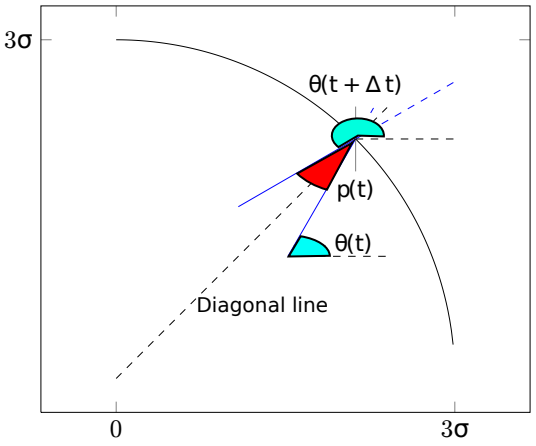


Figure 2.1: The reflexive circular boundary domain. The trajectory of the bacterium is in blue solid line and the angle marked in red is bisected by the diagonal line.

However, the bacterial position is always updated after $\Delta t = 1$. We cannot always expect the bacterium to be exactly at the boundary, even if its direction points to it. Therefore, we allow some computational margin and say that the angle of direction of the bacterium is reflected when its current position is in, or outside the boundary. i.e. $\theta(t+1)$ is given in Eq. 2.2.1 when $||p(t)|| \geq 3\sigma$. In this way, the bacterium will always stay within the domain.

Furthermore, a suitable probability distribution for the run and tumble motion of a bacterium is needed in order to define a stochastic model for the

bacterial behaviour. These quantities are highly correlated to the flagellar behaviour. Thus we find quite necessary to investigate some possible ways of quantifying the CW-CCW states of the flagellar motor and then deducing the tumble and run probability distribution from that.

2.3 Biological experiments

Bacteria normally perceive their external environment by interacting with individual chemoattractant molecules. However, we will not enter into the details of this interaction. Existing work such as the one by Morton-Firth and Bray (1998), deals with this approach to determine the probability of a CCW-rotation of a single flagellum. Their results predict the same phenomena seen in experimental work, which might validate both approaches. Therefore, we follow the experimental work which concluded that the bacteria perceive chemical concentration.

Flagellar behaviour are modulated through an internal mechanism of the bacterium that responds to external cue by sending signals to the flagellar motor. Despite the amount of information we already possess about this chemosensory pathway (Blair, 1995; Lengeler *et al.*, 1999), it is a very complicated mechanism to model mathematically because it involves a lot of variables, and it should be investigated separately. Therefore, we focus on finding the probability of the flagella to go in CCW or CW-rotation by looking into existing approaches.

The probability of a CCW-rotation of a single flagellum, usually called " the CCW-bias" or the "response function" had been investigated by Berg and Tedesco (1975); Block *et al.* (1982, 1983); Segall *et al.* (1986). Most of these studies considered a particular strain of *E. coli* that were grown so that the number of flagella per cell averaged to 1.5.

The bacterium was fixed by tethering one of its flagella to a glass surface and put in a ligand-free medium. In this way the rotational states of the flagellar motor was rather transmitted to the cell body than to the flagella. A CCW/CW-rotation of the cell body corresponded to a flagellar motor indicating a CCW/CW-rotation. The movement of the cell was recorded for several seconds within which the bacterium was exposed to an increase of chemical attractant in their environment. The time spent by the bacterium rotating in both CCW and CW-direction was recorded and plotted as a function of the total time. The same experiments were made on different cells several number of times, which would be similar to observing the behaviour of a large number of cells during the same period. Then at every time the fraction of bacteria that performed a CCW-rotation was taken as the measure of the CCW-bias (Berg and Tedesco, 1975; Block *et al.*, 1982, 1983; Segall *et al.*, 1986).

A fluctuation of the CCW-bias of the cells around the baseline (the pre-

stimuli level of the response) had been observed by experiment carried out on bacteria exposed to chemoattractant molecules as describe above. This shows that the bacteria perceive their external environment and respond to it.

Amongst others, two different approaches have captured our attention. These are the impulse response experiments and the adaptation model.

2.4 The impulse response approach for the CCW-bias

The single flagellum CCW-bias of the bacterium was determined from experiments that consisted of exposing tethered *E.coli* cells as described in Sec. 2.3, to a pulse of chemical attractant delivered iontophoretically (a brief diffusive wave of attractant (Segall *et al.*, 1986)). The fluctuation of the response around the baseline was called the "impulse response" (see Fig. 2.2) and it showed that the cell responds to the concentration of chemicals experienced at time t_0 during a period of about 4 s. If the stimuli was delivered at time t_0 the cell continues to respond to it until around $t_0 + 4$.

Three important phases of the impulse response can be highlighted (Fig. 2.2). The first phase lasts for about 1 s during which the cell's response increases to reach some maximal level indicating that the bacterium is sensitive to the increase of chemical attractant. After the dissipation of the chemical attractant, there is a second phase occurring approximately from $t_0 + 1$ to $t_0 + 4$. During this second phase, the response decreases and undergoes the prestimuli level showing that the bacterium was sensitive to the degradation of its conditions. Finally the response curve relaxes to the baseline $b_0 = 0.64$ which indicates that the cell looses record of the past concentration of chemical.

This is how the 4 s temporal memory of the bacteria had been discovered. In addition, if we change the origin of the x-axis in Fig. 2.2 to be the point of coordinate $(0.64, 0)$, the obtained function integrates to zero. This tells us that the cells compare the stimuli level experienced (Block *et al.*, 1982; Berg, 2006; Nicolau *et al.*, 2009). There are respectively a positive and negative response toward increase and decrease of chemoattractant concentration. The impulse response can be viewed as the memory that the cell gives to the particular pulse of chemoattractant to which it is exposed.

Each pulse of chemoattractant has its corresponding impulse response which increases with the magnitude of the specific pulse used (Segall *et al.*, 1986). However, due to the small size of the bacterium, it is very probable that the response saturates at some concentration level. In particular, the maximal response value can never go above one since it is a probability measure.

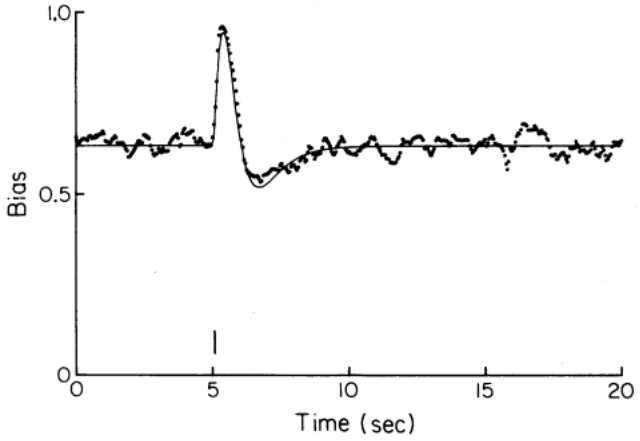


Figure 2.2: The probability of CCW-rotation of a single flagellar motor as a function of time, when the bacterium is subjected to a pulse of chemical attractant delivered at time $t_0 = 5$ (Segall *et al.*, 1986), refer to text for more explanations.

This impulse response is very important since it allows us to predict the response of a cell to any temporal change in concentration of a chemical. Any temporal change can be decomposed into a series of successive pulses. Therefore, the appropriate fluctuation of the response around the baseline b_0 can be obtained by integrating the corresponding series of impulse responses of appropriate size (Block *et al.*, 1982; Segall *et al.*, 1986).

Following Clark and Grant (2005) the form of the impulse response shown in Fig 2.2 could be approached with a curve of the form

$$I_g(t) = ge^{-t}\big(1 - \frac{1}{2}(t + \frac{1}{2}t^2)\big),$$

where g is a positive constant. Thus the CCW-bias is given by

$$b_{ccw(t)} = b_0 + b(t) = b_0 + \int_{-\infty}^{t} c(p(t'))I_g(t - t')dt', \tag{2.4.1}$$

where the bacterium is assumed to compare chemical measurement during $(t-1, t)$ with those experienced during the past $(-\infty, t-1)$, weighting the past time accordingly.

More precisely, $b_{ccw}(t)$ is assumed to fluctuate around the baseline b_0. Its variation is represented in Eq. 2.4.1 by the integral term. The measurement of chemical experienced at time t' is given by $c(p(t'))$ and it is referred to as an impulse of magnitude $c(p(t'))$. Its product with $I_g(t-t')$ is the magnitude of the impulse response of the bacterium to $c(p(t'))$. Finally, we sum over all the past measurement prior to the present time t using the integral $\int_{-\infty}^{t}$, to obtain the total variation of the CCW-bias around the baseline.

From another point of view, considering that bacteria are adaptive to environmental changes, another way of quantifying the response is to consider an adaptation model.

2.5 Adaptation model for the CCW-bias

In a region of zero-gradient (where the distribution of chemical is uniform), the bacteria maintain a constant CCW-bias (Block *et al.*, 1982, 1983). However, when they are subjected to abrupt changes in their environment, they respond in a transient manner that consists of adapting themselves to the new environment (Block *et al.*, 1982, 1983; Segall *et al.*, 1986). Their CCW-biases increase to a higher level for a moment before they resume to their normal behaviour. This is why within any uniformly distributed chemical attractant environment the behaviour of the bacteria is the same as in a ligand free medium.

Further experiments were conducted on tethered cells exposed to gradual change in the concentration of chemical attractant (Block *et al.*, 1983) that are also called "a ramp". Block *et al.* (1983) used two kind of ramps in their experiments, an exponential one and a sinusoidal one. An exponential ramp is define by increasing exponentially the chemoattractant that diffused on the cell body; whereas a sinusoidal ramp is created by diffusing a sinusoidal variation of chemoattractant concentration. Both experiments showed that the CCW-bias of the bacteria reflected the same change as in the chemoreceptor occupancy. Therefore, the CCW-bias was probably a result of a comparison between the present and the recent past receptor bound that the cell experiences (Block *et al.*, 1983).

These observations motivated Block *et al.* (1983) to adopt the Delbruck and Reïchardt(1956) model to approach the CCW-bias. Originally, this model was used to mimic the light adaptation in Phycomyces, and it had been used to model the chemotactic behaviour of *E.coli* in the following way

$$b_{ccw}(t) = g(P(c(t)) - A(c(t))), \tag{2.5.1}$$

where g is a constant of proportionality, $P(c(t)) = \dfrac{c(t)}{k_D + c(t)}$ is the current receptor occupancy modelled by the Michaelis-Menten kinetics law, and k_D is the dissociation constant of the receptors. A is the occupancy to which the bacteria is already adapted, and it satisfies

$$\frac{dA}{dt} = \frac{P - A}{\tau},$$

where τ is the adaptation time constant. Thus,

$$A(t) = e^{-t/\tau}A(0) + \int_0^t P(c(t'))e^{-(t-t')/\tau}dt'.$$

This argument states that as $A \longrightarrow P$, one has $\frac{dA}{dt} = 0$ and the cell is fully adapted. However, this also implies that when the bacteria is adapted to the uniform chemoattractant environment, according to Eq. 2.5.1, its CCW-bias is $b_{ccw} = 0$. As it is not the case for an adapted *E. coli* cell, we rather assume that

$$b_{ccw}(t) = b_0 + g(P(c(t)) - A(t)),$$

where b_0 is the baseline of the CCW-bias, and thus,

$$b_{ccw}(t) = b_0 + g(P(c(t)) - e^{-t/\tau}A(0) - \int_0^t P(c(t'))e^{-(t-t')/\tau}dt'. \qquad (2.5.2)$$

According to both methods, namely the impulse response and the adaptation model, the CCW-bias is always expressed as a function of the chemical concentration that the cell encounters. However, these approaches present some advantages and disadvantages that we discuss in the following section.

2.6 Alternative CCW-bias model

The trouble with the impulse response approach is that the linear dependence of $b(t)$ in Eq 2.4.1 on the concentration of chemical is only valid for small concentration of chemicals (de Gennes, 2004). The impulse response doesn't account for response saturation. The adaptation model rather assumes that the cells perform a temporal comparison of their receptor occupancy than concentration of chemical substances, and takes into account the saturation of the receptors of the bacteria and thus the saturation of the response.

However, following Eq 2.5.2 defining the adaptation model, the bacteria are assumed to compare only the chemical experienced at time t to those experienced during the past. This is in contradiction with the impulse response experiment that showed that the cells compares measurements made between $(t-1, t)$ to the ones between $(-\infty, t-1)$.

Therefore, we speculate that a combination of these two approaches is needed in order to capture all the features of the bacterial response function, and thus we define b_{ccw} as follows

$$b_{ccw}(t) = b_0 + g\int_{-\infty}^{t} P(c(t'))I(t-t')dt', \qquad (2.6.1)$$

where P is the receptor occupancy of the bacterium as defined in Eq. 2.5.1, and

$$I(t) = (1-b_0)e^{-t}\big(1 - \frac{1}{2}(t + \frac{1}{2}t^2)\big).$$

In this case $b_0 + I(t)$ is the saturated impulse response that peaks at maximal 1 at time $t = 0$ (the time at which the cell experiences the concentration of chemical that saturates the response). Here we assume that the bacteria make temporal comparison of their chemoreceptor occupancy. g is a positive constant that amplifies the response and henceforth will be referred as the "amplification parameter".

Due to an uncertainty about the magnitude of the amplification parameter, it will be chosen in such a way that b_{ccw} reflects enough change in the CCW-bias for the bacterial motion to be biased enough and different from a uniform environment behaviour. However, we are not to take very high quantity to avoid an over-biased system and a probability b_{ccw} above one.

Within the bacterial environment the value of b_{ccw} is a random value because it depends on the random trajectory of the bacterium. However, by choosing a biphasic function of the same form as the impulse response as a weight for the chemoreceptor occupancy measurement, we ensure that the CCW-bias of the bacteria relaxes back to the pre-stimuli level when the concentration of chemoattractant in the environment becomes uniform, since $P(c(t)) = c_0$ constant for every t and

$$\int_{-\infty}^{t} P(c(t'))I(t-t')dt' = c_0 \int_{-\infty}^{t} I(t-t')dt' = 0,$$

then we have $b_{ccw} = b_0$ and the cells just move in an unbiased fashion.

Moreover, although we have included the saturation of the bias response into the model, it would not be significant to observe the bacterial motion within an environment where the response would be highly saturated. The bacterial behaviour is already known in such an environment. Therefore we choose to work with concentrations that has maximal magnitude

$$c_{max} = 3k_D,$$

and we normalize the concentration of chemoattractant c by using

$$s = \frac{c}{c_{max}},$$

and thus we define the CCW-bias in the following way

$$b_{ccw}(t) = \min\left(1, \max\left(0, b_0 + g\int_{-\infty}^{t} G(s(t'))I(t-t')dt'\right)\right), \tag{2.6.2}$$

where

$$G(s) = \frac{s}{\frac{1}{3}+s}. \tag{2.6.3}$$

The bounds are there to ensure that the CCW-bias remains between 0 and 1. Nevertheless, we try to make a reasonable choice of g so that we do not need these bounds.

