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Statistical Inference on Interacting Particle Systems

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Abstract

Interacting particle systems, and more specifically stochastic dynamical systems, is a mathematical framework which allows for condensed and elegant modelling of complex phenomena undergoing both deterministic and random dynamics. This thesis is concerned with the topic of statistical inference on large systems of interacting particles, with the specific application of *in vitro* migration of cancer cells. In the first of two papers appended with this thesis, we introduce a novel method of inference based on a higher order numerical approximation of the underlying stochastic differential equations. In the second paper, we formulate a model for glioblastoma cell migration, and conduct inference on this model using microscopy data. This regression shows promising results in its predictive power.

Keywords: stochastic process, agent based modelling, glioblastoma, Bayesian inference, mathematical biology.

List of publications

This thesis is based on the work represented by the following papers:

I. **Lindwall, G.**, Gerlee, P. (2021). A conjugacy for isotropically diffusive particle systems. *Manuscript*.
II. **Lindwall, G.**, Gerlee, P. (2021). Inference on an interacting diffusion system with application to in vitro glioblastoma migration, *Manuscript*.

Author contributions

I. Formulated the core statement, implemented the method in Matlab and conducted the numerical experiments. Wrote the paper.

II. Developed the model in conjunction with co-author. Formulated the inference algorithm, implemented the method in Matlab and conducted the numerical experiments. Wrote the paper.

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Papers I-II

1 Introduction

This thesis is concerned with the topic of statistical inference on large systems of interacting particles, with the specific application of *in vitro* migration of cancer cells in mind. In the opening chapters of this thesis, we will give a short presentation of the factors behind cell migration, which is followed by an an introductory level text on the relevant mathematics. This will provide the reader with sufficient background for the appended papers.

The bulk of the thesis is dedicated to two research paper manuscripts, concerning different aspects of inference and modelling of cancer cell migration. Paper I is of a more practical, computational nature and introduces a method that is employed in Paper II, but with applications in many more fields. Paper II is an applied study that introduces an interacting particle system model for glioblastoma migration along with a maximum likelihood inference algorithm for this model. Paper II is concluded with a discussion of future research prospects in the field of mathematical modelling of cell migration, and the inference on such models.

2 Biological background

The main concern of this thesis is the mathematical modelling of biological phenomena, and specifically the phenomena of cell migration. We will know give a short description of the mechanisms that can be at play during cell migration, and give some suggestions on how they can be formulated in mathematical terms.

2.1 Mechanics behind cancer cell migration

Cell migration is vital in the formation and perpetuation of life, whether we are discussing single cell organisms such as bacteria seeking sustenance or human skin cells migrating to close a wound. Understanding cell migration is essential to understanding life. However, not all aspects of cell migration is benign –it is also responsible for the occurrence of tumours, which is what we are to focus on in this thesis.

On a macroscopic level, a tumour is characterised by two main features; the proliferation rate and the cell migration speed. Both of these features are emergent phenomena stemming from complex dynamics at the cell level [21]. The finer details of tumour growth can thus be studied by studying the driving forces behind locomotion of individual cells.

On a microscopic level, individual cells migrate throughout its local environment, whose non-cellular components is called the extra-cellular matrix (ECM) and consists of water, proteins and polysaccharides. It acts like a scaffolding for cells migration [5]. The mode of migration of a cell has bio-mechanical explanations on the individual cell level that is a field of research in its own [3, 13]. The process of cell migration starts with cell polarisation; a protrusion is created in the direction that the migration will take place. This protrusion

then adheres to the ECM, acting like a cellular 'foot'. The cell then contracts at its new site, resulting in a crawling-like movement. The direction of cell migration in a homogeneous chemical environment is thought of as completely random, and in mathematics we commonly model it using stochastic processes. The ECM however affects this stochastic process in question. As an example, it has been noted that *glioblastoma multiforme* cancer cells migrate more than twice as fast in white brain matter as compared to gray [22].

In chemically heterogeneous environments, we observe the phenomena of *chemotaxis*, where perceived changes in the concentration of chemicals around the cell lead to a directed movement in the cell migration process [1]. This can be both a movement towards an attractive chemical such as a source of sustenance, or away from chemicals toxic to the cell in question. Cells also have the ability to communicate with one another by the means of signal substances [1]. This, along with the phenomena of cell adhesion, makes it possible for cells to migrate en masse, as is seen in tumour growth.

3 Mathematical background

Biology remains the natural science least permeated by mathematics. The development of mathematics has historically been motivated by problems from mechanics and other fields of physics, and to a lesser extent chemistry. Up until the early of the 20th century, biology remained fairly unexplored by the mathematical methodologies, and early advances include excursions in ecology such as predator-prey modelling [23] and modern synthesis in evolutionary biology [10]. With the booming advances in statistics in the 1930s, the modelling of biological phenomena seemed to finally be within our grasp.

The upcoming text up until the included papers will contain a historical treatise of the main subject of this thesis, which is the theory of diffusive many-particle systems and their application to the life sciences. Throughout, an attempt will be made to keep the notation as clean as possible; we will mostly consider one-dimensional examples, but many of the results discussed generalizes to any number of dimensions. When appropriate, more involved notation will be introduced.

We will begin with the history of diffusion from a continuum perspective, and follow that with a summary of some of the first equations formulated with population dynamics in mind. We will make analogies between models of population dynamics to models in statistical mechanics, chemistry and thermodynamics.

