From Microscopic SDE to Stochastic Macroscopic Equation: A Framework for Modeling Diversity in Cancer and Other Complex Living Systems.

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Abstract

Biological living systems in general exhibit complex and diverse dynamics. The latter, in particular, is essential, since diversification increases the odds of survival of an organism while reducing the risk of extinction of the population. Primarily, diversification is a consequence of the randomness in the replication process of a biological cell, which eventually manifests into a motley set of macroscopic features of an individual. These heterogeneous features of individuals constitutes for diversity in population. Cancer is a prime example of such a complex system where the transformed cells exhibit plethora of disparate features, which in turn makes modeling their dynamics quite challenging. In this paper we consider cancer as a prototype of a complex living system and provide two contrasting perspective for studying and modeling it. Based on this we illicit a deeper role of diversification in the evolution of cancer. Following this, we ask ourselves how can model these diverse dynamics in a multiscale setting. The current multiscale modeling techniques lack the ability to capture this diversity at the macroscopic level of experimental observation, thus are inappropriate for describing the behavior of a selfish organism like cancer. We address this shortcoming by providing an abstract but mathematically rigorous framework for deducing stochastic evolution equations at the macroscopic level starting from a microscopic description of the involved dynamics. We achieve this by making use of the connection between stochastic process and the semigroup operator generated by them. In particular, we look at the semigroups generated by Levy processes and their connection with the characteristic functions and Levy symbols. The latter turns out to represent pseudo-differential operators using which we eventually provide a mechanism for constructing stochastic evolution equations. Altogether, this provides the framework for modeling diverse dynamics at the macroscale starting from the microscale.

1 Introduction

The field of multiscale modeling is an active field of research with an aim of accurately and rigorously deducing an equation or a system of equations for the observed phenomenon starting from first principles. The fundamental physical laws of molecular interactions i.e. the basic Newtonian laws of motion serve as the first principles. Such accurate and mathematically rigorous description of the observed phenomenon is indeed helpful to characterize some important parameters such as cell motility or heat conductivity or viscosity, of the respective phenomenon under investigation such as cancer migration or temperature distribution or fluid flow respectively. Figure 1 illustrates the typical methods of multiscale modeling. Contributions in the direction of S1 to S2 dates back to the pioneering works of J.C. Maxwell and L. Boltzmann on the kinetic theory of gases (fluids in general). A first rigorous proof for the Boltzmann equation starting from Newtonian laws is due to O. Lanford [33]. The result was slightly unsatisfactory due to its validity for short time dynamics i.e. just local existence, thereby leaving open the important questions about long time dynamics, i.e. questions relating to the global existence. Some of these gaps were overcome by the works of Illner, Pulvirenti and Shinbrot [29, 30, 44]. It was not until 1989 that a more general global result was made available due to DiPerna and Lions [17]. A significant amount of work (both theoretical and applied) has also been carried out in the direction of S2 to S3 i.e. in the direction of obtaining different types of hydrodynamic limit equations starting from the Boltzmann equation. Hilbert also worked on this problem [22] where he used asymptotic expansions (now known as Hilbert expansions, a slight variant of the Chapman-Enskog expansion, thus sometimes also referred to as Chapman-Enskog-Hilbert expansion) to show that, under appropriate physical setting,
the 0th order term of the expansion solving the Boltzmann equation is a Maxwellian (i.e. the Maxwell-Boltzmann distribution)\cite{16}. These works not only provide a strong foundation but also a starting point for the deduction of most macroscopic equations.

There has also been some progress in the direction of $S_1$ to $S_3$ due to the advances in stochastic calculus. A first attempt in this direction was nearly 60 years ago and is due to C.B. Morrey \cite{37}. Though the work could be considered to be lacking some mathematical rigor, it did introduce in a subtle way the notions of local equilibrium which is nothing but the pointwise quasi-steady rate of the microscopic dynamics in the appropriate limit and after appropriate space time rescaling. We also see here that the author implicitly uses the notion of ergodicity to justify the existence of equilibrium distribution for which the entropy is supposed to be maximized. The latter approach was used by S.R.S Varadhan in \cite{49} and S.Olla in \cite{40} where they perturbed the N-body Hamiltonian system with white noise in order to ensure ergodicity of the system. An implicit assumption in these techniques is that the microscopic dynamics is random or in other words random dynamics is incorporated in the description of microscopic evolution. A more intuitive explanation towards this ideology of modeling is provided in \cite{15,31}.