The CCW-bias of a single flagellum defined in Eq. 2.6.2, includes both temporal comparison of chemoattractant and adaptation to zero-gradient environment. This CCW-bias will reflect the chemotactic ability of *E.coli*. We will define run and tumble probability distribution as a function of this single flagellum bias according to the situations that we will encounter in the forthcoming chapters.

After determining which motion the bacterium undertakes, it is necessary to define some ways of characterising a run or a tumble. However, before defining our approach, it is important to understand the existing ways used to identify run-and-tumble motion via experiments. These are the only ways to get insight about the real bacterial behaviour. A bacterium like *E. coli* can have more than one flagellum, and by definition we know that a run motion is the product of all flagella in the CCW-rotation. Tumbles in contrary can appear in many ways, because not all flagella need to leave the bundle to produce a tumble motion. Depending on existing resources, people had been investigating different ways of quantifying tumble events, and we discuss these issues in the following section.

2.7 Variation in the tumble motion

Biological experiments were used to observe the behaviour of the bacteria. Amongst them we can cite the work by Berg and Brown (1972) and Turner *et al.* (2000). Both of these consisted of monitoring the bacteria within a ligand free environment.

From the tracking experiment by Berg and Brown (1972), one could not follow the behaviour of individual flagella, and thus tumble were identified as soon as the change in angle of direction from run to run were above some chosen threshold value 0.7 rad (Turner *et al.*, 2000). Each time that the change between run to run was observed to be greater than 0.7 rad, the bacterium were assumed to tumble and the magnitude of the change in direction was recorded. These change of directions that were supposed to be the only tumbling events were then averaged and then the resulting average was about 1.1 rad.

However, later on Turner *et al.* (2000) used a newly developed method for fluorescently labelling the cells filaments. They were able to depict the rotational states of individual flagella for *E. coli* bacteria that have more than one flagella. It had been discovered in this way, that in fact, tumble deviation varies according to the fraction of flagella that leaves the bundle i.e. the fraction of CW-rotating flagella.

The fewer flagella out of the bundle, the smaller the tumbling angle deviation is. The higher flagella out of bundle, the higher the tumbling angle deviation is. Therefore, it is highly probable that some events that were considered as a run in the tracking experiment were in fact tumbles produced

by few flagella out of bundle. They were also able to see that tumble deviations produced by few flagella out of bundle becomes rarely significant for higher flagellated bacteria. For these cases, the motion of the cells was observed to resemble more to a run motion. The average change from run to run was found to be around 1.01 rad $\pm\, 0.7$ rad.

In our mathematical model, we are going to define a running and tumbling angle change distribution. The direction of the bacterium can be represented by a single angle that changes depending on its state. We need to define two angle distributions that quantify respectively the directional changes resulting from a run and a tumble.

2.8 Run and Tumble angle deviation

The classical random walk of particle states that the random motion of the particle in a two-dimensional space is modelled by considering all the possible angle of direction in a continuum domain. However, as any directional changes of magnitude α gives the same direction as $\alpha+2k\pi$, $k \in \mathbb{N}$, and thus circular domain was used to draw random angles of directions (Codling *et al.*, 2008). These circular domains were modelled by using a distribution of angles such as the von Mises Distribution or the wrapped normal distribution that only defines the angles modulo 2π (Codling *et al.*, 2008).

However, there could be some particular circumstances where the change in direction effectuated during a tumble is greater than 2π, but could not be measured. Particularly in the case of the multi-flagellated bacterium, where the change in direction increases with the fraction of CW-rotating motor (Turner *et al.*, 2000). The fraction of CW-rotating flagella could produce a change of angle that are greater than 2π. Thus, we may require the possibility of turns greater than 2π, therefore, we differentiate changes of angles of magnitude α and of magnitude $\alpha + 2k\pi$. This assumption induces us to consider a model of directional change different from the classical random walk model and is achieved by considering the set of all possible tumbling change as the real line $\mathbb{R}$.

When the cells remains on a run motion, it tends to maintain its direction, the choice of run angle deviation should be restricted to a very small range of possibility that should all be close to zero. According to the definition of a run, the trajectory of the bacterium is only affected by rotational diffusion, but during a tumble there can be a significant change in the angle of direction. Therefore we have to distinguish between those two states. The direction of the bacterium is determined by the angle of direction $\theta(t)$ at time t.

The concept of rotational diffusion is analogous to translational diffusion in terms of angle orientation of a particle or molecule. Translational diffusion induces the distribution of particle's positions in the space to be at

an equilibrium. Similarly, rotational diffusion maintains their overall orientation angle at an equilibrium distribution.

When the bacterium senses that it is moving to the right direction, the best strategy to adopt in this case is to keep the same direction as before. This is what the flagella bundle is aiming to produce during a run. However, the trajectory of the bacterium is affected by the rotational diffusion (Schnitzer, 1993; Nicolau *et al.*, 2009; Vladimirov *et al.*, 2010) described in the previous paragraph. This induces a small perturbation in the trajectory of the cell. According to Nicolau *et al.* (2009) this small perturbation is taken into account by defining the next angle of direction after one time step Δt by

$$\theta(t + \Delta t) = \theta(t) + \eta D_{rot},$$

where $\eta \sim N(0, 1)$ (meaning that η is a random variable from the normal distribution $N(0, 1)$) is the small stochastic variation of the trajectory and D_{rot} is the rotational diffusion parameter. By using $N(0, 1)$, the support of run angle deviation is also $\mathbb{R}$, however, this distribution is concentrated around zero and thus the probability of choosing high values is very small. In addition, the run angle change becomes further small due to the rotational diffusion coefficient $D_{rot} = 0.15$ rad^2 s^{-1}. As a consequence, it is practically impossible to have high run angle change, which restrict the run angle deviation to a very small region around zero.

Tumble motion in contrast appears as soon as one or more flagella reverse to the CW-direction, which is usually the response of a movement to the wrong direction. To simulate tumbles we define an angle distribution, with modes $\Theta > 0$ and $-\Theta$, we denote it by $\mathcal{N}(\Theta, \epsilon)$, which is defined by

$$\mathcal{N}(\Theta, \epsilon) = (-1)^{B(1,\frac{1}{2})} N(\Theta, \epsilon) \tag{2.8.1}$$

where $N(\Theta, \epsilon)$ denotes the normal distribution with mean Θ and standard deviation ϵ and $B(n, p)$ is the binomial distribution composed with n experiments with p as probability of success. Eq. 2.8.1 means that

$$\text{if } \lambda \sim \mathcal{N}(\Theta, \epsilon) \text{ then } \lambda = (-1)^{r_0}\lambda_1 \text{ where } r_0 \sim B(1, \frac{1}{2}) \text{ and } \lambda_1 \sim N(\Theta, \epsilon).$$

The term $(-1)^{B(1,\frac{1}{2})}$ in the formula of the distribution $\mathcal{N}(\Theta, \epsilon)$ means that there is half-probability that tumble deviation is drawn from $N(-\Theta, \epsilon)$, and half-probability that it comes from $N(\Theta, \epsilon)$ (See Fig. 2.3). This is because the new angle of direction of the bacterium can be either smaller or greater than the previous one. However, we do not know whether or not the positive change or negative change is preferred. The distribution $\mathcal{N}(\Theta, \epsilon)$ allows us to assume that when the bacterium is redirecting its direction, there is a probability $\frac{1}{2}$ that the new angle of direction is either smaller or greater than the previous one.

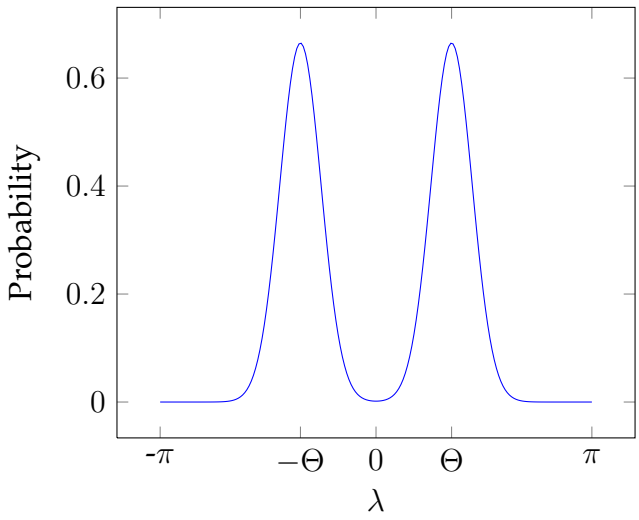


Figure 2.3: The form of the tumbling angle distribution generated by a given fraction of CW-rotating motors. It is composed with two Gaussian functions with respective means Θ and $-\Theta$ and the same standard deviation $\epsilon = 0.3$.

We cannot choose a very high ϵ because the two normal distributions shown in Fig. 2.3 should be as independent as possible. This is to avoid over-sampling the tumbling angle around 0 since it will not be considered as a significant change in the angle of direction.

Thus when the bacterium senses that the current direction is no longer favourable, it effectuates a tumble motion in order to reorient itself to a new direction. The new angle of direction is is modelled by

$$\theta(t + \Delta t) = \theta(t) + \lambda,$$

where $\lambda \sim \mathcal{N}(\Theta, \epsilon)$ is referred to as the tumbling angle deviation.

The experiments of Berg and Brown (1972) and Turner *et al.* (2000) had been investigating the mean angle difference between two runs. This is the average tumbling angle deviation that the bacteria displays within a ligand-free medium. Which means that each time the bacterium effectuates a tumble motion, its tumbling angle deviation was recorded and the mean of the collected data was computed. This quantity is often called "the directional persitence" and its value was computed in both experiments regardless on the number of flagella that the cells possess.

Depending on the parameters that we use in our model, we can have an expression of the directional persistence. However, each F-flagellated bacteria has their own tumbling fashion. Therefore, it is appropriate to define a proper directional persistence for each of them.

2.9 Directional persistence

Persistence refers to a tendency of a particle of keeping the same direction during its movement. However, the bacterium does not always keep moving in the same direction. It changes its direction using tumbles, when the conditions are unfavourable for its survival. Therefore, rather than saying that the bacteria persists in the same direction, we can say that it persists in moving toward a favourable region, and tumbles are used to reorient the cells to the right direction. Therefore, the term directional persistence rather relates to the tumbling angle changes.

In addition, we are interested in the strength of the change in direction during a tumble. Which can be quantified by the magnitude of the tumbling angle deviation. As a result, we define the directional persistence to be the average positive tumbling angle change of a bacterium.

For a multi-flagellated bacterium the tumbling angle change at a given time is correlated with the number of CW-rotating motor at this time, which in turns depends on the external cue that the bacterium measures at the same time. It would not be impossible that the directional persistence of a multi-flagellated bacterium depends as well on the external environment. It would be reasonable to investigate the tumbling tendency of the bacterium at every time step, which is the average positive tumbling angle change at every time step. The directional persistence of the multi-flagellated bacterium is then the average over time of these tumbling tendency measure.

However, the experimental work of Berg and Brown (1972); Turner *et al.* (2000) only displayed positive turning angles. We have also considered the alternative that they might have been only measuring the magnitude of change from run to run, which is the absolute value of the changes, and then averaged these changes to get the directional persistence. However, in our context we ensure that the standard deviation of the tumbling change distribution is always small, so that mathematically speaking the average absolute value of the change in direction and the positive tumbling angle change are very close quantities.

The directional persistence of the multi-flagellated bacteria within a zero-gradient of chemoattractant environment will be compared with its value within a non-zero-gradient environment.

The ability of the bacteria to survive in the environment using chemotaxis is defined as "the chemotactic efficiency" or " the chemotactic performance" of the bacteria. We expect it to be sensitive to the parameters that we use. The tumbling strategy of the bacteria is its ability to effectuate a tumble motions. For the one-flagellated bacterium there is only flagellum, therefore a single tumbling strategy associated. On the other hand, the multi-flagellated bacteria displays several possibility of a tumble motion, and thus its tumbling strategy would be represented by these tumble variation. Amongst others, we will investigate the variation of the chemotac-

tic efficiency of the bacteria with respect to their respective tumbling strategy. Therefore we need to define some ways of evaluating or measuring the chemotactic efficiency. We will define the chemotactic performance measure in Chap. 5.

Due to the dependence of the tumbling angle on the fraction of filament out of bundle, the bacterial behaviour is correlated with the number of flagellar filaments on their body. It is necessary to distinguish a one-flagellated bacteria model from a multi-flagellated one because one flagellum does not induce any variation in tumble motion and thus the tumble variation is not part of the model. The one-flagellated bacteria displays more possibility of run. We start by investigating the one-flagellated bacterial case in the following chapter.

Chapter 3

One-Flagellated bacterium

In this chapter we present the model of *E. coli* run-and-tumble chemotaxis for bacteria with one flagella. The behaviour in this case differs from the multi-flagellated case (Sec. 1.4).

We start by defining an appropriate run and tumble probability distribution within an anisotropic environment, as discussed in Sec. 2.1.

3.1 Run and tumble probability

Denote by $b_{run}(t)$ the probability of a run motion of the bacterium at time t, and $b_{tumble}(t)$ the probability of a tumble motion. The motion for a bacterium that has only one flagellum is entirely governed by the rotational direction of that single flagellum. Consequently, the trajectory is completely determined by a series of alternating run and tumble events.The bacterium runs when its flagellum turns in the CCW-direction and tumbles as soon as the flagellum reverses in the CW-direction. Importantly, there is not any possible mixture of run and tumble motion; the bacterium either runs or tumbles, never both at the same time.

The probability of a run motion is exactly the CCW-bias of a single flagellum described in Eq. 2.6.2. At time t the bacterium opts for a run motion with probability

$$b_{run}(t) = b_{ccw}(t)$$

and a tumble with probability

$$b_{tumble}(t) = 1 - b_{run}(t).$$

The single flagellum CCW-bias b_{ccw} depends on the trajectory of the bacterium. Within a non-zero gradient of chemoattractant distribution, its magnitude depends on the temporal measurement of the chemoreceptor occupancy of the bacterium (see Sec. 2.6 for more details).

A run and a tumble motion of the bacterium could be considered as random variables drawn respectively from some probability distribution generated by $b_{run}(t)$ and $b_{tumble}(t)$.