We then shift focus from the macroscopic to the microscopic point of view, and model spatial evolution of populations as a collection of individual organism using stochastic processes. A discussion of the relevant results from stochastic calculus will also be covered, and we will discover a beautiful connection between the two perspectives, by studying how the behaviour postulated in the continuum models emerges as limit cases of individual-based models.

Lastly, we will cover the necessary aspects of modern statistical theory needed to draw conclusions from models of the kind discussed in the previous sections.

3.1 Continuum description of diffusion

Diffusion describes the process by which physical media tends to spread from areas of high density to areas of lower density over time. In modern science, the first systematic study of diffusion was made by British chemist Thomas Graham in the 1830's. He noted the following;

> "...gases of different nature, when brought into contact, do not arrange themselves according to their density, the heaviest undermost, and the lighter uppermost, but they spontaneously diffuse, mutually and equally, through each other, and so remain in the intimate state of mixture for any length of time." ([19])

Two decades later, physician Adolf Fick set out formulate a universal law of diffusion, based on Grahams research. He drew inspiration from Fourier's law of heat conduction, formulated in 1822.

3.1.1 Origins: Fourier's law and Fickian diffusion

The original, phenomenological basis for Fickian diffusion is based in the theory of conservation laws, an already well studied concept in physics at the time, and an assertion of how material *flux* relates to its local density. We denote by J the flux, and by $c(x,t)$ the concentration of a medium at location x at time t. Fick then concluded that the flux is proportional to the gradient of the concentration. Joseph Fourier drew the same conclusion regarding the transfer of heat, and Fick conjectured that the same formalism is applicable to the diffusion of gases. In one dimension, we state this as

$$J = -D\frac{\partial}{\partial x}c(x,t)$$

where the proportionality constant D is called the *diffusion coefficient*. Fick then formulated the following conservation law;

$$\frac{\partial}{\partial t}\int_{x_0}^{x_1} c(x,t)\mathrm{d}t = J(x_1,t) - J(x_0,t) \tag{3.1}$$

which intuitively can be understood in the following way: the time evolution of the medium concentration in segment of space $[x_0, x_1]$ equals the difference of the flux at the segments boundaries. In higher dimensions, this result is usually referred to as Gauss' law. By setting $x_1 = x_0 + \mathrm{d}x$, taking the limit of $\mathrm{d}x \to 0$ and applying the fundamental theorem of calculus, (3.1) reduces to the following partial differential equation;

$$\frac{\partial}{\partial t} c(x,t) = D \frac{\partial^2}{\partial x^2} c(x,t) \tag{3.2}$$

which is commonly referred to as the *diffusion equation* or *heat equation*. In all future mentions of diffusion-type equations, the independent variables will be suppressed for readability.

3.1.2 Fisher's equation, reaction, diffusion and convection

The diffusion equation is one of the fundamental building blocks in the field of mathematical physics, and its application has indeed diffused into almost every field of science. In the 1930's, the British statistician and biologist Ronald Fisher applied diffusion to a new subject; ecology. More precisely, in his paper *The Wave of Advance of Advantageous Genes* [7], Fisher studied how a certain variant of a gene, a so called allele, would spread throughout a uniform population on a line, given that natural selection favored this new mutation. The application in mind were simple lifeforms such as slugs living along a shoreline. If we by $c(x,t)$ denote the concentration of individuals that express the advantageous gene, *Fisher's equation* in one dimension is given by

$$\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2} + rc\big(1 - \frac{c}{K}\big) \tag{3.3}$$

$$c(x,0) = c_0(x) \tag{3.4}$$

where the new parameters r and K are known as the *growth rate* and the *carrying capacity*. The lack of boundary conditions indicate that the diffusion takes place on the entire real line $\mathbf{R}$. Fisher's equation has since its introduction been the fundamental object in spatial ecology and related fields, but it is an idealised equation to be used as a starting point, not applied directly to novel problems and domains. In fact, Fisher himself was adamant about this upon the equation's introduction 1937.

Nevertheless, Fisher's equation stands today as a powerful tool to express spatial evolution of populations, and the way it succinctly summarizes complex emergent behaviours using three macroscopic and measurable parameters

gives it an unparalleled place in the field of mathematical oncology. As a differential equation, it belongs to the class of equations known as semi-linear reaction-diffusion equations; generally such equations are expressed as

$$\frac{\partial u}{\partial t} = \frac{\partial}{\partial x}\big(D\frac{\partial u}{\partial x}\big) + f \tag{3.5}$$

where $f(u, x, t)$ is the reaction term, and D can now depend on u, x and t. With the reaction term, we aim to encode how a solution u interacts with both the environment and itself. In the original paper by Fisher, the shape of the reaction term is inspired by the law of mass action, commonly employed in chemistry to model chemical reactions in well-stirred mixtures. Today, the most common interpretation of the reaction term is that it is analogous to logistic growth. The logistic differential equation

$$u' = ru\big(1 - \frac{u}{K}\big) \tag{3.6}$$

is commonly used to model population growth in the presence of some limiting factor encoded by K, such as competition for resources. In the modelling of tumours, this is the interpretation most commonly taken.

One of the most interesting aspects of solutions to (3.3) is their *travelling wave* property; given an initial condition of compact support on $\mathbf{R}$, the Fisher equation is satisfied by a solution sporting a clear, sharp wave front that traverses outward from the initial distribution, exemplified in Figure 3.1. This is in sharp contrast to classical diffusion; solutions to (3.2) tend to showcase much wider 'tails'. However, the 'bulk' of the solution to (3.2) explores space at a very slow pace. Another important distinction is that solutions to the diffusion equation conserve mass; solutions to Fisher's equation do not.