One of the major drawback in the above multiscale modeling framework is their inability to capture complex dynamics of a living system. The main reason being that the framework is mainly developed and for inately passive particles. Many adaptations to the above framework have been used to model complex systems. In \cite{28}, authors have adopted kinetic-theory based Boltzmann type equation to model active vehicular traffic wherein the notion of active behavior of a vehicle (modeled as a particle) was introduced. More recently, in \cite{2} kinetic approach was used to model biological system as a dissipative system arising from non-equilibrium boundary interaction. More precisely, they based their model on the approach of Schrödinger wherein the bio-system is feeds on the negative entropy. On the other hand there are considerable works in the direction of adapting the classical kinetic theory for passive particles to a kinetic theory for active particles (KTAP) with the objective of modeling complex dynamics of living systems. For example in \cite{6-8} phenomenological equations at the mesoscopic level have been proposed for describing complex cell-cell and cell-tissue interactions. Since these equations are devised take into consideration multi-scale as well as non-conservative interactions, it allows for modeling a wide range of complex microscopic and macroscopic dynamics \cite{4,5,6,10}. Although very powerful tool, there are two major shortcomings of KTAP: (i) since it mainly devised from phenomenological arguments it lacks rigorous derivation from first principles, (ii) the obtained equations are mainly of deterministic type and thus lack the ability to model diversity and heterogeneity of observed macroscopic dynamics. One way to remedy that is to by incorporating non-determinism at the macroscopic level. This is exemplified in the works of \cite{23,25,26}, where stochastic models were proposed to describe the complex dynamics of cancer cell migration. These models illustrate how randomness play an essential role in bringing forth some of the rare, transient, and interesting events while the averaged dynamics fails to do so. Even more astonishing is that the averaged dynamics tell a very different (or rather an incomplete) story. This is the main drawback of using deterministic models to explain a very diverse, complex, and generic problem such as cancer invasion. A more elaborate comparison between stochastic and deterministic models in acid mediated cancer invasion is provided in \cite{24}. Motivated by the interesting dynamics induced by stochastic models, we ask ourselves the following question: how can one deduce a stochastic macroscopic equation starting from microscopic equations?

In this paper we answer this question by providing an abstract mathematical framework for deducing stochastic evolution equations at the macroscopic level starting from a microscopic description of the involved dynamics. We achieve this by first observing that a certain class of Lévy processes generates transport equations at the macroscopic level. Motivated by this we ask ourselves what different types of macroscopic equations would be possible for other types of Lévy processes. The Lévy-Ito decomposition formula and Lévy-Khintchine formula gives a hint for answering this question. Since we want to deduce stochastic evolution equations, we plan to investigate the situation where
microscopic equations are driven by different types of Lévy processes, where the type of the Lévy process i.e. the law of the Lévy process, is randomly changing with respect to time. Intuitively speaking, because different Lévy processes are characterized by different Lévy symbols, a randomly varying Lévy noise at the microscopic level should result in stochastic evolution equations at the macroscopic level. To make this mathematically rigorous we invoke the theory of semigroups and pseudo-differential operators which enable us to generate a specific class of random operators which in turn allows us to construct a two parameter semigroups. This eventually lead us to a random non-autonomous Cauchy problem at the macroscopic level.

To this end, we first start with a short discussion in Section 2 about some fundamental properties of a complex living system and their implications by considering cancer as a prototypical example. Motivated by these discussions, in Section 3.3 we introduce the necessary concepts required for modeling diversity in living systems. This entails discussion about the properties of Lévy processes, Lévy-Ito decomposition and the Lévy-Khintchine formula. The latter introduces a class of pseudo-differential operators which in turn generates a class of operators. The characterization of the domains of these operators is discussed in Section 3.2. Based on these connections we provide a framework for constructing stochastic evolution equations in Section 3.5. Finally we apply this approach for modeling acid mediated cancer invasion in Section 4.

2 Two contrasting perspectives of cancer

There are two main different philosophies for the cause of cancer. The classical viewpoint is that cancer is a neo-transformation, i.e. cells are transformed to some new (probably non-existent in the evolutionary history) type of cells, while a new emerging philosophy being that cancer is a paleo-transformation i.e. cells are transformed to primitive unicellular type of life forms. These ideologies are in fact two faces of the same coin and provide two distinct microscopic views for modeling the problem of cancer. The following discussion is motivated by [3, 12–14, 20, 35, 38, 39, 42, 45, 53].

2.1 Cancer: An ecosystem of cells

Cancer may be interpreted as an ecosystem of neoplastic and stromal cells inhabiting the tissue containing vital resources for cell sustenance. The ecosystem is composed of different types of neoplastic cells such as cancer cells,
cancer stem cells, cancer associated fibroblasts, etc., and normal healthy cells such as immune cells, endothelial cells, pericytes, etc. Apart from different types of cells, the micro-environment is also composed of extracellular substances such as interstitial fluid, blood vessels, ECM, acid byproducts, and other various vital biomolecules. Figure 2 illustrates the composition of a generic tumor environment. All these elements together form an interactive ecological system which manifests itself as a tumor. Figure 3 illustrates some of the possible sets of interactions between different inhabitants of the tumor ecosystem, such as interactions between cancer cells and endothelial cells, endothelial cells and pericytes, immune cells and cancer associated fibroblasts, etc. Various such complex interactions is what orchestrates a metastatic progression of cancer. An obvious implication of this is that the development and progression of a tumor is very much dependent on its environment. Due to the heterogeneity in the tissue architecture and composition, the way an incipient tumor develops would be different therefore leading to diverse and heterogeneous cancer types. The former (i.e. diversity of cancer types) accounts for the differences between various cancers such as prostate cancer, breast cancer, melanoma, glioma, cervical cancer, etc., while the latter (i.e. heterogeneity of cancer types) accounts for differences in two or more samples of the same type of cancer across different individuals or same individuals. This motivates the study of cancer from an ecological perspective.