The probability of a run motion $b_{run}(t) = b_{ccw}(t)$ depends on the trajectory of the bacterium which remains a random walk, however biased it is. Therefore, $b_{run}(t)$ and $b_{tumble}(t)$ are also random quantities and it is not straightforward to find an exact formulation for the run and tumble probability distribution. However, using only the probabilities of run and tumble, we should be able to determine the actual motion of the bacterium. We discuss some possible ways of sampling a run or a tumble in the following section.

3.2 Sampling random run or tumble

We are interested in sampling run and tumble events from their respective probability distributions. As mentioned earlier, the right shape of the run or the tumble distribution cannot be determined because they depend on the random position of the bacterium. The only elements that we have are the respective run or tumble probability at any time t.

There are many different ways of sampling a random event by only using the probability of success of this event. We cite two methods:

1 Monte Carlo sampling consists of associating a random event with a random variable from the uniform distribution $U(0,1)$. For example if we want to sample a random tumble, we know that if $r \sim U(0,1)$ then

$$\text{Prob}_{U(0,1)}(r < b_{tumble}(t)) = b_{tumble}(t).$$

Therefore the two events "tumble at time t" and "$r < b_{tumble}(t)$" can be considered equivalent because they share the same probability of success.

2 The Binomial distribution, $B(n,b)$, gives the probability of the number of successes in a sequence of n independent yes/no experiments; each success having probability b. The single flagellum of the bacteria can only have two states which are: CCW with probability b_{ccw} and CW with probability $b_{cw} = 1 - b_{ccw}$. One can consider tumbling as being a successful CW-event at time t. Given that n_{cw} is a random variable from $B(1, b_{cw}(t))$, where n_{cw} is the number of flagella turning in the CW-direction, the cell runs at time t is equivalent to $n_{cw} = 0$ and conversely the cell tumbles at time t is equivalent to $n_{cw} \geq 1$.

The second method will be used to sample the run and tumble motion of a bacterium in our simulation. In the next section we introduce the model for the one-flagellated case.

3.3 Mathematical model for the one-flagellated bacteria

The following coupled set of equations comprise Model 3.3.1, and is used to simulate the trajectory of a single bacterium. The notation is identical to that used in Chap. 2.

$$s(t) = s(p(t)) = e^{-\frac{||p(t)||^2}{2\sigma^2}}, \tag{3.3.1a}$$

$$b_{run}(t) = b_{ccw}(t) = \min\left(1, \max\left(0, b_0 + g\int_{-\infty}^{t} G(s(t'))I(t-t')dt'\right)\right), \tag{3.3.1b}$$

$$b_{tumble}(t) = 1 - b_{run}(t), \tag{3.3.1c}$$

$$\Delta\theta(t) = \begin{cases} \lambda \sim \mathcal{N}(\Theta, \epsilon) & \text{with probability } b_{tumble}(t) \\ \eta D_{rot}\,(\eta \sim N(0,1)) & \text{with probability } b_{run}(t) \end{cases}, \tag{3.3.1d}$$

$$\theta(t+\Delta t) = \begin{cases} 2\beta(t) - \theta(t) + \pi & \text{if } ||p(t)|| \geq 3\sigma, \beta \text{ is given by Eq. 2.2.1} \\ \theta(t) + \Delta\theta(t) & \text{otherwise} \end{cases}, \tag{3.3.1e}$$

$$p(t+\Delta t) = p(t) + \nu\Delta t\begin{pmatrix} \cos\theta(t+\Delta t) \\ \sin\theta(t+\Delta t) \end{pmatrix}. \tag{3.3.1f}$$

The anisotropic bacterial environment is governed by the function s described in Sec. 2.6, this is a dimensionless quantity. $s(t)$ (Eq. 3.3.1a) is the normalized chemoattractant concentration that the bacterium perceives at time t. The concentration parameter σ defines the spread of chemoattractant molecules (Sec. 2.1). The signal that the cell compares simplifies to G which is given by Eq. 2.6.3 as we assume that the peak of chemoattractant concentration is $3k_D$ (refer to Sec. 2.6) to avoid a saturated bias and produce a zero-gradient environment behaviour.

The parameter g, defined in Sec. 2.6, amplifies the response of the bacteria to its external environment. We choose a reasonable value for g, such that the CCW-bias does not exceed one, nor goes below zero in the case of high concentration changes. Furthermore, the upper and lower bounds for the expression of b_{ccw} ensures that it is a probability measure.

In Sec. 3.1, we deduced that the probability of run, b_{run}, is the probability of CCW-motion of the flagellum. Consequently, we can obtain b_{run} from Eq. 3.3.1b. As detailed in Sec. 2.6, the bacterium is assumed to "remember" the chemoreceptor occupancy experienced in the past, giving more weight to the recent past. This memory spans approximately 4s.

The run and tumble motions can be considered as random variables with respective probabilities, b_{run} and b_{tumble}. The angle deviation expressed in Eq. 3.3.1d can represent either a running or a tumbling angle deviation de-

pending on the situation of the bacterium. A tumble appears with probability b_{tumble} and the tumbling angle deviation is sampled from the distribution $\mathcal{N}(\Theta, \epsilon)$ as defined in Sec. 2.8. A run motion appears with probabilty b_{run}, and the angle deviation is just a small stochastic variation in the trajectory that represents the effects of rotational diffusion.

The behaviour of the bacteria far away from the source is not of interest because the concentration of chemical in that region is almost zero everywhere. Therefore, we define a reflective boundary for the domain of study. We choose the boundary $C(0, 3\sigma)$ because the distribution of chemoattractant is mostly significant in that region. At time t the bacterium can be at the boundary or outside, and we define the angle of direction at time $t + \Delta t$ in Eq. 3.3.1e to ensure that it stays within the domain.

Finally, the position of the bacterium at time $t + \Delta t$ ($\Delta t = 1$, see Sec. 2.1) is given by Eq. 3.3.1f, where ν is the average velocity of the bacterium and $(\cos\theta(t + \Delta t), \sin\theta(t + \Delta t))$ is the unit vector pointing in the new direction.

To our knowledge, it is difficult to analytically study Model 3.3.1 and we therefore use computer simulation and numerical analysis to investigate the bacterial behaviour. The details of the model implementation can be found in App. A.

The tumbling strategy of the bacterium consists of choosing a random tumbling angle deviation from the distribution $\mathcal{N}(\Theta, \epsilon)$. The mean positive tumbling angle deviation is referred to as the directional persistence. The directional persistence of the one-flagellated bacteria is described in the next section.

3.4 Directional persistence

For a one-flagellated bacterium, tumbling events are all equivalent, being the result of a single CW-rotating flagellum. Therefore the tumbling angle distribution is the same each time the bacteria goes into a tumble motion. This means that the tumbling angle deviation, λ, is always sampled from a unique distribution as defined in Sec. 2.8.

The directional persistence φ_1 of the one-flagellated bacteria is given by the positive mode of the tumbling angle distribution Θ, i.e. $\varphi_1 = \Theta$.

Model 3.3.1 is built to study the motion of the one-flagellated bacterium. However, bacteria are known to possess more than one flagellum. In particular, *E. coli* is usually known to possess in average six flagella (Blair, 1995). In addition, it is also known that under certain conditions, depending on their external environment, modulating the number of flagella is part of the bacterial survival strategy. Therefore, we would like to observe the impact of the number of flagella on the chemotactic efficiency of the bacteria.

The experiments conducted by Turner *et al.* (2000) showed that multi-flagellated bacteria are capable of adjusting their tumbling angle deviation.

It is necessary to build a separate model for this kind of bacteria. The following chapter presents a model for the multi-flagellated bacteria. The model should account for any multi-flagellated bacteria. However, we restrict our investigations to bacteria that has at most six flagella.

Chapter 4

Multi-flagellated bacteria

In the case of the one-flagellated bacterium described in Chap.3, tumbling events were all equivalent, the result of a single tumbling angle distribution, $\mathcal{N}(\Theta, \epsilon)$. This caused the directional persistence to be the positive mode of the distribution. However, for multi-flagellated bacteria it is necessary to introduce the concept of partial tumbling. This is because not all flagella are required to turn in the CW-direction for a tumble event. Each F-flagellated bacteria can have its own directional persistence and we have more than one distribution to consider.

In this chapter we propose a model for this latter kind of bacteria. We begin by defining a model for the tumble variation.

4.1 Modelling the tumble variation

In contrast to the one-flagellated case, one flagellum in the CCW-direction is not sufficient to produce a run motion. All flagella on the cell body has to turn in the CCW-direction and form a bundle to propel the cell in the forward direction. Partial tumbling appears as soon as there is one CW-rotating flagellum, which means that any events that contain at least one CW-turning flagellum is a tumble event.

Turner *et al.* (2000) has shown that the tumbling angle deviation varies with respect to the number of CW-rotating flagella. The smaller the fraction of flagella that turn in the CW-direction, the smaller the angle deviation is.

Each fraction of CW-rotating motors produces their own tumbling angle deviation, therefore it is reasonable to associate a particular tumbling angle distribution $\mathcal{N}$ as described in Sec. 2.8 to each of them. In addition, the experimental data of Turner *et al.* (2000) suggests the possibility of a non-linear dependence of the tumbling angle with respect to the fraction of CW-rotating flagella. A reasonable way of incorporating this feature into the model is to assume that there is cooperative behaviour between the flagella in producing the tumbling angle deviation. That is to emphasize that the

more flagella the bacterium has, the less probable is a significant change of direction produced by fewer CW-rotating motors.

These assumptions are modelled by setting the positive mode Θ_F of the tumbling angle distribution of a F-flagellated bacterium, associated to a particular fraction of CW-rotating flagella in the following way,

$$\Theta_F(F_{cw}(t)) = \frac{F_{cw}(t)^l}{{F_0}^l + F_{cw}(t)^l}\phi_F. \tag{4.1.1}$$

$F_{cw}(t)$ is the fraction of flagella in the CW-rotating direction at time t and l is a Hill coefficient. ϕ_F is the reference angle for the positive mode, Θ_F, of the tumbling angle distributions. The positive mode is always some fraction of ϕ_F.

In addition, by assuming that l increases with the total number of the flagella on the cell body (Table. 4.1), we underline the difficulty of seeing a significant change in the tumbling angle produced by a small fraction of CW-rotating flagella for higher flagellated bacteria as shown in the experimental data of Turner *et al.* (2000)(Fig. 4.1). The value of F_0 provides the half saturation of the directional change and we estimated a value of $F_0 = 0.5$.

There are now F tumbling angle distributions of the form, $\mathcal{N}(\Theta_F(F_{cw}), \epsilon_F)$, to consider in the model. The maximal tumbling angle change distribution is approximately $\mathcal{N}(\phi_F, \epsilon_F)$, in other words the largest positive mode that any of the distributions can have is ϕ_F. Whatever the tumble variation strategy, the bacteria turns maximally when all its flagella are rotating in the CW-direction.

Furthermore, to emphasize the decay of the tumbling angle with respect to the fraction of CW-rotating motors, we assume that the standard deviation of the tumbling angle distribution described in Eq. 2.8.1 also decreases with the fraction of CCW-rotating flagella. We model this as a simple linear decay,

$$\epsilon_F(t) = \epsilon_F(F_{cw}(t)) = F_{cw}(t)\epsilon_0, \tag{4.1.2}$$

where ϵ_0 is the maximal standard deviation which is associated to having all flagella turning in the CW-direction. We choose an ϵ_0 that is greater than the standard deviation of the tumbling change distribution in the one-flagellated model because it will be effectively divided amongst the $F_{cw} \in 1, ..., F$.

It is not possible to model such a tumble variation without any evaluation of the fraction of CW-rotating motors, F_{cw}. Therefore, we need to find a reasonable expression to do this.

4.2 The fraction of CCW-rotating flagella

Determining a suitable expression for the number of CW-rotating flagella is not straightforward. The rotational states, CW or CCW, of individual

Table 4.1: The Hill coefficient defining the tumbling angle of each flagellated bacteria assuming that, as F increases, it becomes more and more difficult for the F-flagellated bacteria to effectuate a high change of direction with a small fraction of CW-rotating motor (refer to text for more explanation).

F	2	3	4	5	6
l	1	2	3	4	5

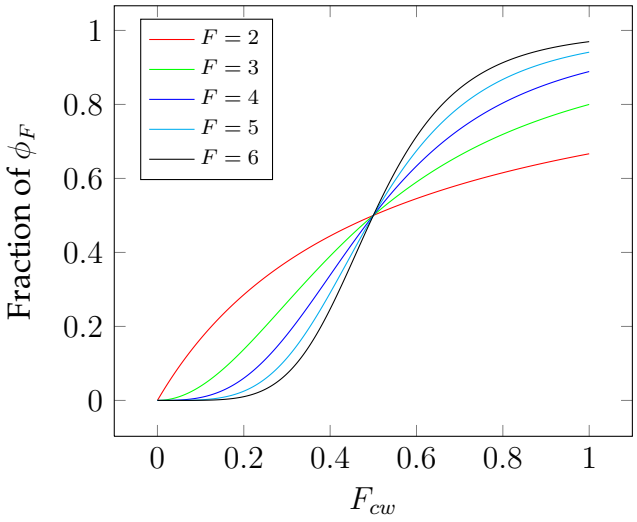


Figure 4.1: The fraction of tumbling angle deviation ϕ_F used by a F-flagellated bacteria as a function of the fraction of CW-rotating flagella. As F increases the portion of ϕ_F used for tumbling decreases for small F_{cw}, so that the motion of the bacteria tends more and more to a run motion.

flagella is very hard to picture without analysing the chemosensory pathway and building an appropriate model. Biochemically, a protein molecule within the cell body called, CheYp, interacts with flagellar motors to signal CW-rotation. In particular, the interaction of the CheYp protein with all the flagellar motors needs to be modelled to determine the rotational states of each. To our knowledge, this approach has not been investigated thoroughly. Usually, one only considers the CCW-bias of a single-flagellum as a function of the concentration of CheYp, without entering into the biochemical detail of the CheYp-Flagellar motor interaction (Morton-Firth and Bray, 1998; Tindall *et al.*, 2008).

We model the CCW-bias by making the simplest assumption, which is that the rotational states of individual flagella are independent of the rotational states of the others. Furthermore, we assume that they all have the

same CCW-bias, b_{ccw}, as described by Eq. 2.6.2. It follows that one can consider the number of CW-rotating flagella $n_{cw}(t)$ as a random number coming from the binomial distribution $B(F, b_{cw}(t))$, where b_{cw} denote the CW-bias of a single flagellum and is given by

$$b_{cw}(t) = 1 - b_{ccw}(t),$$

then,

$$F_{cw}(t) = \frac{n_{cw}(t)}{F}.$$

If $n_{cw}(t) \sim B(F, b_{cw}(t))$, then it follows that we have a run at time t when $n_{cw}(t) = 0$, and a tumble at time t for any $n_{cw}(t) \geq 1$.