An intuitive argument in favor of reaction-diffusion as the driver of biological phenomena is provided in Chapter 11 of Murray's excellent text book *Mathematical Biology I* [17]. Here, Murray argues that pure diffusion is simply too slow to be an adequate model of biological phenomena, no matter what D is. He finds that under similar circumstances, the reaction term in even a simple model such as (3.3) works as a driving factor, increasing the transportation of biological media by several orders of magnitude. Thus, a common approach to this day in mathematical biology is to tweak the reaction term to suit the circumstances of the phenomena that is being modeled. In addition to the reaction term added to the basic diffusion in (3.5), one may also add a convection

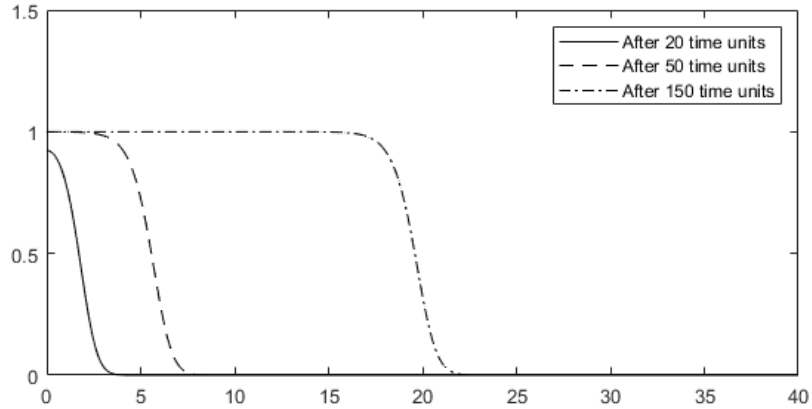

Figure 3.1: Solutions to (3.3)-(3.4) with $D = 0.1$, $r = 1.25$, $K = 1$ and $u_0(x) = \frac{4}{5}(1 + \exp(30(x^2 - 0.05)))^{-1}$ at three different times. Note the consistent wave front. In the modelling of cancer tumours, this wave front is interpreted as the edge of the tumour, moving with some degree of infiltration (given by the slope of the wave front) towards the surrounding tissue.

term, resulting in a reaction-convection-diffusion equation

$$\frac{\partial u}{\partial t} + \frac{\partial h}{\partial x} = \frac{\partial}{\partial x}\left(D\frac{\partial u}{\partial x}\right) + f \tag{3.7}$$

where $h(u, x, t)$ is the convection term, and models a directed transport phenomena with velocity h'. The non-linear toy example equation of this kind is the Burger's equation, given by

$$\frac{\partial u}{\partial t} - \nu u\frac{\partial u}{\partial x} = D\frac{\partial^2 u}{\partial x^2}. \tag{3.8}$$

This equation describes a self-propelling behaviour, where the convection speed the is proportional to the local concentration. This equation was originally formulated to study shock waves in liquids, but found some use in biology when studying cell cultures where volume exclusion is taken into account [8]. Most importantly, these types of equations arise when considering the *diffusion scaling* of transport equations of the Boltzmann kind, but that type of equations lies beyond the scope of this thesis.

3.2 Stochastic processes and diffusion

We will now shift our focus away from the macroscopic perspective of PDE modelling of tumours in favour of creating models based on single-cell modelling. The modelling of cancer cells using stochastic processes is inspired by the field of statistical mechanics, and as such we find it fitting to begin this treatise by its most fundamental construct, Brownian motion.

3.2.1 The simple random walk and Brownian motion

Consider a uniform lattice on $\mathbf{R}$ with spacing Δx, and further consider a particle being located $x = 0$ at time $t = 0$. In every time step Δt, the particle jumps to either $-\Delta x$ or Δx with equal probability, and this process is repeated every time step. Then, the probability to reach the lattice point m after n time steps, where $m \in \mathbb{Z}$, $n \in \mathbb{N}$, is given by

$$p(m,n) = \frac{1}{2^n}\frac{n!}{a!(n-a)!}, \qquad a = \frac{n+m}{2}.$$

Now assume that $n \gg 1$, i.e the random walker has been jumping around for a really long time. We find by using Stirling's formula $n! \sim (2\pi n)^{1/2} n^n e^{-n}$ that asymptotically,

$$p(m,n) \sim \big(\frac{2}{\pi n}\big)^{1/2} e^{-m^2/(2n)}.$$

Now say that we are interested in the limit of an infinitely fine grid, i.e $\Delta x \to 0$, $\Delta t \to 0$, and declare the continuous variables $m\Delta x := x$ $n\Delta t := t$. The probability of finding the particle in the small interval $(x, x + 2\Delta x)$ is then given by

$$u(x,t) := \frac{p(\frac{x}{\Delta x}, \frac{t}{\Delta t})}{2\Delta x} \sim \Big(\frac{\Delta t}{2\pi t(\Delta x)^2}\Big)^{\frac{1}{2}} \exp\Big(-\frac{x^2}{t}\frac{\Delta t}{(\Delta x^2)}\Big).$$