Recent advances in gene sequencing techniques has resulted into comprehensive listing of somatic mutations responsible for cancer development. These studies indicate that the evolution of cancer genome is not only diverse, i.e. it varies across different tumor types but is also heterogeneous, i.e. it varies within same tumor arising across different individuals and within a single individual [53]. Because of these variations and because of ecological constraints such as competition, predation, parasitism, mutualism, etc., clones with varying genome experience diverse selection forces, thereby producing significant variation in the evolutionary path of a tumor [35]. Here the selection forces could be both natural and/or artificial selection. The former is induced due to genetic mutations that increase the fitness condition and are heritable after successive reproduction. The latter is induced via external interferences such as drugs and therapy which choose for more resistive clones of the population. Also, these selection forces act at various levels, namely- at the level of individual cells, at the level of population and at the level of the tumor itself [35]. Altogether, they work towards conferring malignancy to the tumor. One of the key malignant feature is the ability to invade and metastasize, which is majorly influenced by the instability and heterogeneity at the level of genes, clones, population, micro-environmental ecosystem and the organism itself. Cancer cells are endowed with diverse cellular mechanisms that enable them to disassociate from the primary tumor and to start wandering through the local tissue and eventually enter the circulatory system. A comprehensive review on some of the different mechanics of movement employed by cancer cells can be found in [19]. These mechanisms can be categorized as single cell movement and collective movement. The former involves EMT and amoeboid type movement, while the latter involves clustered or cohort movement and movement of sheets or strands of cells. Figure 3 illustrates these different categories of cell movement, while Figure 4 depicts how cells switch between different movement mechanisms as a response to the changes in their intracellular and extracellular molecular pathways. For the sake of completeness we also include Figure 5 depicting the different bio-mechanical steps involved in the process of cellular motion, which includes (i) the formation of protrusions such as lamilapodia, filopodia, (ii) formation of focal contacts i.e. attachment of cells to ECM fibers, (iii) cleaving of ECM via proteolysis near the focal points, (iv) contraction of the cell due to the binding of myosin II to actin filaments, (v) finally detachment of the rear end which results in a displacement of the cell. To summarize, the genetic instability within cancer cells generates a wide fitness landscape and the micro-environmental ecosystem selects for cells that are fit enough to survive and reproduce further. Many iterations of such Darwinian dynamics leads to the development of a diverse, heterogeneous, malignant, and invasive tumor. Next we shall look at a contrasting viewpoint for the process of carcinogenesis and for the behavior of cancer cells.

2.2 Cancer: A selfish organism

A typical perspective is that cancer is a transformation of normal healthy cells into a new kind of cells that possess the hallmark of neoplasms. In this philosophy, individual cells, that result after neoplastic transformation have no individuality, instead they are seen as a mere chemical system and are assumed to be lacking the ability to act for their own self interest i.e. they are, in some sense, assumed to be lacking any motive or intent. The whole process of cancer development and progression is viewed from a mechanistic perspective, where the focus is more on the biochemical mechanisms that make the cells behave in a certain way. This is simply a physicists perspective, where all matter, including living cells, are considered to be purely mechanistic. Such a philosophy fails to explain the motive or the purpose for the cells to behave the way they do and is too narrow to model a complex and diverse disease such as cancer. The notion of individuality and self interest is a vital factor that contribute towards the complexity of
Figure 3: Illustration of plausible interactions within a tumor microenvironment and different mechanisms of cancer cell movement