In summary,

$$\text{Tumbles} = \{n_{cw} = k \text{ such that } k \in \{1, ..., F\}\}, \text{ and,} \tag{4.2.1a}$$

$$\text{Runs} = n_{cw} = 0. \tag{4.2.1b}$$

According to Eq. 4.2.1 the set of run events is very small compared to the set of tumble events. As a result, by assuming that the bacterial flagella share the same CW-bias, we also assume that the mutli-flagellated bacteria is less capable of a true run motion. It is then important that the tumble variation compensate for this lack of run events. Since the binomial distribution favours tumbles with a smaller fraction of CW-rotating flagella, this partially remedies any discrepancies. The binomial distribution also gives small probabilities of tumbles produced by high fraction of CW-rotating flagella. Hence, high tumbling angle change is unlikely to happen. From this, we infer that higher flagellated bacteria can only effectuate a very limited tumbling change. of direction.

At this stage, the multi-flagellated bacteria model can be presented.

4.3 Mathematical model for multi-flagellated bacteria

In this section we assemble the model for a multi-flagellated bacterium in Model 4.3.1.

$$s(t) = s(p(t)) = e^{-\frac{||p(t)||^2}{2\sigma^2}}, \tag{4.3.1a}$$

$$b_{ccw}(t) = \min\left(1, \max\left(0, b_0 + g\int_{-\infty}^{t} G(s(t'))I(t-t')dt'\right)\right), \tag{4.3.1b}$$

$$b_{cw}(t) = 1 - b_{ccw}(t), \tag{4.3.1c}$$

$$n_{cw}(t) \sim B(F, b_{cw}(t)) \tag{4.3.1d}$$

$$\Delta\theta(t) = \begin{cases} \lambda \sim \mathcal{N}(\Theta_F(F_{cw}(t) = n_{cw}(t)/F), \epsilon_F(t)) & \text{if } n_{cw}(t) \neq 0 \\ \eta D_{rot}\ (\eta \sim N(0,1)) & \text{otherwise} \end{cases}, \tag{4.3.1e}$$

$$\theta(t+\Delta t) = \begin{cases} 2\beta(t) - \theta(t) + \pi & \text{if } ||p(t)|| \geq 3\sigma, \beta \text{ is given by Eq. 2.2.1} \\ \theta(t) + \Delta\theta(t) & \text{otherwise} \end{cases}, \tag{4.3.1f}$$

$$p(t+\Delta t) = p(t) + \nu\Delta t\begin{pmatrix} \cos\theta(t+\Delta t) \\ \sin\theta(t+\Delta t) \end{pmatrix}. \tag{4.3.1g}$$

$\Theta_F(t)$ and $\epsilon_F(t)$ are respectively governed by Eq. 4.1.1 and Eq. 4.1.2. And the amplification parameter g is chosen using the same criteria as for the one-flagellated case.

The anisotropic bacterial environment remains unchanged, represented by Eq. 4.3.1a, which is the same as Eq. 3.3.1a. σ is the concentration parameter that controls the spread of chemoattractant (refer to Sec. 2.1).

In addition, the run and tumble probability is different from those defined in Chap. 3. Each flagellum on the cell body has its own behaviour. Assuming that the motions of the flagella are independent from one another and that they have the same probability of CCW-rotation, the CCW-bias of a single flagellum can be governed by Eq. 4.3.1b which is the CCW-bias defined in Sec. 2.6. The number of flagella turning in the CW-rotation n_{cw} is expressed in Eq. 4.3.1d (refer to Sec. 4.2 for more details).

The bacterium effectuates a run only when all its flagella turns in the CCW-direction, i.e. when $n_{cw} = 0$ (Sec. 4.2). Tumbles can appear as soon as one flagellum reverses to the CW-direction. The angle deviation is expressed in Eq. 4.3.1e.

The rest of the equations in Model 4.3.1 are the same as in Model. 3.3.1. The angle of direction of the bacterium is updated with Eq. 4.3.1f, checking boundary condition with reflective boundary $C(0, 3\sigma)$ and the position of the bacterium is updated using Eq. 4.3.1g.

Furthermore, due to the dependence of tumbling fashion on the fraction of CW-rotating flagella and the number of flagella F on the cell body, each F-flagellated bacterium now has its own directional persistence. However, the directional persistence that results from the multi-flagellated bacteria model is different from the one obtained in the one-flagellated bacteria

model. In the next section we define the directional persistence of the F-flagellated bacteria when $F > 1$.

The details of the numerical implementation of Model 4.3.1 can be found in App. A and the investigations that we perform on the multi-flagellated bacterial behaviour are described in Chap. 5.

4.4 Tumbling tendency and directional persistence per F-flagellated bacteria

The positive mode of the tumbling angle distribution of a F-flagellated bacterium is likely to be any of the $\Theta_F(k/F),\ k \in 1, ..., F$. As a result, the tumbling tendency of the bacterium as defined in Sec. 2.9 is the weighted average of all positive directional change. The tumbling angle deviation is eventually sampled from one of the $\mathcal{N}(\Theta_F(k/F), \epsilon_F)$, $k \in 1, ..., F$ with a certain probability of being used at every time step. Hence, we have the following expression of the tumbling tendency at time t.

$$\begin{aligned}\bar{\Theta}(t) = &\sum_{k=1}^{F}\{\text{Probability that } F_{cw} = k/F \text{ at time } t\} \\ &\times \Theta_F(k/F),\end{aligned} \tag{4.4.1}$$

Then we have

$$\begin{aligned}\bar{\Theta}(t) &= \sum_{k=1}^{F} P_{\text{binom}}(n_{cw} = k,\ F,\ b_{cw}(t))\Theta_F(k/F) \\ &= \sum_{k=1}^{F} P_{\text{binom}}(n_{cw} = k,\ F,\ b_{cw}(t)) \quad \frac{k^l}{F^l {F_0}^l + k^l}\phi_F,\end{aligned} \tag{4.4.2}$$

where $P_{\text{binom}}(n_{cw} = k,\ F,\ b_{cw}(t))$ is the probability that $n_{cw} = k$ according to the binomial distribution $B(F, b_{cw}(t))$ as defined in Sec. 4.2. This is because the bacterium is assumed to sample its tumbling angle using the tumbling angle distribution generated by $F_{cw} = k/F$ with probability $P_{\text{binom}}(n_{cw} = k,\ F,\ b_{cw}(t))$.

In addition, the quantity Θ_F depends on the fraction of CW-rotating motors F_{cw}, and this depends on the external environment. Therefore, the tumbling tendency of the multi-flagellated bacteria depends on the external environment as well. Since we are only taking the tumble deviation after observing a tumble motion, we estimate the number of tumbles over time. The directional persistence would be the average magnitude of tumbling tendency if a tumble appears. The total probability of tumble at time t is

given by,

$$\begin{aligned} b_{tumble}(t) &= \sum_{k=1}^{F} P_{\text{binom}}(n_{cw} = k,\ F,\ b_{cw}(t)), \\ &= 1 - P_{\text{binom}}(n_{cw} = 0,\ F,\ b_{cw}(t)), \end{aligned}$$

Therefore the estimated number of tumbles over time is,

$$N_{tumble} = \sum_{t=0}^{S} b_{tumble}(t),$$

where S is the total simulation time.

Hence, the directional persistence of the F-flagellated bacteria that we denote, φ_F, is the average over time of this tumbling tendency where the bacterium tumbles. Therefore,

$$\varphi_F = \frac{\sum_{t=0}^{S} \bar{\Theta}(t)}{N_{tumble}}. \tag{4.4.3}$$

However, in a zero-gradient environment, including the ligand free environment, the probability of tumble is the same every time. The total probability of tumble in a zero-gradient environment is given by

$$b_{tumble} = 1 - P_{\text{binom}}(n_{cw} = 0,\ F,\ 1 - b_0) = 1 - {b_0}^F.$$

The tumbling tendency becomes independent of time and the zero-gradient environment directional persistence is expressed in the following equation:

$$\varphi_F = \sum_{k=1}^{F} \frac{P_{\text{binom}}(n_{cw} = k,\ F,\ 1 - b_0)}{1 - {b_0}^F} \quad \frac{k^l}{F^l {F_0}^l + k^l} \phi_F. \tag{4.4.4}$$

Remark In fact, although we distinguished between the one-flagellated and the multi-flagellated bacteria, we can say that Model 3.3.1 for the one-flagellated bacteria is a particular case of the multi-flagellated Model 4.3.1. Since there is no fraction of flagella to consider in the model, we can set $F_0 = 0$. By fixing $\epsilon_F = \epsilon$ to 0.3, Model 4.3.1 resumes to Model 3.3.1. From Eq. 4.4.2, the probability terms will simplify, because $F = 1$ and $b_{tumble}(t) = P_{\text{binom}}(n_{cw} = 1,\ F, b_{cw}(t))$ for every t, the summation term over k can be removed because there is only one k, then from Eq. 4.4.3 we can get $\varphi_F = \Theta_F(F_{cw} = 1) = \Theta = \varphi_1$.

We conclude this chapter with some discussion about Models 3.3.1 and 4.3.1.

4.5 General remarks about the models

In this section, we compare our tumble variation model to the simple random walk model.

If we assume that the length ς of the steps that the particle can perform is constant, the simple random walk model in polar coordinates allows the next position of the particle to be any position on the circle with radius ς centred on the current position of the particle. Any turn of magnitude $\alpha + 2k\pi$ would result in the same direction. Reasoning in this way, the turn angle deviations should only be defined modulo 2π. Such a model requires directional change distributions such as the von Mise distribution or the wrapped normal distribution to simplify the modelling (Codling *et al.*, 2008).

The motion of a single flagellated bacterium is governed by its single flagellum and thus we only use a unique tumbling angle distribution. There is no variation in the tumbling fashion of the bacterium, and the form of the turning angle distribution is given by Fig. 2.3. Therefore, its tumbling motion is similar to the simple random walk of a particle with constant step length ν. Using the distribution in Fig. 2.3 will induce the periodicity of period 2π on the result of any investigation. The property of an angle implies that if $0 < \alpha < \pi$, then the angle $\pi + \alpha$ is equivalent to $-(\pi - \alpha)$. Therefore, any results obtained using the tumbling angle distributions $\mathcal{N}(\pi + \alpha, \epsilon)$ and $\mathcal{N}(-(\pi - \alpha), \epsilon)$ will be the same. In addition, the distribution $\mathcal{N}$ is symmetrical with respect to 0, i.e. $\mathcal{N}(-\Theta, \epsilon) = \mathcal{N}(\Theta, \epsilon)$, using $\mathcal{N}(\pi + \alpha, \epsilon)$ is the same as using $\mathcal{N}(\pi - \alpha, \epsilon)$. Consequently, any results obtained using $\Theta \in (0, 2\pi)$ will be symmetrical with respect to $\Theta = \pi$.

For the F-flagellated bacterium with $F > 1$, there are variations in the tumbling events. Each fraction of CW-rotating flagella generates its own turning angle distribution, and thus there are F possibilities of turning angle distribution. The hypothesis that the change of direction depends on the fraction of CW-rotating flagella (Turner *et al.*, 2000) already implies that the tumbling motion of the multi-flagellated bacteria may be further biased by the external environment. This is because the rotational states of the flagella depends on the external environment. Since we assumed that the number of CW-rotating flagella is following a Binomial distribution, our total turning angle probability diverges from that in Fig. 2.3. Instead it looks like the distribution in Fig. 4.2 representing the total tumbling angle deviation strategy of a four-flagellated bacterium when it is only allowed to do at most two turn i.e. when $\phi_F = 4\pi$, within a zero-gradient environment (the distribution is given in Eq. 4.5.1). Thus, the total turning angle distribution that we use in our context is different from the simple random walk notion. It is rather biased by the number of CW-rotating motor. The form of the probability distribution of a multi-flagellated bacteria described by the model will always resemble that in Fig. 4.2, and the number of positive modes of the

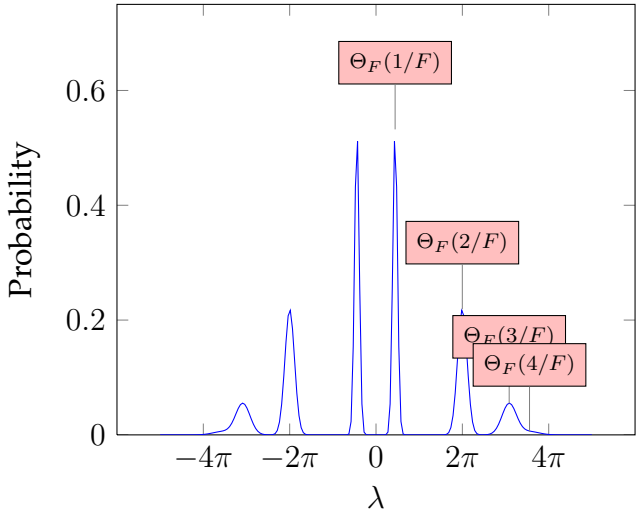


Figure 4.2: The model of the tumbling angle distribution in a zero-gradient environment for a bacterium that has $F = 4$ flagella, and that can at most effectuate a tumbling change deviation of $\phi_F = 4\pi$ rad. The Θ_Fs are respectively the mean positive tumbling angle deviation generated by a given fraction of CW-rotating motors.

distribution is the same as the number of flagella.

Total tumbling angle distribution for $F = 4$ in a zero gradient environment

$$= \sum_{k=1}^{F} \frac{P_{\text{binom}}(n_{cw} = k,\ F,\ 1 - b_0)}{1 - {b_0}^F} \mathcal{N}(\Theta_F(k/F), \epsilon_F(k/F)) \tag{4.5.1}$$

In addition, although the tumbling angle distribution of the multi-flagellated bacteria (Ex: 4.2) remains symmetrical around 0 the periodicity is completely removed. This is because the positive modes of the respective $\Theta_F(F_{cw})$ depend on each other, they are all a function of ϕ_F. Thus if one changes by changing ϕ_F then all the others change. Due to the Hill function considered in Eq. 4.1.1, there is no guaranty that if one of the $\Theta_F(F_{cw})$ shifts by 2π or of any other amount that the others would also. Therefore, using this tumble variation distribution we cannot work modulo 2π, nor modulo any other number, and we loose the periodicity.

At this stage, we can perform some simulations of the models. This can be done by addressing particular problems and interpreting the numerical results.