Finally, by considering the limit where Δx and Δt approach zero so that

$$\lim_{\substack{\Delta x \to 0 \\ \Delta t \to 0}} \frac{(\Delta x)^2}{2\Delta t} = D > 0 \tag{3.9}$$

we get the classical result

$$u(x,t) = \frac{1}{\sqrt{4\pi D t}} e^{-x^2/(4Dt)} \tag{3.10}$$

where D is a diffusion coefficient and (3.9) is known as the *diffusion limit*. Note that (3.10) is the distribution of a normal random variable with mean 0 and variance $2Dt$. Denote by $x(t)$ the random walker's location at time t. In the diffusion limit, we have that a random walker starting at $x = x_0$ satisfies the following

$$\mathbb{P}(x(t) \in \Omega) = \int_\Omega \frac{1}{\sqrt{4\pi Dt}} e^{-(y-x_0)^2/(4Dt)} \mathrm{d}y, \quad \Omega \subset \mathbf{R}$$

and most importantly, we have that

$$x(t) - x_0 \sim \mathcal{N}(0, 2Dt), \tag{3.11}$$

i.e the continuous random walk has *Gaussian increments*. This property, along with independence of increments and continuity of paths (not shown here) are the defining properties of *Brownian motion*, which is the essential building block in continuous time stochastic processes. Note that this derivation of Brownian motion is quite informal, and there exists a rich literature on the subject for readers interested in a more rigorous treatment of its fundamentals, see for example [16]. The treatise given here was mainly inspired by [17] and [11].

3.2.2 Itô calculus and the Fokker-Planck equation

We will now head straight into the main application of Brownian motion, namely stochastic calculus. Let $W(t)$ be a standard Brownian motion, i.e a continuous stochastic process with independent Gaussian increments with variance t. An Itô-process is then given as

$$x(t) = x_0 + \int_0^t a(x(s), s)\mathrm{d}s + \int_0^t b(x(s), s)\mathrm{d}W(s) \tag{3.12}$$

where we can interpret both of these integrals in a Riemann-Stieltjes sense. The first integral is referred to as the *drift term*, and models deterministic dynamics driving the stochastic process $x(t)$. The second integral is an Itô-integral, where $\mathrm{d}W(s)$ is to be interpreted as a Gaussian increment of infinitesimal size. If $b = 0$, we see that by differentiating (3.12) we get a general ordinary differential equation in $x(t)$. One can as such with a slight abuse of notation discuss *stochastic differential equations* (SDE) on the form

$$\mathrm{d}x(t) = a(x(t), t)\mathrm{d}t + b(x(t), t)\mathrm{d}W(t), \quad x(0) = x_0. \tag{3.13}$$

Stochastic integrals such as the one featured in (3.12) give rise to a multitude of interesting phenomena not observed in deterministic calculus. Chief among them is the stochastic analog to the chain rule, known as Itô's lemma. If $\varphi(x) \in C_0^2(\mathbf{R})$, we have the following result;

$$\mathrm{d}\varphi(x(t)) = \big(a\frac{\partial\varphi}{\partial x} + \frac{b^2}{2}\frac{\partial^2\varphi}{\partial x^2}\big)\mathrm{d}t + b\frac{\partial\varphi}{\partial x}\mathrm{d}W(t). \tag{3.14}$$

An intrinsic property of stochastic integrals is their *martingale property*, essentially meaning that $\mathbf{E}[\int_0^t f(x(s))\mathrm{d}W(s)] = 0$. With this in mind, let us now take the expectation of the function $\varphi(x)$ with respect to a probability measure generated by the stochastic process (3.12). This measure is given by the probability density at a point x at time t given an initial distribution $p_0(x)$, and we will call this measure $p(x,t)$. By considering (3.14) and using the martingale property, we get

$$\begin{aligned}
\frac{\mathbf{E}_p[\varphi]}{\mathrm{d}t} &= \mathbf{E}_p\big[a\frac{\partial\varphi}{\partial x} + \frac{b^2}{2}\frac{\partial^2\varphi}{\partial x^2}\big] \Longrightarrow \\
\frac{\mathrm{d}}{\mathrm{d}t}\int_{\mathbf{R}}\varphi p\mathrm{d}x &= \int_{\mathbf{R}}\big[a\frac{\partial\varphi}{\partial x} + \frac{b^2}{2}\frac{\partial^2\varphi}{\partial x^2}\big]p\mathrm{d}x \Longrightarrow \\
\frac{\mathrm{d}}{\mathrm{d}t}\langle\varphi,p\rangle &= \langle a\frac{\partial\varphi}{\partial x},p\rangle + \langle\frac{b^2}{2}\frac{\partial^2\varphi}{\partial x^2},p\rangle
\end{aligned} \tag{3.15}$$

where we have used that expectation with respect to a probability measure p defines a linear operator $\mathbf{E}_p[\cdot] = \langle\cdot,p\rangle$. We note that (3.15) is a differential equation in p written in weak form. By integration by parts and using that φ is of compact support, we can rewrite (3.15) as

$$\langle\varphi,\frac{\partial p}{\partial t}\rangle = -\langle\varphi,\frac{\partial}{\partial x}[ap]\rangle + \frac{1}{2}\langle\varphi,\frac{\partial^2}{\partial x^2}[b^2p]\rangle$$

which weakly defines the partial differential equation

$$\begin{aligned}
\frac{\partial p}{\partial t} &= -\frac{\partial}{\partial x}[ap] + \frac{1}{2}\frac{\partial^2}{\partial x^2}[b^2p] \\
p(x,0) &= p_0(x)
\end{aligned} \tag{3.16}$$

which is known as the *Fokker-Planck* equation. It has the remarkable property of describing the evolution of a probability density of a stochastic process given by (3.12). We also note that (3.16) is a diffusion-style differential equation, indeed being a linear convection-diffusion equation. The Fokker-Planck equation serves as a bridge from the microscopic description of diffusion phenomena described by random walks and the macroscopic description given by Fickian