Figure 4: Illustration of plasticity in cell movement, where depending on the molecular interactions cells can switch between different mechanisms of movement. Loss of proteases leads to a switch from EMT to amoeboid type of movement, loss of cell-cell adhesion due inhibition of cadherins leads to a switch from collective epithelial sheet movement to EMT type single cell movement, loss of cell-ECM adhesion due to the inhibition of $\beta_1$-integrins leads to a switch from cluster type collective movement to amoeboid type single cell movement.
Figure 5: Illustration of the different bio-mechanical processes or steps involved in the movement of a cell [19].
the disease and could in turn be helpful for developing robust models for the cancer invasion. In contrast to this, a fairly new philosophy is to look at cancer as a consequence of a de-evolution process (i.e. reverse evolution, evolution towards primitive life form). In this perspective cancer is seen as a transformation from collaborative multicellular cells to a selfish free unicellular type of cells. This neither contradicts nor denies the existence and importance of the bio-chemical mechanisms that are responsible for inducing various behavior of cancer cells. Instead, it assigns a notion of individuality to the transformed cells. Since the DNA has been passed on via millions of years of evolutionary processes, from unicellular free living organisms to multicellular collaborative organisms \[14\], it is not totally surprising to hypothesize that mutations can reactivate or enable certain parts of the DNA, phenotypically making them more like primitive life forms. The analogy becomes clear if we relate the behavior of cancer cells and other unicellular organisms like bacteria. Cancer cells grow uncontrollably, they scavenge for nutrients, they move and migrate to other more fertile space, all of which are characteristic of a primitive unicellular organisms. Not only that, some bio-chemical processes are similar to those of primitive unicellular cells, e.g. cancer cells rely on primitive metabolic pathways like glycolysis, they avoid DNA damage by maintaining the length of telomere strand even after successive replication, just like germ cells and unicellular organisms \[12\]. Moreover, looking at the evolutionary pattern of multicellular tissues, organs and so forth, the analogy becomes even more obvious. According to \[38\], the origin of multicellularity is attributed to the genetic variations that led to the acquisition of cell-cell adhesion, communication, cooperation, and specialization. The acquisition of such features can be possible if neighboring cells show (i) alignment-of-fitness, i.e. they have no inter-cellular conflicts and (ii) export-of-fitness i.e. are able to independently collaborate towards a sustained reproductive goal. Based on this there are two possible paths to multicellularity: (i) unicellular organism ⇒ clonal cells ⇒ multicellular organism or a more direct path such as (ii) siphonous (a giant unicellular algae cell) ⇒ multicellular organism. Now, if we ask ourselves as to what would happen if mutations in a multicellular organism lead to the loss of its vital functionalities, then it is clear that we either get a bunch of clonal cells or just independent individual unicellular organisms which is exactly the scenario in a tumorous tissue. This philosophy of de-evolution and its connection to cancer dynamics is presented next.

### 2.2.1 Evolution and de-evolution of cells:

According to Darwin’s theory of evolution, multicellular organisms have evolved, over a period of millions of years, from unicellular ones through random processes such as genetic alterations and natural selection. The tree of evolution clearly indicates a bottom up process where the unicellular organisms are at the root while multicellular organisms occupy their place at the trunk and leaves of the tree. This is the case because genetic/chemical alterations and environmental forces propelled unicellular organisms to aggregate and start to collaborate which eventually gave rise to functionally sophisticated life units such as tissues, organs, and in turn organisms. There are also cases where complex multicellular organisms have evolved (or de-evolved) to simpler forms of life like viruses. For example, certain species of Cnidaria have de-evolved from multicellular free-living autonomous animals into parasitic organisms comprising of only a handful of cells. Such parasites constitute the class of organisms called Myxozoans \[39\]. This unique reverse evolution is again due to genetic alterations and environmental selection.

Cancer is a disease in which some of the cells within a multicellular life unit (e.g. tissue or organ) have functionally turned into a more primitive life form. What this means is that tumor cells are no more adhering to the rules of their pre-destined functionality but instead they become rogue cells acting in a primitive and selfish way which is often deleterious to the multicellular life unit that it is still a part of. A simple example is the case of melanoma (a type of skin cancer): the pigment producing cells called melanocytes undergo transformations (via mutations induced mainly through exposure to UV radiations) and are no more just responsible for melanine production but they start exhibiting the features of an independent unicellular organism. This means that melanocytes after being carcinogenized start replicating profusely, boost their nutrition supply (e.g. via angiogenesis), may even start to migrate, etc. All these are features of an autonomous living organism (say like protozoans). Thus carcinogenesis is, in a very vague sense, similar to the de-evolution of Cnidarians to Myxozoans, with the main difference that carcinogenesis induces a switch from a stable, cooperative (altruistic), and functionally pre-determined behavior to an unstable, selfish, and functionally free behavior while the de-evolution process of Cnidarians to Myxozoans involves a rather drastic physical transformation. This novel analogy can be backed up by the biological finding that many protozoan life cycles features have been observed in mammalian cancers undergoing polyplody \[42\]. Another aspect of cancer is that it is not a modern disease, but an ancient one, whose roots go back to the time of the beginning of the cellular life itself. In the early stages of unicellular life, natural selection favored organisms that were fast growing, space invading, and had low mortality rate etc. However, for the development of multicellularity there
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laws of survivability. Briefly, what this means is that a living system (which is inherently assumed to be complex) is 

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longevity. 

Motivated by these intuitive arguments, one is led to the task of finding the fundamental reason for the complexity 

and diversity observed in cancer. More importantly, one is also led to the question of how to model such diverse and 

complex living systems. In order to answer such fundamental questions we have to resort to an abstract formulation 

of living systems and analyze its implications. This is addressed in Section 2.3 below.

2.3 Diversity of cancer

For modeling any natural phenomenon it is important to understand the fundamental motive and purpose as to why such phenomenon occurs in the first place, and in the context of biology (especially population biology) it is imperative to understand the purpose and aim of the underlying phenomenon being modeled. There is a fundamental difference between mere chemical systems and organisms or general living systems (which are more than just chemical systems). The term living system makes it obvious as to what the goal or the aim of the system is, it is simply to stay alive for as long as possible. Unlike lifeless chemical or physical systems where the dynamics of certain phenomena are governed by physical and chemical laws, the dynamics of a living system is mainly driven by the laws of survivability. Briefly, what this means is that a living system (which is inherently assumed to be complex) is capable of bending or evading or circumventing certain physio-chemical laws, in favor of certain other physio-chemical laws, with the sole purpose of surviving. It is absolutely important to note here that the previous statement does not state that the physical or chemical laws are not applicable. Of course everything that happens is indeed according to some physical laws, but the point is that under different conditions and different circumstances different laws are in action and this changes the results of the outcome. Thus living systems strive to be alive by altering the conditions and/or circumstances and/or environment such that the laws of physics that are in action favor their survivability. Therefore already this basic law of survivability provides a glimpse for the reason for complexity of living systems.