Chapter 5

Numerical investigation and results

One of the many problems that one may want to investigate is finding the optimal tumbling strategy of the bacteria. That is the tumbling angle change variation that they should adopt in order to have a better survival. Tumbling strategy varies from one bacteria to another. We are seeking to know whether or not there are particular tumble strategy that the cell should adopt in order to get a better chemotactic efficiency.

For bacteria that has a single flagellum, there is not any possible variation in their tumbling angle deviation. Therefore, they have to possess some precise tumbling strategy to maintain their directions toward a zone of high nutrient and to stay in that region. As their probability of run and tumble depends on their single flagellum, it is more probable for them to go on a run motion, when the conditions are good. Their tumbling angle strategy should provide a good chemotactic performance for them in order to survive. For this kind of bacterium there is only a single turning angle strategy, which is represented as Θ. The tumbling angle distribution used by the one-flagellated bacteria is unique and has the same shape as $\mathcal{N}(\Theta, \epsilon)$ (Fig. 2.3), which is periodic of period 2π, therefore we should restrict our numerical simulations to $(0, 2\pi)$, but in order to check the periodicity of the results we run the numerical simulations for $\Theta \in (0, 4\pi)$.

In contrast, a multi-flagellated bacterium displays a large variety of tumbling angle fashion. It runs only when all its flagella are in the CCW-rotation. Since we have assumed the bacterial flagella has the same probability of CCW-CW rotation, and that they are independent, the number of CW-rotating flagella follows a binomial distribution that changes with time, which is the single flagellum's CCW-bias described in (Eq. 2.6.2). This implies that it becomes more and more difficult for a the multi-flagellated bacterium to effectuate a run motion as its number of flagella gets higher. This lack should be compensated by a good tumble variation strategy. We are interested to find the optimal tumbling strategy for a F-flagellated bacterium.

Any F-flagellated bacteria display exactly F-tumbling angle strategy, and its tumbling angle distribution at every time steps, and its tumbling angle distribution has F positive modes (Ex. 4.2). All the $\Theta_F(F_{cw})$ are correlated with each other via Eq. 4.4.3 by $\phi_F = \max(\Theta_F(F_{cw}))$, therefore if we want to know, which configuration of angle provides the most beneficial tumbling strategy, we need to study the sensitivity of the chemotactic efficiency with respect to ϕ_F. However, due to computational matter we are going to restrict our domain of study within the interval $(0, 10\pi)$.

Before investigating the variation of the chemotactic efficiency, it is necessary to define reasonable ways of measuring the chemotactic performance of the bacterium. This is discussed in the next section.

5.1 Chemotactic performance measure

Chemotactic efficiency determines whether or not the chemotactic ability of the bacterium is good enough to provide a better survival. As we mentioned in Sec. 1.4, the chemotactic performance measure that we are going to investigate is the ability of the bacterium to converge and to aggregate in a near neighbourhood of the source. The bacterium has a better survival strategy when it converges and stays around the source because it can obtain more nutrients.

The main problems that can arise are how to determine whether or not the bacterium converges to the source; and if it converges, how to know if it stays around the source.

To determine whether or not the bacteria converge and displays a steady state around the target region, which is the source placed a the origin of the plan, it is sufficient to study the variation of the spread of the bacterial position with respect to the source. This is the measure of the standard deviation of the bacteria around the source. In order to measure this quantity, we simulate the 100 bacteria within our chosen chemoattractant distribution. Initializing their positions in the bacterial environment in such a way that their standard deviation from the source is large enough at the beginning, so that we can see their progression.

$$STD(t) = \sqrt{\frac{1}{100}\sum_{i=1}^{100} x_i^2(t) + \frac{1}{100}\sum_{i=1}^{100} y_i^2(t)} \tag{5.1.1}$$

The bacterial steady state would be observed when the $STD(t)$ tends to a constant value STD_0. However aggregation around the source is only reached when STD_0 is small. This will mean that the bacteria reaches a steady state and that the steady state zone is the closest to the source of food. In this case the bacteria have a better chance to survive because the nutrient is highly concentrated in that region. The steady state standard

deviation from the source of the bacteria would be represented by STD_0 given as follows

$$STD_0 = \lim_{t\to\infty} STD(t) \tag{5.1.2}$$

If STD_0 exists and is minimal, this means that the bacteria are mostly located near the source and this would imply that they have the highest chemotactic efficiency.

However, we cannot simulate the bacterial behaviour for a very long time, because of computational costs. Therefore, we will limit the simulation time to $S = 10000$ and assume that if the bacteria do not aggregates around the source within this time, then their chemotactic efficiency is very poor.

Remark: All data representing STD resulting from the numerical simulation are smoothed using the Vandermonde method, which approximates a quadratic polynomial to the data. We found that a polynomial of degree six provides the best fit. Fig. 5.2 is an example of the agreement of the fitting, but other original data are available upon request.

5.2 Simulation and results

The numerical implementation of Model 3.3.1 for the one-flagellated bacteria and Model 4.3.1 for the multi-flagellated bacteria can be found in App. A.

We start by displaying some example of trajectories of a single bacterium for different values of F in Fig 5.1. We observe that the trajectory becomes smoother as the bacteria has more flagella. This is due to the large choices of small tumbling angle deviation that the multi-flagellated bacterium possess.

We collected the bacterial positions at every time step and computed $STD(t)$ (Eq. 5.1.1). Fig. 5.3 are sample results of our investigation about $STD(t)$. We choose to display here the results obtained from the simulation for $\sigma = 40\nu\Delta t = 1000$ because this is the concentration parameter that provides the greatest domain of study which is $C(0, 3\sigma)$. We can see that the simulation time is more than enough to provide a steady state behaviour of the bacteria because after some time we do not observe any more variation in $STD(t)$. For $\sigma = 20\nu\Delta t = 500$ and $\sigma = 30\nu\Delta t = 750$, we obtain the same behaviour of $STD(t)$(data not shown), i.e. we also find that the simulation time is long enough to provide the steady state of the bacteria.

For having a better look at the results, we are going to approximate the steady state behaviour of the bacteria in a two dimensional figure, by estimating the steady state limit of $STD(t)$ which is STD_0. As depicted in Fig. 5.3, $STD(t)$ tends to a constant curve, however, because of some pos-

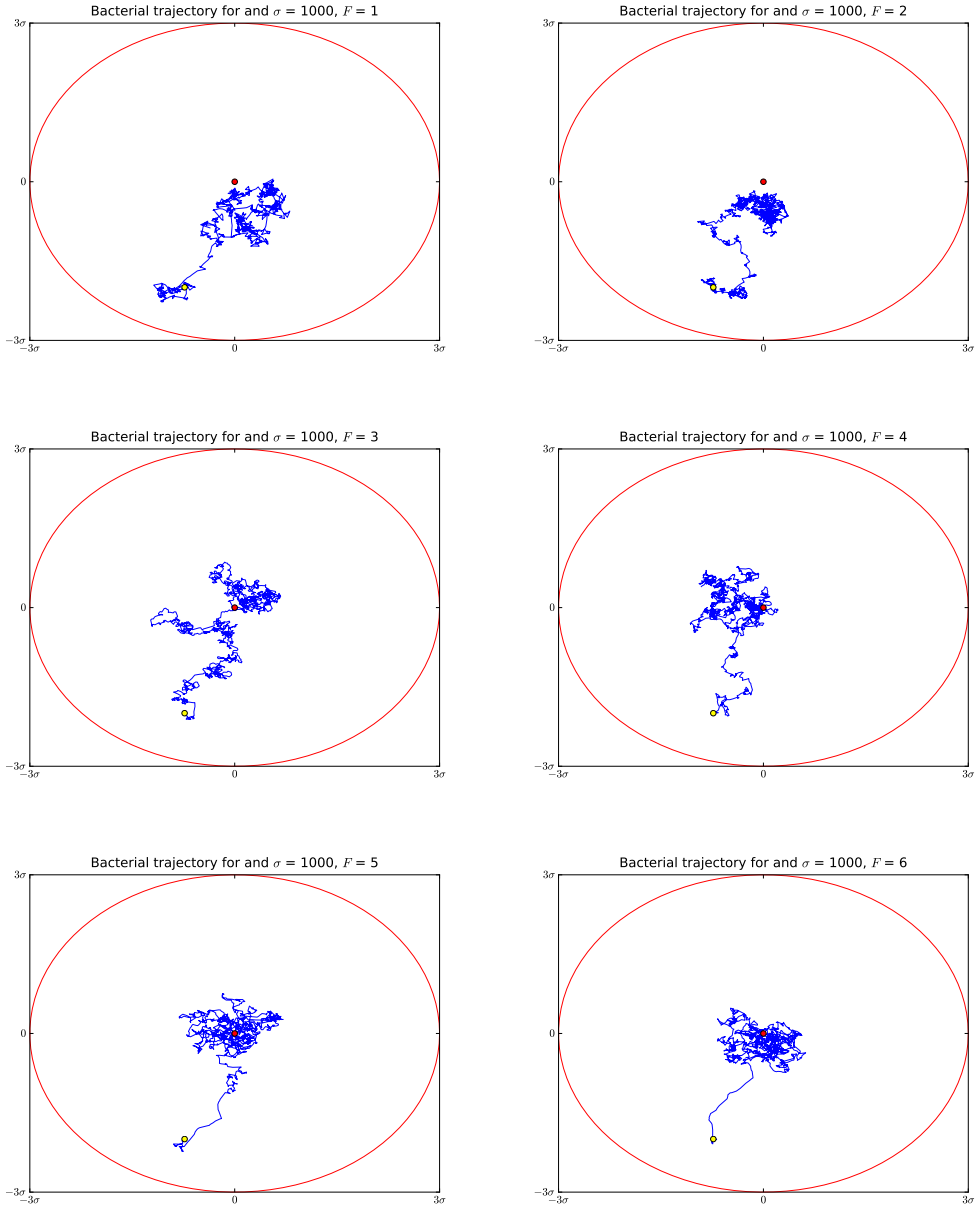
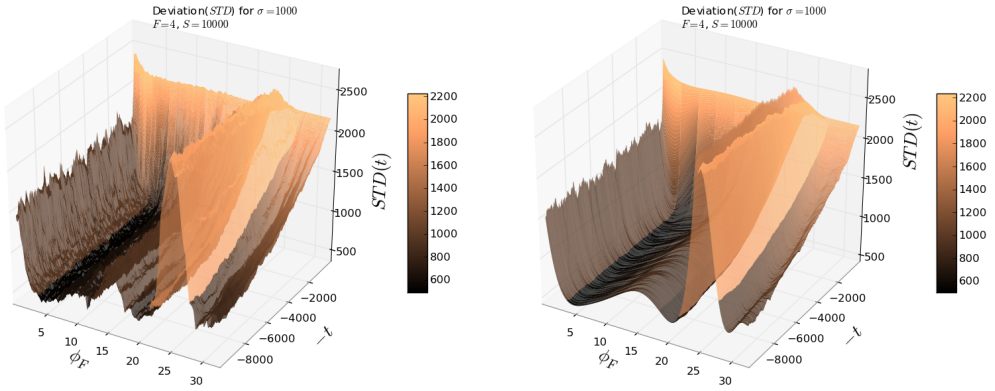


Figure 5.1: Example of trajectories of a single bacterium for different values of F. The bacterium start its motion at the yellow bullet, and tends to reach the source of chemoattractant marked with a red bullet. $\Theta = \varphi_F = 1.1$ rad, Θ refers to the single flagellated bacterium and φ_F refers to the multi-flagellated bacterium.

sible fluctuations due we measure STD_0 as the average last 2000, $STD(t)$, i.e.



(a) (b)

Figure 5.2: Sample comparison of (a) real STD data and (b) smoothed data.

$$STD_0 = \frac{1}{2000} \sum_{t=S-2000}^{S} STD(t), \tag{5.2.1}$$

where S is the simulation time defined in Sec. 5.1

Moreover, we would like to compare the optimal tumbling angle strategy of the bacteria within the different chemoattractant environment. To do so, we need to normalize STD_0 with respect to the radius of the domain, which is 3σ, because the initial positions of the bacteria are different depending the domain where they are simulated. Then, Fig. 5.4 represents the chemotactic efficiency of the bacteria for each different chemical distributions.

For both one-flagellated and multi-flagellated bacteria, Fig. 5.1.1 shows that the chemotactic efficiency provided by tumbling variations around the angle zero is always the poorest. This is reasonable considering that a small tumbling angle change would not redirected the direction of the bacteria, and the chances of finding a better directions are very small. Although the bacteria notice that the direction is unfavourable, it keeps moving in the forward direction and even in the case they arrive at the source, they are not be able to stay around it.

As expected, we see that the results in Fig. 5.4 is periodic with period 2π and symmetric around π, for the single flagellated bacteria. The tumbling change distribution of the one-flagellated bacteria is periodic, with period 2π and this is why we have the periodicity.