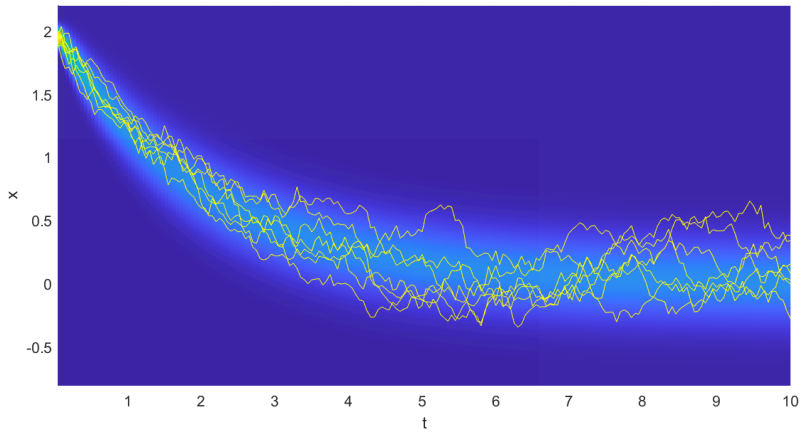

Figure 3.2: Seven realisations of the SDE $\mathrm{d}x(t) = -0.5x(t)\mathrm{d}t + 0.225\mathrm{d}W(t)$ along with the solution to the corresponding Fokker-Planck equation $p(x,t)$. For any time $t > 0$, the state of the SDE solution is a sample from a probability distribution given by $p(x,t)$.

diffusion. As a final exercise, we shall consider the Fokker-Planck equation for standard Brownian motion with diffusion coefficient $b = \sqrt{2D}$ and drift coefficient $a = 0$. The Fokker-Planck equation in this case becomes

$$\frac{\partial p}{\partial t} = D\frac{\partial^2 p}{\partial x^2}$$

which is the exact same equation as (3.2). Thus we establish that Brownian motion is the microscopic equivalent of standard diffusion. We note once again that the formality has been kept to a minimum in this chapter; we have foregone to mention conditions on a and b for existence of solutions and have been playing fast and loose with subtle measure theoretic considerations when manipulating expectations. For a rigorous treatment of Itô's lemma, we once again refer to [16].

3.2.3 Interacting particles and nonlinear diffusion

Now that we have the concept of SDE:s and the Fokker-Planck equation freshly in our minds, we will move on to the main application for this thesis, namely interacting particle systems. In a mathematical oncology setting, agent-based models are a fairly recent development, but similar methods have a rich history in chemistry and physics. Our chosen approach is to model our tumour on

a cell-by-cell level. Every cell is then described by an SDE model designed to mimic the behaviour laid out in Chapter 2. The general form of such an equation system is

$$\begin{aligned} \mathrm{d}\mathbf{x}_1(t) &= \mathbf{a}_1(\mathbf{x}(t),t)\mathrm{d}t + \mathbf{b}(\mathbf{x}(t),t)\mathrm{d}\mathbf{W}_1(t) \\ \mathrm{d}\mathbf{x}_2(t) &= \mathbf{a}_2(\mathbf{x}(t),t)\mathrm{d}t + \mathbf{b}(\mathbf{x}(t),t)\mathrm{d}\mathbf{W}_2(t) \\ &\vdots \\ \mathrm{d}\mathbf{x}_N(t) &= \mathbf{a}_N(\mathbf{x}(t),t)\mathrm{d}t + \mathbf{b}(\mathbf{x}(t),t)\mathrm{d}\mathbf{W}_N(t) \end{aligned} \tag{3.17}$$

where we assume the tumour constitutes N cells enumerated $i = 1, \ldots, N$. By $\mathbf{x}_i(t)$ we denote the location of cell i at time t, and by $\mathbf{x}(t)$ we denote the location of all cells; $\mathbf{x}(t) = [\mathbf{x}_1(t), \mathbf{x}_2(t), \ldots, \mathbf{x}_N(t)]$. Note here the bold font, indicating that we have moved from strictly discussing one-dimensional diffusions to diffusions in an arbitrary number of dimensions d. Thus, we have that $\mathbf{a}_i(\cdot,t) : \mathbf{R}^d \mapsto \mathbf{R}^d$, $\mathbf{W}_i(t)$ are independent $d \times M$-dimensional Brownian motions and $b(\cdot,t) : \mathbf{R}^d \mapsto \mathbf{R}^D \times \mathbf{R}^M$. We will, for the sake of simplicity, assume that $M = 1$, $\mathbf{b} = b\mathbf{I}$, and

$$\mathbf{a}_i(\mathbf{x}(t),t) = \nabla_{\mathbf{x}_i} \sum_{i=1}^{N} \sum_{j=i+1}^{N} U(\mathbf{x}_i(t) - \mathbf{x}_j(t)) \tag{3.18}$$

where U will be referred to as the *pairwise interaction potential*. This setting puts us on equal footing with [15] and [18], who have written extensively on the subject of interacting particle systems with biological applications in mind. With the notation and setting out of the way, we can continue by stating the corresponding Fokker-Planck equation to (3.17). Let $P(\mathbf{x},t)$ the probability measure generated by (3.17). We then have that

$$\frac{\partial}{\partial t} P(\mathbf{x},t) = \nabla_{\mathbf{x}} \cdot \Big[\frac{b^2}{2} \nabla_{\mathbf{x}} P(\mathbf{x},t) + \nabla_{\mathbf{x}} \mathbf{a}_i(\mathbf{x}) P(\mathbf{x},t) \Big], \tag{3.19}$$