In order to elaborate more on this we provide a novel abstract characterization of a generic living systems using the following properties:

**Autonomy:** A living system must have necessary mechanisms to produce or harvest energy in order to sustain itself and to survive and reproduce successfully. Such mechanisms need to exist only up until successful reproduction and upbringing of the progeny to independence. This is also the stage where new information is acquired and the system undergoes suitable changes and adaptations in order to better sustain itself.

**Replication:** A living system must be able to successfully replicate and create either a clone or a modified version of itself. The functionality of replication also includes the job of raising and nurturing the newborn up to its independence, i.e. up to the stage where the newborn achieves its autonomy. In this sense the replicant must also be a living entity, although not immediately but after reaching the state of independence. Here again it is implicitly assumed that the new born inherits the mechanism of reproduction from its parent and is able to reproduce upon attaining autonomy. We shall omit those systems that are not capable of replication from being called as a living system, since there is no possibility for such systems to continue their tree and consequently are destined for extinction. The reproduction stage is where the transfer of information happens. All or part of the information, mainly the mechanism of replication and the tricks and trades of survivals, acquired up until the time of replication is passed on to the child living system during the process of creation or/and during the time of nurturing until it reaches independence. The above two properties are general enough to not only cover all known biological life forms till now.
but also to include non-biological life forms like computer programs and abstract logical systems. The two properties can be in short called axioms of life and they are the fundamental driving force of all things alive. Another crucial aspect that can be deduced from the axioms is that: in order to increase the chances of survival and thus increase the chances of reproduction, it is necessary that the living systems diversify their mode of operation or sustenance. What this means is that: replication should not result in an exact copy of the parent but instead it should be a modified copy. More precisely, the progeny should be a modified version of the progenitor. This is not a necessity but just a beneficial strategy for increasing the odds of survival. We shall elaborate on this via an example.

Consider two living systems $X$ and $Y$ belonging to Universe A and Universe B respectively. Universes A and B are independent of each other and have the same type of food resource named as $A$ and $B$, respectively. Each living entity $X$ and $Y$, for its sustenance, consumes food $A$ and $B$ at rates $k_x$ and $k_y$, respectively. Letting $a(t)$ and $b(t)$ denote the concentrations of $A$ and $B$ at time $t$, we see that $a(t) = a(0)e^{-k_x t}$ and $b(t) = b(0)e^{-k_y t}$. If $X$ and $Y$ replicates at time $t_x$ and $t_y$, respectively, then for any $t > \max(t_x, t_y)$ we get that $a(t) = a(t_x)e^{-2k_x(t-t_x)}$ and $b(t) = b(t_y)e^{-2k_y(t-t_y)}$. Depending on initial concentrations $a(0)$ and $b(0)$, rates $k_x$ and $k_y$, and replication times $t_x$ and $t_y$, either $a(t) \geq b(t)$ or vice versa. The interesting case for us to consider is $a(0) = b(0) = r_0$, $k_x = k_y = k$ and $t_x = t_y = t_r$. The only difference between both systems is that, when $A$ replicates it produces an exact copy of itself, while when $B$ replicates it produces a modified copy of itself. This modification manifests as a change in the consumption rate $k_y$ of $B$. Let $k'$ be the consumption rate of the replicant of $Y$. Then for $t > t_r$ we have that $a(t) = a(t_r)e^{-2k(t-t_r)}$ while $b(t) = b(t_r)e^{-(k+k')(t-t_r)}$. Now depending of whether $k' > k$ or $k' < k$ we get either $b(t) = a(t)$ or $b(t) > a(t)$. Hence, for $k' < k$, $Y$ improves its chances of survival and for $k' > k$, $Y$ worsens its chances of survival. Therefore of all the three cases, i.e. $k' = k$, $k' > k$ and $k' < k$, only the last case improves the longevity of life of $X$ or $Y$. Now after multiple iterations of replication, population $Y$ (provided $k' < k$) will have outlived $X$. Figure 6 illustrates the decay profile of the food density of $A$ and $B$ belonging to Universes A and B, respectively. The different consumption rates of each replicant of system $Y$ are sampled from a uniform distribution. Based on this we see that in the expectation system $Y$ has better odds of survival since the food is available for a longer time. It must be noted here that in this example the choice of uniform distribution was purely for the sake of simplicity. In fact in reality it may very well belong to other distributions. Thus the possibility that the modifications of a replicant may belong to different distributions establishes the fundamental basis for the diversity and heterogeneity that prevails among living systems. From this simple example it becomes clear that maximization of survivability requires diversification but of course with the risk of extinction. This example also illustrates that if the process of replication is random or uncertain, then the game of survival also becomes random. This motivate one to consider that randomness and uncertainty are one of the primary, if not the only, source of diversity in living systems. Since all biological living systems replicate randomly, diversification and randomness becomes an inherent property of their evolution. Consequently, we may conclude that the axioms of life consist of three properties: autonomy, replication and diversification.
Motivated by these considerations, the rest of the work focuses on the topic of multiscale modeling of complex living systems such as cancer. To this end, in Section 3 we present a novel framework for deducing stochastic equations at the macroscopic level, which in some sense captures the diversity of living systems.