On the other hand, for $F > 1$ we do not have any more periodicity in the results for Fig. 5.4. The tumble variation distribution of a F-flagellated bacteria that has the form of Fig. 4.2, and all the modes are correlated to each other via the hill function introduced in the expression of $\Theta_F(F_{cw})$ Eq. 4.1.1 that was considered as the dependence of the tumbling on the fraction of

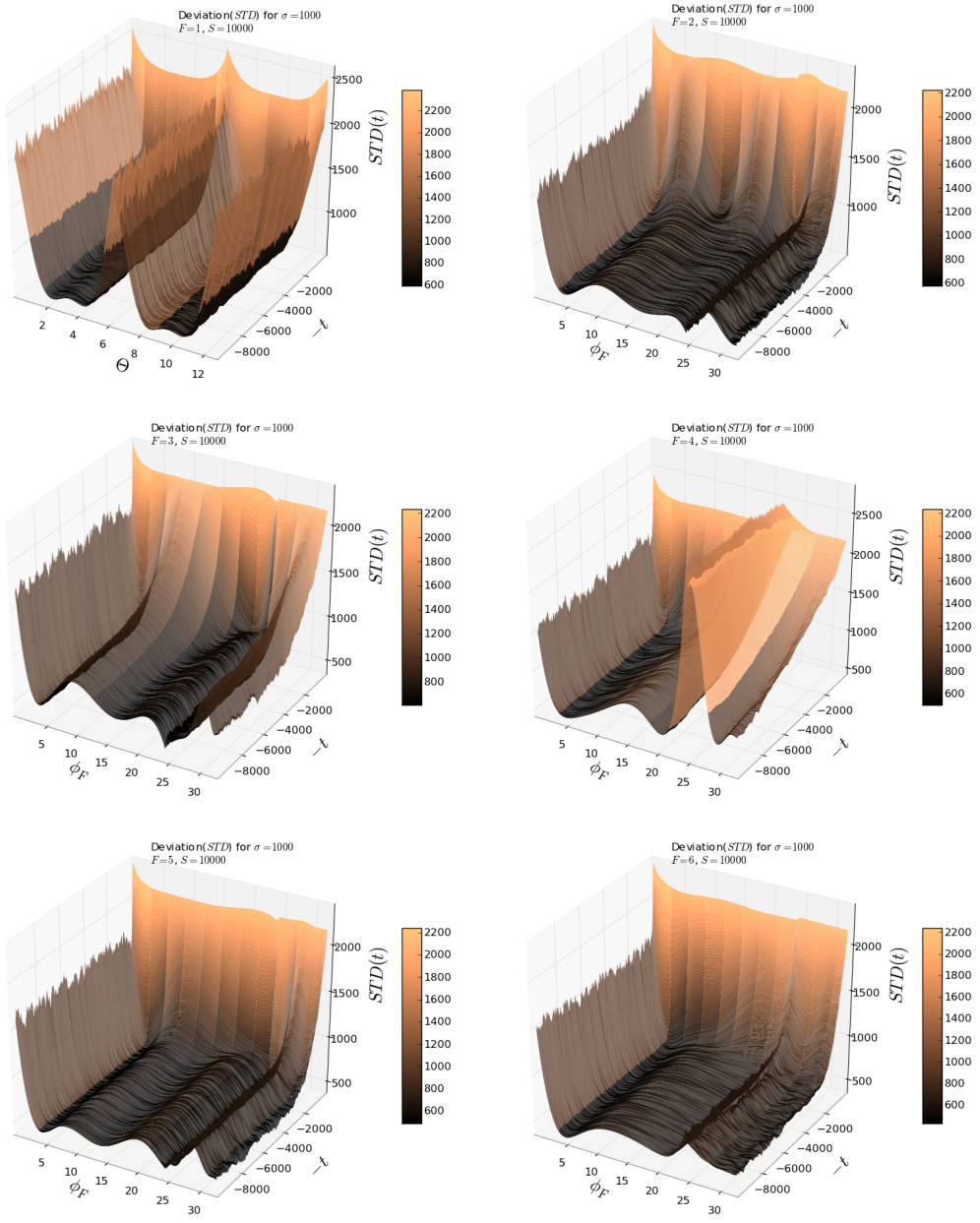


Figure 5.3: The standard deviation of the position of the bacteria as a function of function of Θ for the one flagellated bacteria, $\phi_F = \max(\Theta_F(F_{cw}))$ for the multi-flagellated and $-t$ with $t \in 0, ..., S$ and $\sigma = 1000$. The plot is made along the negative time for a clear vision of the time-evolution of the system, but the value at $-t$ corresponds to the value at t, otherwise we would see the back of these graphs.

CW-rotating motors. However, the chemotactic efficiency are maximized when $\phi_F < 2\pi$, which means when the bacterium effectuates at most one turn in addition to the usual tumble revolution. However, we also observe that the curves of chemotactic efficiency do not displays much variation although the maximal possible tumbling angle change ϕ_F increases. This is due to the fact that when the tumbling change becomes greater than 2π, the modulo 2π of the tumble variation may resume to a reasonable tumbling angle changes. The results of any investigation using α and $\alpha + 2\pi$ will always resumes to the same. Although the F modes Θ_F of the tumbling angle distribution do not always shift the same amount together so that we can consider periodicity, the modulo 2π of the modes can be reasonable to provide a good chemotactic efficiency. Nevertheless, it can happen that the modulo 2π of the angles used in the tumbling strategy of the bacteria resumes to a smaller tumbling strategy, and we know that small change of direction during a tumble does not provide a good chemotactic efficiency because the trajectory of the bacteria would remain the same. We can see an evidence of this possibility in the figure representing the 4-flagellated bacteria, the curve of chemotactic efficiency increases around $\phi_F \in (6\pi, 8\pi)$, indicating that the chemotactic performance of the bacteria is very poor in that region.

From Fig. 5.4 we can also deduce that as the number of flagella on the cell body increases, the steady states bacterial convergence zone gets closer to the source. When we measure a quantity that we denote ϱ, and that represents the minimal $\frac{STD_0}{3\sigma}$. Higher flagellated bacteria always display the smaller ϱ compared to the other bacteria. Although the optimal directional persistence for each F-flagellated bacteria are different, higher flagellated bacteria always have minimal chemotactic performance measure. This indicates that they converge nearest to the source.

In addition, the parameters Θ and ϕ_F that provides the optimal tumbling strategy of the bacteria is often independent from the chemoattractant distribution that we chose. We depict in Fig. 5.5 the optimal tumbling angle strategy of the bacteria. Each curves in this figure represents the tumbling strategy of a particular F-flagellated bacterium, the tumbling deviation of the bacterium can only come from the tumbling angle distribution generated by some fraction of flagella. A F-flagellated bacterium, can have exactly F possible tumbling angle distribution with parameters $\Theta_F(F_{cw})$ emphasized by the points in each curves (Fig. 5.5) and a standard deviation of tumbling angle distribution that increases linearly with the fraction of CW-rotating motors F_{cw}.

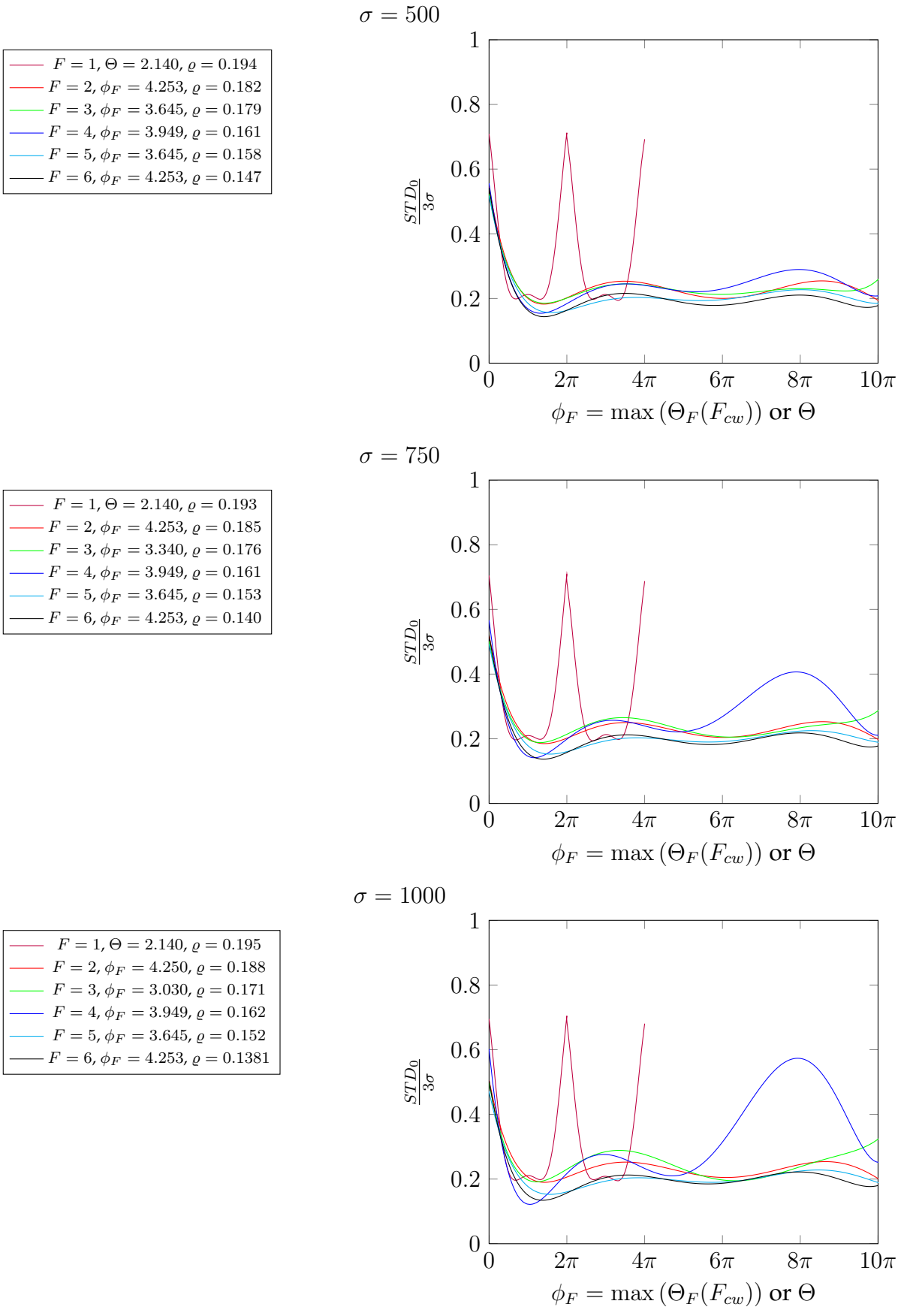


Figure 5.4: The steady state standard deviation STD_0 of the bacteria from the source, normalized by the radius of the domain of study. ϕ_F is the parameter providing optimal tumbling strategy of a F-flagellated bacteria, i.e providing the minimal STD_0. And for $F = 1$ it is Θ that is on the x-axis. the Θ indicated in the corresponding legend is the optimal tumbling strategy of the F-flagellated bacteria. In addition the ϱ is the minimal normalized steady state standard deviation.

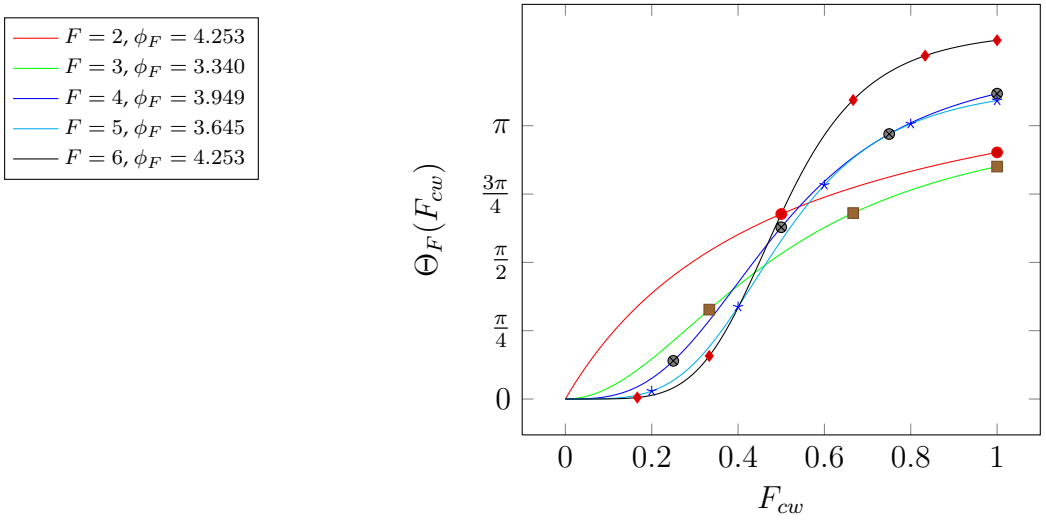


Figure 5.5: The optimal tumbling angle strategy for a given F. The markers points of each given curve represent the predicted $\Theta_F(F_{cw})$s for each fraction of CW-rotating flagella for a F-flagellated bacteria, it can only take one of these discrete values. ϕ_F is the providing the optimal tumbling strategy of a F-flagellated bacteria.

5.3 Tumbling tendency and directional persistence

As explained in Sec. 4.4 the tumbling tendency of the multi-flagellated bacteria, which is its average positive tumbling angle deviation at every time step, is correlated to the bacterial environment Eq. 4.4.2. This is because of the dependence of the tumbling angle change on the fraction of CW-rotating motors, which depends in return on the bacterial environment via $b_{ccw}(t)$. In this section we, will compare the turning tendency generated by the optimal tumbling strategy of a bacterium in a non-zero gradient environment and in a zero-gradient environment.

For this purpose we took a single F-flagellated bacterium from the previous simulation, i.e. the simulation time is $S = 10000$, using its optimal tumbling strategy shown in Fig. 5.5, with several non-zero gradient environment and a zero-gradient environment and compare the distribution of tumbling tendency over the time.

Remark: We choose randomly one bacterium from the 100 bacteria that we have simulated in the previous investigations. When we conducted the same investigation on another simulated bacterium, we found the same results.

Fig. 5.6 represents the distribution of tumbling tendency of the bacterium

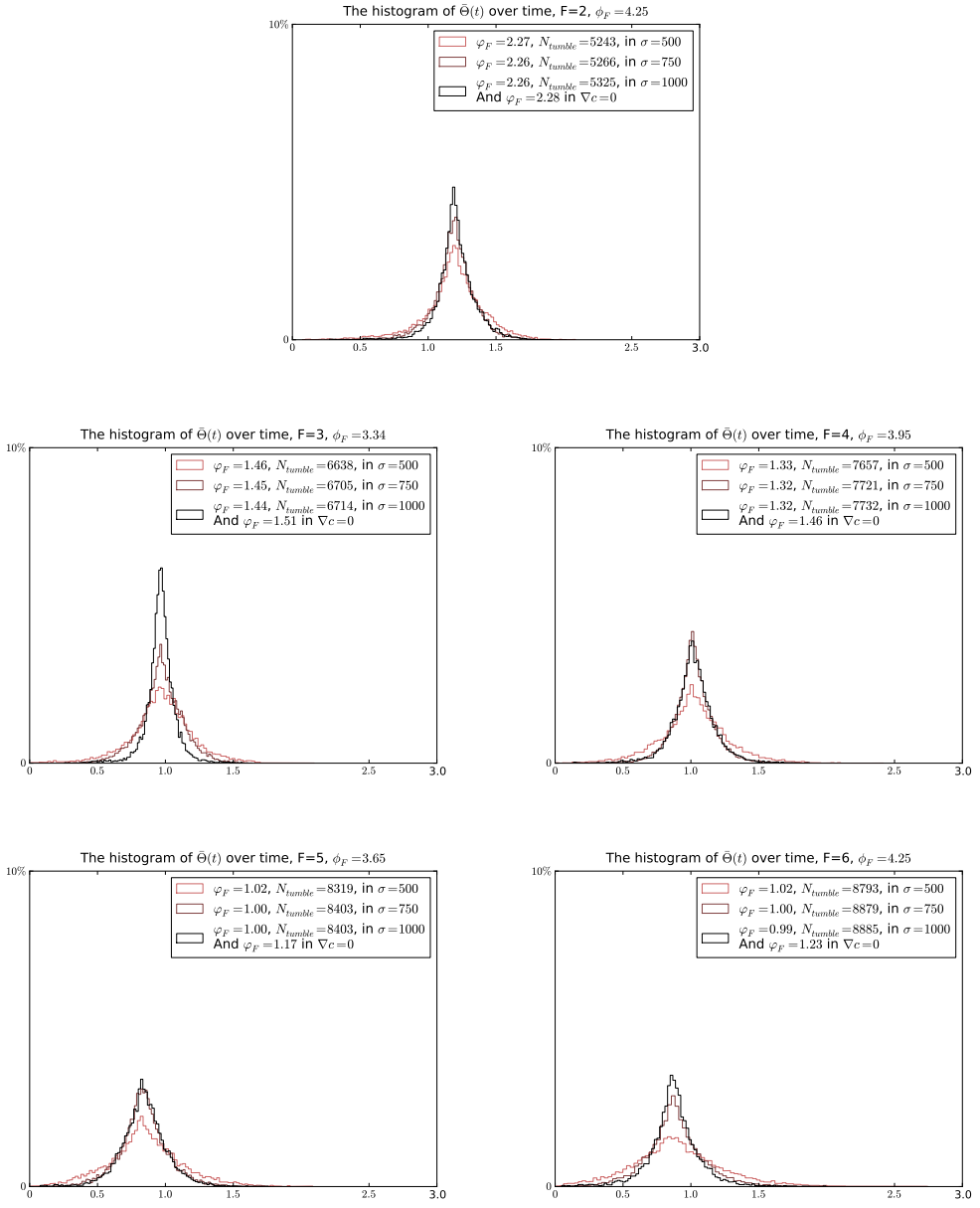


Figure 5.6: The histogram of the of tumbling tendency generated by the optimal tumbling strategy over time for a gradient of chemoattractant and the corresponding directional persistence φ_F in a zero-gradient environment $\nabla c = 0$. N_{tumble} is the estimated number of tumble.