where the derivation is similar to the one conducted for (3.16), but of course a lot more technical, and the curious reader can find justifications in [15], [18] and [9]. Note that this is a differential equation in Nd dimensions, and when dealing with such enormous dynamics, one typically attempts to reduce its dimension. We will introduce the most naive way of doing this, which is by assuming that the particles are essentially uncorrelated. This is called the

mean-field limit, and mathematically we can summarise it as

$$P(\mathbf{x},t)=\prod_{i=1}^{N}p_i(\mathbf{x},t)$$

where $p_i(\mathbf{x},t)$ is the marginal distribution of the i:th particle. By repeatedly marginalizing (3.19), we can derive an equation for $p_i(\mathbf{x},t)$ from (3.19);

$$\frac{\partial p_i}{\partial t}=\nabla_{\mathbf{x}}\cdot\big[\frac{b^2}{2}\nabla_{\mathbf{x}}p_i+p_i\nabla_{\mathbf{x}}(U*p_i)\big] \tag{3.20}$$

where the convolution $U*p$ comes from the following calculation, building upon the weak convergence of probability measures: define by $\mu^N(t)$ the *empirical distribution* for (3.17) in the following manner;

$$\mu^N(t)=\frac{1}{N}\sum_{i=1}^{N}\delta_{\mathbf{x}_i(t)}(\mathbf{x})$$

and further note that (3.18) can be written as

$$\mathbf{a}_i(\mathbf{x}(t),t)=\sum_{j\neq i}\nabla_{\mathbf{x}_i}U(\mathbf{x}_i(t)-\mathbf{x}_j(t))=\nabla_{\mathbf{x}_i}\big\{U*\mu^N(t)\big\}.$$

In the limit of infinitely many particles, we have that $\mu^N(t)\to_w P(\mathbf{x},t)$, giving us the asymptotic relationship seen in (3.20) after repeated integration.

As a final exercise in interacting particle systems, we shall see how one can derive Burgers equation (3.8) by considering (3.20) in one dimension and the limit $U\to\nu\delta$. In one dimension, (3.20) becomes

$$\begin{aligned}\frac{\partial p}{\partial t}&=\frac{b^2}{2}\frac{\partial^2 p}{\partial x^2}+p\frac{\partial}{\partial x}(U*p)\\ &\quad\{\delta*p=\int_{\mathbf{R}}\delta(x-y)p(y)\mathrm{d}y=p(x)\}\Longrightarrow\\ \frac{\partial p}{\partial t}&=\frac{b^2}{2}\frac{\partial^2 p}{\partial x^2}+\nu p\frac{\partial p}{\partial x}\end{aligned}$$

which is exactly the same as (3.8). Thus, we see that Burgers equation is the PDE describing the evolution of a system of interacting particles with infinitely short, infinitely repulsive interactions.

3.2.4 Fisher's equation - a microscopic derivation

In the previous segment, we illustrated how interacting particle systems driven by Brownian motion could give rise to convection phenomena. In this last chapter on stochastic processes, we will instead see how particle systems of a varying size give rise to reaction phenomena, and how we can derive Fisher's equation by considering the frontier of branching Brownian motion (BBM). This derivation is based on a classic result by H.P McKean [14] along with an intuitive argument presented in the PhD thesis by Brunet [4].

The simplest form of BBM is modelled as following: at time $t = 0$, a one-dimensional Brownian motion starts at the origin. It continues up until an exponentially distributed holding time T, i.e $\mathbf{P}(T > t) = e^{-t}$. At this moment, the particle splits in two, and the two new particles repeat the process. After a time t, we have N_t particles. One can see that this works as a simple model for cell division. Now, denote by $u(x,t)$ the quantity

$$u(x,t) = \mathbf{E}\big[\prod_{i=1}^{N_t} \theta(x + x_i(t))\big] = \mathbf{P}[\max_i x_i(t) < x]. \tag{3.21}$$

One can interpret (3.21) as the distribution of the right-most particle generated by the BBM. Now consider the state of u at a time $u(x, t + \mathrm{d}t)$ given that $u(x,t)$ is known, and that no branching has taken place yet. We have for small $\mathrm{d}t$ that

$$u(x, t + \mathrm{d}t) = \underbrace{(1 - \mathrm{d}t)\mathbf{E}[u(x + \mathrm{d}W(t), t)]}_{\text{no branching during dt}} + \underbrace{\mathrm{d}t u(x,t)^2}_{\text{branching}}$$

where we use that $\exp(-\mathrm{d}t) = 1 - \mathrm{d}t + \mathcal{O}(\mathrm{d}t^2)$. Here, we chose to ignore the fact that the branching particles move a little during this time frame, and only apply diffusion to the non-branching case. Thus, the branching event results in "two copies" of the density occupying the space x at time t, giving us the square of u. Now we Taylor expand $\mathbf{E}[u(x + \mathrm{d}W(t), t)]$ around x with respect to $\mathrm{d}W(t)$, and get (from Itô's formula) that

$$u(x, t + \mathrm{d}t) = u + \mathrm{d}t\big[\frac{\partial^2 u}{\partial x^2} + u - u^2\big]. \tag{3.22}$$

And by the limit $\mathrm{d}t \to 0$, we have also motivated Fisher's equation by considering Brownian motion under idealized circumstances. This highlight the power of connecting microscopic biologically motivated models to macroscopic phenomena, and can give rise to new and exciting equations by formulating them from the bottom up.