# 3 Modeling diversity in Cancer

Before discussing about the modeling, we shall first introduce some basic relevant concepts.

## 3.1 Lévy processes and their properties

**Definition 3.1** (Lévy process). A stochastic process \( X = (X_t)_{t \geq 0} \) is said to be a Lévy process if:

1. \( X_0 \) is almost surely equal to 0.
2. \( X \) has independent and stationary distribution, i.e. \( X_{t_1} - X_{t_2} \) is independent from \( X_{t_2} - X_{t_3} \) for \( t_3 \leq t_2 \leq t_1 \) and \( \mathcal{L}(X_{t_1} - X_{t_2}) \sim \mathcal{L}(X_{t_1} - X_{t_2} - X_0) \) for \( t_1 \geq t_2 \), where \( \mathcal{L}(X_t) \) denotes the law of the r.v. \( X_t \).
3. \( X \) is stochastically continuous, i.e.

\[
\lim_{t \to s} P(|X_t - X_s| > a) = 0, \forall a > 0, \forall s \geq 0
\]

**Definition 3.2** (Lévy measure). Let \( \nu \) be a Borel measure defined on \( \mathbb{R}^d - \{0\} \). Then \( \nu \) is said to be a Lévy measure if

\[
\int_{\mathbb{R}^d - \{0\}} (||y|^2 \wedge 1) \nu(dy) < \infty
\]

**Theorem 3.1** \([1]\). If \( X = (X_t)_{t \geq 0} \) is a Lévy process, then its characteristic function \( \phi_{X_t} := E[e^{i\cdot\cdot\cdot X_t}] \) is given as:

\[
\phi_{X_t}(\xi) = e^{-t\psi(\xi)}, \xi \in \mathbb{R}^d, t \geq 0
\]

where \( \psi \) is called the Lévy symbol (or simply symbol) of \( X_t \).

**Theorem 3.2** (Lévy-Khintchine formula). In general, if \( X \) is a Lévy process then its symbol \( \psi \) takes the following form

\[
\psi(\xi) = -i(b, \xi) + \frac{1}{2}(\xi, Q\xi) + \int_{\mathbb{R}^d - \{0\}} [1 - e^{i(\xi, y)} + i(\xi, y) \mathbb{I}_{B(0,1)}(y)] \nu(dy),
\]

where \( (b, \xi) \) denotes the Euclidean inner product and \( B(0,1) \) denotes the unit open ball in \( \mathbb{R}^d \) centered at the origin. The triple \( (b, Q, \nu) \) are called the characteristics of \( X \). This is the famous Lévy-Khintchine formula and can be proved using the well known Lévy-Itô decomposition.

**Theorem 3.3** (Lévy-Khintchine \([48]\)). A function \( \psi : \mathbb{R}^d \to \mathbb{C} \) is continuous and negative definite (CNDF) if and only if there exists a number \( a \geq 0 \), a vector \( b \in \mathbb{R}^d \), a symmetric and positive semi-definite matrix \( Q \in \mathbb{R}^{d \times d} \) and a Lévy measure \( \nu \) on \( \mathbb{R}^d \setminus \{0\} \) such that

\[
\psi(\xi) = a + i(b, \xi) + \frac{1}{2}(\xi, Q\xi) + \int_{y \neq 0} \left( 1 - e^{i(\xi, y)} + i \frac{\xi}{1 + ||y||^2} \right) \nu(dy).
\]

The quadruple \((a, b, Q, \nu)\) is uniquely determined by \( \psi \) and vice versa.

More specifically, for a real valued continuous negative definite function (CNDF) we have the following characterization:

**Corollary 3.1.** Let \( \psi : \mathbb{R}^d \to \mathbb{R} \) be a real valued CNDF. Then it has the following representation

\[
\psi(\xi) = a + \frac{1}{2}(\xi, Q\xi) + \int_{y \neq 0} \left( 1 - \cos((\xi, y)) \right) \nu(dy)
\]

where \( a, Q \) and \( \nu \) are as in Theorem 3.3.
**Theorem 3.4** ([1]). Let $\psi_1 : \mathbb{R}^+ \to \mathbb{R}$ and $\psi_2 : \mathbb{R}^d \to \mathbb{R}^+$ be CNDF, then their $\psi_1 \circ \psi_2$ is again a CNDF.