over time. Each histograms on the figure represents the distribution of the tumbling tendency for a particular gradient environment. In the legend there is the estimated number of tumbles and the associated directional persistence, as well as the zero-gradient environment directional persistence. We can see that the expected number of tumbles increases with the number of flagella of the bacterium. This is the direct results of using the binomial distribution as the distribution of the number of CW-rotating flagella. The more flagella the cell has the less probable is a run motion because the probability of run at every time step would be $b^F_{ccw}(t)$, and the more there is tumbles. Nevertheless, this lack of run has been compensated by the tumble variation of the multi-flagellated bacterium.

In addition, we observe in Fig. 5.6 that the directional persistence of the bacterium in every chemical environment remains unchanged. However, the spread of the distributions are different, and we can see that as σ gets larger, the standard deviation of the tumbling tendency distribution gets smaller. This suggests that, when the chemical gradient of the environment gets small, then the bacterium adapts a more precise range of tumbling tendency. Whereas, when the chemical gradient is high, the bacterium uses a wider range for its tumbling tendency.

Moreover, the difference between the non-zero and the zero-gradient directional persistence gets larger as there is more flagella on the cell body. This situation might be a direct results of the tumble variation, because the more there is tumble variation, the more correlation there will be between the external environment and the tumbling tendency. The tumbling tendency is more adjusted to the external environment and this might be the reason, why the higher flagella the bacterium has a better chemotactic efficiency within a non-zero gradient environment.

Chapter 6

Discussion and conclusion

6.1 Work summary

Throughout the document we presented two possible models that can be used to model to *E. coli* run and tumble chemotaxis, for a one-flagellated bacterium and a multi-flagellated one. We used the chemotactic response models presented by Block *et al.* (1982) and Block *et al.* (1983) to approach the run and tumble probability distribution by introducing the temporal comparison of chemoreceptor occupancy in the formulation of the CCW-bias of the bacterium instead of temporal comparison of chemoattractant concentration. We analysed the variation of chemotactic performance according to the tumbling strategy of the cells and the number of flagella that the cells possess by giving more importance to their convergence in a near neighbourhood of the source of food.

We also distinguished between a change of direction of magnitude α and $\alpha + 2k\pi$, in order to introduce the possibility of having change of direction greater than 2π. This assumption induces the tumbling behaviour of one-flagellated bacterium to be similar to the simple random walk notion because Model. 3.3.1 uses only use the single turning angle distribution that is periodic with period 2π. Once we have introduced tumble variation, particularly the assumption that the tumbling angle change increases with the fraction of CW-rotating flagella using Eq. 4.1.1, the tumbling change distribution of the F-flagellated becomes non-periodic.

The Model 3.3.1 for the one-flagellated bacteria displays the dependence of the bacterial motion on its single flagellum. When they are moving in the right direction they have a high probability of run. However, they are not able to adjust their tumbling angle. The numerical simulations show that they have their best chemotactic efficiency when they are redirecting their motion using high turning angle strategy. Since the tumbling angle distribution of the one-flagellated bacterium is periodic with period 2π, we got the periodicity in the results of our investigations in Chap. 5.

On the other hand, for the Model 4.3.1 of the multi-flagellated bacteria, we assume that the bacteria has a difficulty effectuating a run motion that is compensated with tumble variation. As we mentioned in Sec. 4.5 choosing the model of tumble variation as in Eq. 4.1.1 induces a non-periodic tumbling angle distribution. $\Theta_F(F_{cw})$ is taken as some portion of some angle reference that we denoted ϕ_F, and the binomial distribution favour tumbling events from smaller CW-rotating flagella F_{cw}. The tumbling angle strategy of the bacteria looks like Fig. 4.2, and since the $\Theta_F(F_{cw})$ are correlated to each other we cannot have any periodicity in the distribution. Thus the obtained results cannot be periodic. However, the simulations shows that the optimal tumbling strategy would be to effectuate change of directions less than 2π.

From analysing Fig. 5.4 we deduce that the more there is tumble variation, that is the more flagella the bacteria possess, the higher their chemotactic efficiency is, however different their optimal persistence are. The multi-flagellated bacterial chemotaxis model shows that it is more advantageous for the bacteria to have a high flagellar number. The bacteria aggregates in a smaller zone nearer to the source. Which is reasonable since the bacteria are more able to direct their movement. The ability of more modulating their direction during a reorientation is much useful for the bacteria to maintain their position in a high density nutrient zone and thus provides a high survival strategy. This could be as Vladimirov *et al.* (2010) discovered from their model, another mechanism that the bacteria uses for their survival.

Finally, we have investigated the possibility that the directional persistence of the bacteria depends on the external environment. The directional persistence measure was found experimentally by looking at many different cells within a ligand free environment. In our context we defined the tumbling tendency of the bacterium, which is the average positive tumbling angle change that the bacterium might display at every time, and we defined the directional persistence to be the average tumbling tendency over time. The dependence of the tumbling angle on the fraction of CW-rotating motors, suggests that the tumbling angle also depends on the external environment, because the CCW-CW states of the flagella depends on the external environment. Therefore, the directional persistence might depend on the external environment as well. When we analysed the distribution of the tumbling tendency of a bacterium in Sec. 5.3. For different non-zero gradient environment, we observe had the range of the tumbling tendency gets larger as the gradient of chemical increases. The directional persistence remains the same for all non-zero-gradient environment that we used (Fig. 5.6).

We also observe that as the number of flagella of the cell increases, the difference between the directional persistence within zero-gradient and non-zeros gradient environment gets larger. This suggests that the external environment has more influence on the tumbling tendency of the bacterium

when this one has higher flagella. We speculate that this is the reason why the higher flagellated bacteria responds the best to the external environment by having the higher chemotactic performance.

The total directional persistence of the bacteria regardless of the number of flagella of the cell, obtained from the estimated optimal tumbling strategy is 1.54 rad within a non-zero-gradient environment and 1.63 rad within a zero gradient environment. These results are correlated with the values of the parameters that we have used in the simulation. Further adjustment on the models may still be required. Particularly in the levels of parameter estimation, for instance the hill coefficient l in Eq. 4.1.1, and ϵ_0 in Eq. 4.1.2, we might do further quantitative analysis of the experimental data of Turner *et al.* (2000). Nevertheless, we shall keep in mind that, unlike the experimental works, we have made a distinction between tumbling angle change of magnitude α and $\alpha + 2\pi$.

In the next section we discuss some possible model extension.

6.2 Perspective

In order to simplify our work, we considered the number of CW-rotating motor on the cell body as a binomial random variable. In order to use the binomial distribution, we had to assume that the the rotational state of a flagellum are independent from the rotational states of the others. By making this assumption, the run events becomes seldom as the number of flagella of the cell gets higher. However, there is possibility that this simplification does not reflect the reality. As a consequence, the model could be more appropriate if we introduced the right mechanism responsible for the rotational states of the bacteria, which is the "Chemosensory pathway".

In particular, the rotational state of a single flagella is governed by the interaction of a protein called CheYp and the flagellar motor. We could define a separate chemosensory pathway model that would output the fraction of CW-rotating flagella. In this way the fraction of CW-rotating flagella would be governed by an independent function that we could easily introduce into the models.

The behaviour of the bacteria subjected to chemorepellent environment can also be modelled using the same approach, by assuming that the cell tumbles when the chemorepellent concentration is increasing and runs over wise. This could be done by adapting the function used to model the CCW-bias in Eq. 2.6.2 to represent the CW-bias. This would mean that the bacteria tumbles more when the chemorepellent concentration level increases, because this indicates a motion in the wrong direction. However, the expression in Eq. 2.6.2 accounts for adaptation of the bacterium to chemoattractant environment. This means that a zero-gradient chemoattractant environment behaviour is the equivalent to the ligand free environment be-

haviour. If we also assume the same for a chemorepellent, then we also assume that the bacterium behaves normally and then survives whereas it is constantly subjected to poison. Therefore, some reasonable assumption should be taken to modify Eq. 2.6.2 so that it can mimic the chemorepellent CW-bias.

The present modelling approach could also be extended to the predator-prey interaction between bacteria, providing that the chemorepellent behaviour of the bacteria is known. The predatory bacteria can be considered moving toward its prey as it is moving toward a source of chemoattractant, and the prey rather considers the predator as a source of chemorepellent that it should run away from.

Nevertheless, this approach in modelling bacterial chemotaxis also present advantages and disadvantages. We discuss these in the following section.

6.3 Model criticism and discussion

Stochastic models such as these have the advantage of being more flexible to changes. More realism can always be incorporated into the model. For example, changing the anisotropic bacterial environment would not be a problem because it is governed by an independent equation. A more realistic way of determining the rotational states of the bacteria would be to study the interaction of CheYp protein with individual flagellar motor within the chemosensory pathway to obtain the exact number of CW or CCW-rotating flagella at any time and introduce it in the model.

Stochastic models can be used to answer specific questions. For example in our case, the model was used to investigate the optimal tumbling variation strategy for chemotactic efficiency, which deterministic model cannot predict.

However, there is a large number of unknown parameters and variables that had to be considered. Several assumptions had to be taken for simplify the model. Therefore the results are highly likely to change upon these assumptions.

Particularly, the independence of the flagella might be plausible, but we cannot guaranty that they all display the same CCW-bias. In this case we will need to consider different CCW-bias for each of them. This means that if we label the flagella of the cell by $F_i, \in 1, ..., F$, then we have to come up with some reasonable CCW-bias b_{ccw,F_i} for each of them, without omitting the response to external environment. In this case, the Binomial distribution is no longer representative of the distribution of the number of CW-rotating motors. One need to use a more general probability distribution, such as the "Poisson Binomial distribution". This distribution will allow us to determine the number of CCW-rotating motors amongst the flagella of the bacterium, giving their respective b_{ccw,F_i} to each motor F_i. The challenging

part in this approach is to find a reasonable expression for every b_{ccw,F_i}. In our opinion, more experimental investigations are needed in this area. We should not restrict ourselves in observing the response of a single motor, but needs to find an efficient way for observing the response of every flagella, or the variation of the number of CW-rotating flagella upon stimuli.

From another point of view, we may not avoid the possibility that the bacterial flagella are not independent, as most biological system displays cooperative behaviour. To our knowledge, not a lot of study has been effectuated to determine whether or not there is a relationship between them. We could also think of a model in which the CW-bias of one flagellum depends on the CW-bias of all the others, in such a way that the probability of $n_{cw} = k + 1$ depends on the probability that $n_{cw} = k$ (n_{cw} being the number of CW rotating motors). i.e.

$$\text{Prob}(n_{cw} = k + 1) = f(\text{Prob}(n_{cw} = k)). \tag{6.3.1}$$

However, it is not straightforward to determine a suitable expression of the function f that would quantify the dependence between the flagellar motor states.

Alternatively, we can directly investigate the mechanism responsible for the rotational states of the flagella, which is the interaction between CheYp proteins and the flagellar motor within the chemosensory pathway. Several amount of work has already been investigating the chemosensory pathway. However, most of these works were only focusing on the variation of the concentration of CheYp proteins as a function of external cue(Tindall *et al.*, 2008). Amongst these, there is the stochastic simulator of Morton-Firth and Bray (1998), who looked at the effect of external environment in order to determine the concentration of CheYp using a stochastic approach. But only the CCW-bias of a single flagellum was formulated using the estimated concentration of CheYp. A hill function were always used to approximate the CCW-bias found from the experimental work of Berg and Brown (1972).

There is no doubt that determining the biases by which individual flagellum rotates CCW or CW would be challenging. Partly because of the complexity of experimental investigation. However, the experimental data of Turner *et al.* (2000) tells us that the rotational states of individual flagellum are involved in the change of direction between run to run. Consequently, there is a strong probability that the external environment plays an important role in the chemotactic efficiency of *E. coli*, since the CCW-CW-biases of each flagellum depends on the external environment. We should not ignore this part while modelling *E. coli* run-and-tumble motion in the micro-scale level, particularly within a non-zero gradient environment.

Given this difficulty of finding the rotational states of each bacterial flagella, some assumptions are needed for simplicity. Vladimirov *et al.* (2010) used a chemosensory pathway to determine the frequency at which tumbles appears. Particularly, the frequency of a tumble produced by given number

of CW-rotating motors. They looked for these frequencies by simulating the bacteria within a ligand free environment. One of their assumptions was to reuse these frequency in their anisotropic model, by simulating bacteria within a non-zero gradient environment. However, the rotational states of the flagella depends on the external environment and it might happen that the frequency of $n_{cw} = k$ in a ligand free and in a non-zero gradient environment are different. Therefore, there remains a little doubt about their approach.

These remarks were the particular problems that we encountered in our modelling of bacterial chemotaxis within the stochastic framework. There are still some general notion that cannot be tackled. As an example, the bacterial interaction and growth cannot be captured the models. Moreover, we cannot indefinitely incorporate extra elements in a stochastic model because of the number of extra parameters to consider and computational matter, especially for a large number of bacteria. Therefore, the macro-scale level model still plays important role in understanding the bacterial behaviour. Both deterministic and stochastic approaches can be used depending on the questions that we want to investigate but the real challenge would be to make a link between those two method.