3.3 Elements of computational statistics

The goal of this thesis is two-fold. On one hand, we aim to evaluate methods of modelling glioblastoma migration by using SDE:s. On the other, we wish to conduct inference on these interacting particle systems based on real data. For this purpose, we will present a short discussion of relevant topics in statistical inference. In this chapter, we will stick to nomenclature common within Bayesian inference; most importantly we will refer to systems of SDE:s such as (3.17) as *stochastic dynamical systems*.

3.3.1 Transition probabilities in dynamical systems and construction of likelihood functions

With our recent discussion of the Fokker-Planck equation, we have illustrated that the state of stochastic dynamical system described by an SDE can be sampled directly from the solution to its corresponding PDE (3.19), illustrated by Figure 3.2 for a simple one-dimensional case. Given this, assume that we have observed a system undergoing stochastic dynamics at times t_0, t_1, ... t_K, and refer to these observations as $\mathbf{x}_k$, $k = 0, \dots, K$. On each of these time intervals, we can find the transition density $P_k(\mathbf{x}, t)$ by solving (3.19) using the initial condition

$$P_k(\mathbf{x}, t_k) = \frac{1}{N} \sum_{i=1}^{N} \delta_{\mathbf{x}_{ik}}(\mathbf{x}) \tag{3.23}$$

i.e the empirical density generated by the observation, if $\mathbf{x}_{ik}$ is the k:th observation of the i:th particle. The probability density for the state $\mathbf{x}(t)$ of the particle system for $t \in [t_k, t_{k+1})$ is now clearly defined by (3.19) along with the initial condition (3.23). Assume now that $\mathbf{a}$ or $\mathbf{b}$ in (3.17) have some parameters θ for which we wish to conduct statistical inference given the observations $\mathbf{x}_{0:K}$, where $0 : K$ indicates is used to refer to a collection of observations. Since the transition density will depend on these parameters, we will use the notation $P_k(\mathbf{x}, t; \theta)$. We are now ready to construct a likelihood for the observation $\mathbf{x}_{k+1}$ in the following manner;

$$p(\mathbf{x}_{k+1} | \mathbf{x}_k, \theta) := P_k(\mathbf{x}_{k+1}, t_{k+1}; \theta) \tag{3.24}$$

and we get the likelihood for our entire sequence of observations

$$p(\mathbf{x}_{0:K} | \theta) = \prod_{k=0}^{K-1} p(\mathbf{x}_{k+1} | \mathbf{x}_k, \theta). \tag{3.25}$$

One can then use the likelihood (3.25) to evaluate how *likely* a sequence of observations $\mathbf{x}_{0:K}$ are given a parameter set θ. The theory presented in this segment is nothing that cannot be found in an ordinary text book on Bayesian inference or machine learning, see Bishops textbook [2] for an excellent overview of many related topics.

3.3.2 Simulation of SDE:s and Monte Carlo methods

Before diving into the problem of maximizing the likelihood (3.25), we need to introduce two constructs that will be of help later; the *Euler-Maruyama* scheme for an SDE, and how to approximate a solution to a Fokker-Planck equation using *Monte Carlo* methods. For a generic one-dimensional SDE such as (3.13), we can approximate the state of a future time t_1 given a known state $x(t_0) = x_0$ as

$$y_1 = x_0 + (t_1 - t_0)a(x_0, t_0) + \sqrt{t_1 - t_0}b(x_0, t_0)Z$$

where $Z \sim \mathcal{N}(0, 1)$ and y_1 is an approximation of $x(t_1)$. Repeating this process, we get the Euler-Maruyama approximation $y_{0:K}$

$$y_0 = x_0 \tag{3.26}$$

$$y_{k+1} = y_k + (t_{k+1} - t_k)a(y_k, t_k) + \sqrt{t_{k+1} - t_k}b(y_k, t_k)Z \tag{3.27}$$

defined on grid points t_k, $k = 0, \ldots, K$. One can now approximate the solution to (3.16) at a time $T = t_K$ by performing S iterations of (3.26)-(3.27); we have a weak convergence

$$\lim_{S\to\infty} \frac{1}{S} \sum_{s=1}^{S} \varphi(y_{k(s)}) = \int_{\mathbf{R}} \varphi(x)p(x, T)\mathrm{d}x \tag{3.28}$$

where φ is a test function and $y_{k(s)}$ corresponds to the s:th sample. This is known as the Monte Carlo approach to finding a transition density, and a lot more on this subject can be found in the monolithic text book by Kloeden and Platen [12]. Through Monte Carlo simulation, we can now look back at Figure 3.2 and note a duality. When introduced, we viewed Figure 3.2 as an example of how one can obtain the state of a stochastic dynamical system by solving the PDE (3.16). Now however, we can see it the other way; how one can approximate a solution to (3.16) using simulation by (3.26)-(3.27).

3.3.3 Bootstrap particle filter for likelihood approximation

In theory, one could think that the likelihood expression (3.25) is now readily available by repeatedly solving the PDE (3.19) K times, using the observations as initial conditions. However, solving partial differential equations is hard, making this approach impractical. One could perhaps use numerical methods for PDE:s such finite elements, but often Monte Carlo approaches can approximate (3.25) to a very high degree of accuracy. One method is to use *particle filters*, which we will now give a description of. This description is more or less based on [20].