**Proposition 3.1.** For every fixed $(b, Q, \nu)$, the characteristics of a Lévy process $X$, we have that $|\psi(\xi)| \leq C(1+|\xi|^2)$.

**Proof.** Let $(b, Q, \nu)$ be the characteristics of a Lévy process $X$, then the symbol $\psi$, given by the Lévy-Khintchine formula, is

$$\psi(\xi) = -i(b, \xi) + \frac{1}{2}(\xi, Q\xi) + \int_{\mathbb{R}^d \setminus \{0\}} [1 - e^{i(\xi, y)} + i(\xi, y) \mathbb{1}_{\mathcal{B}(0, 1)}(y)] \nu(dy).$$

So taking the euclidean norm, we have that

$$|\psi(\xi)|^2 \leq (b, \xi)^2 + \frac{1}{4}(\xi, Q\xi)^2 + \left(\int_{\mathbb{R}^d \setminus \{0\}} \right)^2$$

$$\leq |b|^2|\xi|^2 + \|Q\|_\infty^2|\xi|^4 + \int_{\mathbb{R}^d \setminus \{0\}} |e^{i(\xi, y)} - 1|^2 \nu(dy) + \int_{\mathcal{B}(0, 1)} |(y, \xi)|^2 \nu(dy)$$

$$\leq |b|^2|\xi|^2 + \|Q\|_\infty^2|\xi|^4 + \int_{\mathcal{B}(0, 1)} |e^{i(\xi, y)} - 1|^2 \nu(dy) + \int_{\mathcal{B}(0, 1)} e^{i(\xi, y)} - 1 - i(y, \xi)^2 \nu(dy)$$

$$\leq |b|^2|\xi|^2 + \|Q\|_\infty^2|\xi|^4 + 4\nu(B(0, 1)) + \int_{\mathcal{B}(0, 1)} (y, \xi)^4 \left|\frac{e^{i(\xi, y)} - 1 - i(y, \xi)^2}{(y, \xi)^2}\right|^2 \nu(dy)$$

$$\leq |b|^2|\xi|^2 + \|Q\|_\infty^2|\xi|^4 + 4\nu(B(0, 1)) + \int_{\mathcal{B}(0, 1)} |y|^4 |\xi|^4 \left|\frac{e^{i(\xi, y)} - 1 - i(y, \xi)^2}{(y, \xi)^2}\right|^2 \nu(dy)$$

$$\leq |b|^2|\xi|^2 + \|Q\|_\infty^2|\xi|^4 + 4\nu(B(0, 1)) + \int_{\mathcal{B}(0, 1)} \left|\frac{1 - \cos((y, \xi)^2) + ((y, \xi) - \sin((y, \xi))^2)}{(y, \xi)^2}\right|^2 \nu(dy)$$

$$\leq |b|^2|\xi|^2 + \|Q\|_\infty^2|\xi|^4 + 4\nu(B(0, 1)) + 2\int_{\mathcal{B}(0, 1)} |y|^4 |\xi|^4 \nu(dy)$$

$$\leq |b|^2|\xi|^2 + \|Q\|_\infty^2|\xi|^4 + 4\nu(B(0, 1)) + 2\int_{\mathcal{B}(0, 1)} |y|^2 \nu(dy)$$

$$\leq |b|^2|\xi|^2 + \|Q\|_\infty^2|\xi|^4 + 4\nu(B(0, 1)) + 2C_\nu|\xi|^4$$

$$\leq C_b|\xi|^2 + C_A|\xi|^4 + C + 2C_\nu|\xi|^4$$

$$\leq C^2(1 + |\xi|^2)^2$$

$$\Rightarrow |\psi(\xi)| \leq C(1 + |\xi|^2).$$

This provides the basis for characterizing function spaces associated with the symbols $\psi$ of the Lévy processes.

### 3.2 Function spaces associated to negative definite functions

In this section we shall discuss about the function spaces associated with pseudo-differential operators and how this can be made use to characterize the domains of the operators generated by Lévy processes. Furthermore, we also provide some connections to the Bessel potential spaces $H^s_p(\mathbb{D})$. First let us recall the definition of the Fourier transform and its inverse.

Fourier transform $\mathfrak{F}$ is a bijective mapping from $\mathcal{S}(\mathbb{R}^d)$ to $\mathcal{S}(\mathbb{R}^d)$, i.e. $\mathfrak{F} : \mathcal{S}(\mathbb{R}^d) \mapsto \mathcal{S}(\mathbb{R}^d)$. For every $\xi \in \mathbb{R}^d$ the Fourier transform of $f \in \mathcal{S}(\mathbb{R}^d)$ is defined as

$$(\mathfrak{F}f)(\xi) = \hat{f}(\xi) = \frac{1}{(2\pi)^{d/2}} \int_{\mathbb{R}^d} e^{-i(\xi, x)} f(x) dx.$$
Lemma 3.1. Let $f \in \mathcal{S}(\mathbb{R}^d)$ be a real valued CNDF having the representation \((8)\), then we have that $T_2f(x) = \mathfrak{F}^{-1}[m_2(x,\xi)m_1(x,\xi)\mathfrak{F}f(x)]$. 