6.4 Conclusion

In conclusion, we can say that there are many ways of quantifying a biological phenomenon. These could be simple and complicated depending on the questions that we want to investigate. However, this study contributes in understanding the bacterial behaviour subjected to any chemoattractant environment. The optimality of chemotactic efficiency displayed by the higher-flagellated bacteria might help us to understand the situations where the bacterium modulates its flagella number. Nevertheless, we have no doubt that further investigations, experimental as well as mathematical, are needed toward the study of the variation of the chemotactic efficiency of the bacteria depending on their number of flagella.

Appendices

Appendix A

Model implementation

We are using Python programming language to simulate the bacterial behaviour. We build the code in such a way that one can easily change the parameters and variables and investigate the model accordingly. We also separate the code into several modules so that it can be more flexible to changes. This appendix explains one by one the modules used in our numerical simulation, as well the parameters and variables that are involved.

Bacterial environment

In order to measure the concentration of chemoattractant molecules in a particular place using the anisotropic bacterial environment described in Sec. 2.1, we input the bacterial position p as a vector of tow element x and y position, the concentration parameter σ and the place were we put the source of chemical substance (which is a vector position as well). Then we have the following python module for describing the bacterial environment, since we have already normalized the concentration by using $c_{max} = mk_D$, c_{max} (here we take $m = 3$) no longer appear in the computation of the chemical density.

```
def chemical(p, sigma, source):
    """
    p is the position at which the concentration of chemical is evaluated.
    source is the position of the source of chemoattractant.
    sigma is the concentration parameter.
    sum((p-source)**2) = euclidean distance.

    """
    result = scipy.exp(-(sum((p-source)**2))/(2*sigma**2))
    return result
```

Bacterial response function

Several modules are required to compute the CCW-bias of a single flagella that is described in Sec 2.4. We define these as follows

- We need a module that compute $I(t)$, thus we define

```
def I(t):
    response = 0.36*scipy.exp(-t)*(1-0.5*(t + 0.5*t**2))
    return response
```

- Since the bacterial position is only updated at each discreet time t we approximate the position of the bacteria at continuous time $t < l < t + 1$ by linear interpolation and thus we have

```
def Pos(p1, p2, l, t):
    """
    p1 is the position at time discreet time t.
    p2 is the position at time discreet time t+1.
    l is the time at which we want to evaluate the position.
    """
    h = l-t
    return (1-h)*p1 + h*p2
```

- The signal that the cell is assumed to compare is G, and we inputs the normalised chemical density as s, the amplification parameter $g = 50$ and m in case we want to change m when we set $c_{max} = mk_D$. We add an extra parameter n in case we want to use a more general hill function as a compared signal, but in all our present simulation $n = 1$, then we have

```
def G(s, g, n, m):
    kd = 1/m
    measure = g*s**n/(kd**n + s**n)
    return measure
```

To compute the CCW-bias of the single flagellum at a given time t as shown in Eq. 2.6.1 we need to integrate the signal G experienced during the previous positions multiplied with the appropriate cell's response to it. However, we will not consider all the previous position of the bacteria because the impulse response shows the short term memory of the bacteria and for T large enough we have

$$I(T) \approx 0,$$

Thus we just consider the 10 last positions of the bacteria as a vector of length $T = 10$ and since the index of a vector of length T in a Python script starts by 0 and ends by $T - 1$, the CCW-bias is given by

$$b_{ccw}(t) = \sum_{i=0}^{T-2} \int_{t-(i+1)}^{t-i} G(chemical(p(t')))I(t-t')dt',$$
$$= \sum_{i=0}^{T-2} \int_{T-1-(i+1)}^{T-1-i} G(chemical(Last(l)))I(T-1-l)dl,$$

where $Last$ is a vector composed with the T last positions of the bacteria which we update at every time step, it is of length T, $Last(l)$ is the position of the bacteria at between the discreet positions $Last[T-1-(i+1)]$ and $Last[T-1-i]$ that corresponds to $t < t' < t+1$ and this is why we need the interpolation function Pos.

$$Last(l) = Pos(Last[T-1-(i+1)],\ Last[T-1-i],\ l,\ T-1-(i+1)),$$

This transformation is possible due to the fact that the chemical concentration does't depend on time but only on the positions and because we have

$I(t-t')$ for $t' \in [t-(i+1), t-i]$ $=I(T-1-l)$ for $l \in [T-1-(i+1), T-1-i]$

thus we have the above expression of $b_{ccw}(t)$ provided we give the right position at l that corresponds to the position at time t'.

The following function is the function that we integrate to obtain the CCW-bias

```
def db(l, i, T, Last, g , n , m, sigma, source):
    """
    Last is the vector of T previous bacterial position
    V is the higher index of the vector Last
    """
    V = T - 1
    result = G(chemical(Pos(Last[V-(i+1)], Last[V-i], l, V-(i+1)),
           sigma, source), g, n, m) * I(V-l)
    return result
```

And the CCW-bias is given by

```
def CCW(Last, g, n, m, sigma, source, T):
    b = 0.64 # prestimuli baseline CCW-bias
    V = T - 1
    for i in xrange(0, T-1):
        CR = scipy.integrate.quad(db, V-(i+1), V-i,
            args= (i, T,  Last , g, n, m, sigma, source))
        b + = CR[0]
    return b
```

Angle variation

Here we define the variation in the angle of direction of the bacteria, depending on the CCW-bias defined previously and the number of flagella on the cell body.

```
def dTheta(Theta, eps, Drot, F, l, F0, bccw):
    # To ensure that the probability value doesn't go above 1 or below 0
    bcw = 1 - min(1, max(0, bccw))
    ncw = scipy.random.binomial(F, bcw)
    # tumble apear when 1 or more flagella are in the CW-rotation thus
    if ncw != 0:
        fcw = ncw/F
        # in the case of one flagella
        if F == 1:
            vphi= Theta
            eps1 = eps
        # in the case of multiple flagella
        else:
            vphi = Theta*(fcw**l/(F0**l + fcw**l))
            eps1 = fcw*eps
        # Sampling from the tumbling angle distribution
        s0 = random.choice([-1,1]) # 0.5 chance to have -1 or 1
        vphi = s0*vphi
        theta = random.normalvariate(vphi, eps1)
    else: # the bacteria runs
        eta = random.normalvariate(0,1)
        theta = eta*Drot
    return theta
```

Bacterial position

Finally we use all the previously defined modules to compute the bacterial position at any discreet time. We always input the initial positions of all the bacteria as a vector of X-coordinates and Y-coordinates where each couple $(X[k], Y[k])$ represents the position of a particular bacterium. And the result is a vector composed with the position of the bacteria at any time $i \in 0, ..., S-1$. We define four steps to compute the bacterial positions

1 Checking the boundary conditions

```
def Btest(X, Y, boundary):
    Bool = scipy.sqrt(X**2 + Y**2)<boundary
    return Bool
```

2 Computing the next angle of direction, and the next position, we need to keep the angle of direction because it appears in the computation of the angle of reflection at the boundary. We furthermore need to initialise the system until getting the T previous positions that we use to compute the CCW-bias

```
def dP(t, X, Y, memPos, boundary, g, n, m, sigma, source, T ,
    Theta, actTheta, F, l, F0, eps, Drot):
    Bool = Btest(X, Y, boundary)
    K = len(Bool)
    """
    actTheta is the current angle of direction.
    nexTheta will be the next angle of direction used to compute
    the next position.
```

```
    X, Y are the current X-Y positions of the bacteria.
    memPos is the past T positions of the bacteria.
    K is the number of simulated bacteria. Each k in K refers to
    a particular bacterium.
    """
    nextTheta = scipy.zeros(K)
    for k in xrange(K):
        if Bool[k]:
            if t<T:# unbiased movement while t<T
                nextTheta[k]= actTheta[k]
                        + dTheta(Theta, eps, Drot, F, l, F0, 0.64)
            else: # biased movement from t>=T
                # last T position of bacteria k
                Posk = memPos[:, :, k]
                b0 =  CCW(Posk, g, n, m, sigma, source, T)
                nextTheta[k]= actTheta[k]
                        + dTheta(Theta, eps, Drot, F, l, F0, b0)
        else:
            # angle of reflection
            nextTheta[k]= 2*Beta([X[k], Y[k]]) - actTheta[k] + scipy.pi
    nextdir = scipy.array([scipy.cos(nextTheta),scipy.sin(nextTheta)])
    return (nextTheta, nextdir)
```

where

```
def Beta(U):
    if U[0]!=0:
        return scipy.arctan(U[1]/U[0])
    elif U[0]==0 and U[1]>0:
        return pi/2
    else:
        return 3*pi/2
```

3 And finally we update and collect all the positions of the bacteria with the following function

```
def Traj(Theta, X0, Y0, g, n, m, nu, sigma, Drot, F, l, F0, eps, S
, T, source, boundary):
    if type(X0)!= numpy.ndarray or type(Y0)!= numpy.ndarray:
        raise "X, and Y must be arrays of the coordinates
              of the bacteria"
    else:
        # Initial X, Y positions of the bacteria
        Initial = scipy.array([X0, Y0])
        # Initialise current angle of direction
        actTheta = scipy.zeros(len(X0))
        # Initialise the T past position, we need it in the dP
        memPos =  scipy.zeros((T, 2, len(X0)))
        pos = dP(1, X0, Y0, memPos, boundary, g, n, m, sigma,
            source, T, Theta,  actTheta, F, l, F0, eps, Drot)
        # Compute the next position
        # nu is the average bacterial velocity
        nextP = Initial + nu*pos[1]
        # add the next position to the Position data
        Res = scipy.concatenate(([Initial] , [nextP]))
        # Update current angle of direction
        actTheta = pos[0].copy()
        for i in xrange(2, S):
            # Update T last position, not taken into account until i>=T.
            memPos = Res[-T:]
```

```
        # The current position of the bacteria.
        P = Res[-1]
        pos = dP(i, P[0], P[1], memPos, boundary, g, n, m, sigma,
         source, T, Theta, actTheta, F, l, F0, eps,Drot)
        nextP = P + nu*pos[1]
        Res = scipy.concatenate((Res, [nextP]))
        actTheta = pos[0].copy()
    return Res
```

List of References

Berg, H.C. (2006). Marvels of bacterial behavior. *Proceedings of the American Philosophical Society*, vol. 150, pp. 428–442.

Berg, H.C. and Brown, D.A. (1972 October). Chemotaxis in escherichia coli analysed by three-dimensional tracking. *Nature*, vol. 239, no. 5374, pp. 500–504.

Berg, H.C. and Tedesco, P.M. (1975 August). Transient response to chemotactic stimuli in escherichia coli. *Proceedings of the National Academy of Sciences*, vol. 72, no. 8, pp. 3235–3239.

Blair, D.F. (1995 October). How bacteria sense and swim. *Annual Review of Microbiology*, vol. 49, no. 1, pp. 489–520. ISSN 0066-4227.

Block, S.M., Segall, J.E. and Berg, H.C. (1982 November). Impulse responses in bacterial chemotaxis. *Cell*, vol. 31, no. 1, pp. 215–226. ISSN 0092-8674.

Block, S.M., Segall, J.E. and Berg, H.C. (1983 April). Adaptation kinetics in bacterial chemotaxis. *Journal of Bacteriology*, vol. 154, no. 1, pp. 312–323.

Clark, D. and Grant, L. (2005 June). The bacterial chemotactic response reflects a compromise between transient and steady-state behavior. *Proceedings of the National Academy of Sciences of the United States of America*, vol. 102, no. 26, pp. 9150–9155.

Codling, E.A., Plank, M.J. and Benhamou, S. (2008). Random walk models in biology. *Journal of the Royal Society Interface*, vol. 5, pp. 813–834.

de Gennes, P.G. (2004 December). Chemotaxis: the role of internal delays. *European Biophysics Journal*, vol. 33, no. 8, pp. 691–693.

Fredrickson, J.K., Zachara, J.M., Balkwill, D.L., Kennedy, D., mei W. Li, S., Kostandarithes, H.M., Daily, M.J., Romine, M.F. and Brockman, F.J. (2004). Geomicrobiology of high-level nuclear waste-contaminated vadose sediments at the hanford site and washington state. *Applied and Environmental Microbiology*, vol. 70, pp. 4230–4241.

Lengeler, J.W., Drews, G. and Schlegel, H.G. (1999). *Biology of the Prokaryotes*. Blackwell Science.

Morton-Firth, C. and Bray, D. (1998). Predicting temporal fluctuation in an intracellular signalling pathway. *Journal of Theoretical Biology*, vol. 192, pp. 117–128.

Murray, J. (2004). *Mathematical Biology I: An Introduction*. Springer.

Nicolau, D., Armitage, J. and Maini, P. (2009 August). Directional persistence and the optimality of run-and-tumble chemotaxis. *Computational Biology and Chemistry*, vol. 33, no. 4, pp. 269–274. ISSN 1476-9271.

Schnitzer, M. (1993 October). Theory of continuum random walks and application to chemotaxis. *Physical Review E*, vol. 48, no. 4, pp. 2553–2568.

Sears, C.L. (2005 October). A dynamic partnership: Celebrating our gut flora. *Anaerobe*, vol. 11, no. 5, pp. 247–251. ISSN 1075-9964.

Segall, J., Block, S. and Berg, H. (1986 December). Temporal comparisons in bacterial chemotaxis. *Proceedings of the National Academy of Sciences*, vol. 83, no. 23, pp. 8987–8991. ISSN 0027-8424.

Tindall, M.J., Porter, S.L., Main, P.K., Gaglia, G. and Armitage, J.P. (2008). Overview of mathematical approaches used to model bacteria chemotaxis i: The single cell. *Bulletin of Mathematical Biology*, vol. 70, pp. 1515–1569.

Turner, L., Ryu, W.S. and Berg, H.C. (2000 May). Real-time imaging of fluorescent flagellar filaments. *Journal of Bacteriology*, vol. 182, no. 10, pp. 2793–2801.

Vladimirov, N., Lebiedz, D. and Sourjik, V. (2010 March). Predicted auxiliary navigation mechanism of peritrichously flagellated chemotactic bacteria. *PloS Computational Biology*, vol. 6, no. 3, p. 1000717.

Vladimirov, N., Løvdok, L., Lebiedz, D. and Sourjik, V. (2008 December). Dependence of bacterial chemotaxis on gradient shape and adaptation rate. *PloS Computational Biology*, vol. 4, no. 12, p. 1000242.