Particle filtering is a *Sequential Monte Carlo method* used to sample from *hidden states* of our dynamical system. In our application, a hidden state would be any configuration the particle system takes at times $t \neq t_k$. Intuitively, one can understand that a hidden state "close to t_{k+1}" contains more information about the likelihood structure of at time t_{k+1} than the observed state at t_k. The question is then how to access this hidden state, and the answer to that question is to use the Euler-Maruyama scheme as an *importance sampler*. By letting $\mathbf{y}_k$ be a hidden state on the interval (t_k, t_{k+1}), we can rewrite the left-hand side of (3.24) as

$$p(\mathbf{x}_{k+1}|\mathbf{x}_k, \theta) = \int_{\mathbf{R}^{ND}} p(\mathbf{x}_{k+1}|\mathbf{y}_k, \theta) p(\mathbf{y}_k|\mathbf{x}_k, \theta) \mathrm{d}\mathbf{y}_k \tag{3.29}$$

We can then make an analogy to (3.28) where the transition probability $p(\mathbf{x}_{k+1}|\mathbf{y}_k, \theta)$ in (3.29) takes the role of a test function, and compute this integral using Monte Carlo simulation of the hidden state. With S samples from the hidden state, this gives us

$$p(\mathbf{x}_{k+1}|\mathbf{x}_k, \theta) \approx \frac{1}{S} \sum_{s=1}^{S} p(\mathbf{x}_{k+1}|\mathbf{y}_{k(s)}, \theta). \tag{3.30}$$

For improved accuracy, one shall inject multiple hidden states between each observation, and apply variance reduction techniques; see for example [6] for a review article on such techniques. With (3.30), we now have a tractable expression for the likelihood (3.25), and can employ tools from mathematical optimization to solve the problem

$$\max_{\theta} p(\mathbf{x}_{0:K}|\theta).$$

Bibliography

[1] Bruce Alberts. Molecular biology of the cell, 2008.

[2] Christopher M Bishop. *Pattern recognition and machine learning*. Springer Verlag, 2006.

[3] Dani L Bodor, Wolfram Pönisch, Robert G Endres, and Ewa K Paluch. Of cell shapes and motion: the physical basis of animal cell migration. *Developmental cell*, 52(5):550–562, 2020.

[4] Éric Brunet. *Some aspects of the Fisher-KPP equation and the branching Brownian motion*. Ph.d. thesis, UPMC, 2016.

[5] Arnaud Chauviere, Thomas Hillen, and Luigi Preziosi. Modeling the motion of a cell population in the extracellular matrix. *Discrete Contin. Dyn. Syst*, pages 250–59, 2007.

[6] Garland B Durham and A Ronald Gallant. Numerical techniques for maximum likelihood estimation of continuous-time diffusion processes. *Journal of Business & Economic Statistics*, 20(3):297–338, 2002.

[7] Ronald Aylmer Fisher. The wave of advance of advantageous genes. *Annals of eugenics*, 7(4):355–369, 1937.

[8] A Gamba, D Ambrosi, A Coniglio, A De Candia, S Di Talia, Enrico Giraudo, Guido Serini, Luigi Preziosi, and Federico Bussolino. Percolation, morphogenesis, and burgers dynamics in blood vessels formation. *Physical review letters*, 90(11):118101, 2003.

[9] Carl Graham, Thomas G Kurtz, Sylvie Méléard, Philip Protter, and Mario Pulvirenti. *Probabilistic Models for Nonlinear Partial Differential Equations: Lectures Given at the 1st Session of the Centro Internazionale Matematico Estivo (CIME) Held in Montecatini Terme, Italy, May 22-30, 1995*. Springer, 2006.

[10] Julian Huxley et al. Evolution. the modern synthesis. *Evolution. The Modern Synthesis.*, 1942.

[11] Fima C Klebaner. *Introduction to stochastic calculus with applications*. World Scientific Publishing Company, 2012.

[12] Peter E Kloeden and Eckhard Platen. *Numerical Solution of Stochastic Differential Equations*. Springer, 1992.

[13] Adam A Malik and Philip Gerlee. Mathematical modelling of cell migration: stiffness dependent jump rates result in durotaxis. *Journal of mathematical biology*, 78(7):2289–2315, 2019.

[14] Henry P McKean. Application of brownian motion to the equation of kolmogorov? petrovskii? piskunov. *Communications on pure and applied mathematics*, 28(3):323–331, 1975.

[15] Sylvie Méléard and Sylvie Roelly-Coppoletta. A propagation of chaos result for a system of particles with moderate interaction. *Stochastic processes and their applications*, 26:317–332, 1987.

[16] Peter Mörters and Yuval Peres. *Brownian motion*, volume 30. Cambridge University Press, 2010.

[17] James D Murray. *Mathematical biology: I. An introduction*, volume 17. Springer Science & Business Media, 2007.

[18] Karl Oelschläger. On the derivation of reaction-diffusion equations as limit dynamics of systems of moderately interacting stochastic processes. *Probability Theory and Related Fields*, 82(4):565–586, 1989.

[19] Jean Philibert. One and a half century of diffusion: Fick, einstein before and beyond. *Diffusion fundamentals*, 2006.

[20] TB Schön and F Lindsten. Learning of dynamical systems–particle filters and markov chain methods. *Draft available*, 2015.

[21] Johan Skog, Tom Würdinger, Sjoerd Van Rijn, Dimphna H Meijer, Laura Gainche, William T Curry, Bob S Carter, Anna M Krichevsky, and Xandra O Breakefield. Glioblastoma microvesicles transport rna and proteins that promote tumour growth and provide diagnostic biomarkers. *Nature cell biology*, 10(12):1470–1476, 2008.

[22] Kristin R Swanson, Ellsworth C Alvord Jr, and JD Murray. A quantitative model for differential motility of gliomas in grey and white matter. *Cell proliferation*, 33(5):317–329, 2000.

[23] Peter J Wangersky. Lotka-volterra population models. *Annual Review of Ecology and Systematics*, 9(1):189–218, 1978.