Proof. Let $T_1f(x) = g(x)$, then $\mathfrak{F}[T_1f(x)] = \mathfrak{F}[g(x)]$, then we have that

\[
\mathfrak{F}[T_2T_1f(x)] = \mathfrak{F}[T_2g(x)] = m_2(\xi)\mathfrak{F}[g(x)] = m_2(\xi)\mathfrak{F}[T_1f(x)] = m_2(\xi)m_1(\xi)\mathfrak{F}[f(x)]
\]

$\Rightarrow T_2T_1f(x) = \mathfrak{F}^{-1}[m_2(\xi)m_1(\xi)\mathfrak{F}[f(x)]]$. \(\blacksquare\)

Definition 3.5 ($\psi$-Bessel potential space of order $s \geq 0$ \(9\)). Let $\psi : \mathbb{R}^d \rightarrow \mathbb{R}$ be a real valued CNDF having the representation \(2\). Then the $\psi$-Bessel potential space of order $s \geq 0$ with respect to $L^p(\mathbb{R}^d)$ for $p \in [1, \infty)$ is the space

\[
H_p^{\psi,s}(\mathbb{R}^d) = \{ u \in L^p(\mathbb{R}^d) : \| u \|_{H_p^{\psi,s}} < \infty \}
\]

where

\[
\| u \|_{H_p^{\psi,s}} := \|(1 + \psi(D))\hat{u}\|_{L^p}.
\]

and

\[
\psi(D)u = \mathfrak{F}^{-1}(\psi\mathfrak{F}u), \quad u \in \mathcal{S}(\mathbb{R}^d)
\]

It is worth mentioning some relations between classical Bessel potential spaces and $\psi$-Bessel potential spaces:

Remark 3.1 \(9\). 1. For $\psi(\xi) = |\xi|^2$, $H_p^{\psi,s}(\mathbb{R}^d)$ is the classical Bessel potential space $H_p^s(\mathbb{R}^d)$. And for $s \in \mathbb{N}$, it is in turn equivalent to the Sobolev space $W_p^s(\mathbb{R}^d)$. 

For every $x \in \mathbb{R}^d$, the inverse Fourier transform of $f \in \mathcal{S}(\mathbb{R}^d)$ is given by

\[
(\mathfrak{F}^{-1}f)(x) = \hat{f}(x) = \frac{1}{(2\pi)^{d/2}} \int_{\mathbb{R}^d} e^{i(x,\xi)}f(x)dx
\]

Definition 3.3 (Fourier multiplier). A Fourier multiplier $m$ is a mapping $\xi \mapsto m(\xi)$ from $\mathbb{R}^d$ to $\mathbb{C}$, i.e. $m : \mathbb{R}^d \rightarrow \mathbb{C}$ where $m(\xi)$ is defined as

\[
\mathfrak{F}[T_m]\mathfrak{F}(f)(\xi) = m(\xi)\mathfrak{F}(f)(\xi)
\]

for all $f \in \mathcal{S}(\mathbb{R}^d)$ and some operator $T_m$ on $\mathcal{S}(\mathbb{R}^d)$.

Definition 3.4 (Space of Fourier multipliers \(18\)). Let $p, q \in [1, \infty)$, then the space $\mathcal{M}_{p,q}$ of Fourier multipliers is given as

\[
\mathcal{M}_{p,q} = \{ m \in \mathcal{S}'(\mathbb{R}^d) : \| m \|_{\mathcal{M}_{p,q}} < \infty \}
\]

where

\[
\| m \|_{\mathcal{M}_{p,q}} = \sup_{p \neq L(\mathbb{R}^d)} \left\{ \left\| \mathfrak{F}^{-1}[m\mathfrak{F}\phi] \right\|_{L^p(\mathbb{R}^d)} : 0 \neq \phi \in \mathcal{S}(\mathbb{R}^d) \right\}
\]
2. For $p = 2$, we have that $H^\psi_{\psi,s}(\mathbb{R}^d)$ is a Hilbert space for all $s \geq 0$, and in this case it is simply denoted by $H^\psi_{\psi,s}(\mathbb{R}^d)$.

We now state some important embedding results that later help us in specifying continuously varying random operators in Section 3.5.

**Theorem 3.5** [18]. Let $\psi : \mathbb{R}^d \rightarrow \mathbb{R}$ be a real valued CNDF having the representation (2), $p \in (1, \infty)$ and $r \geq 0$. Then for any $s \in \mathbb{R}$,

$$H^\psi_{\psi,s+r}(\mathbb{R}^d) \hookrightarrow H^\psi_{\psi,s}(\mathbb{R}^d).$$

(9)

If $s \geq 0$, then (9) also holds for $p = 1$.

**Theorem 3.6** [18]. Let $\psi_1, \psi_2 : \mathbb{R}^d \rightarrow \mathbb{R}$ be two CNDFs. Let $p, q \in [1, \infty)$ and $s, r \in \mathbb{R}$. Then for any $s \in \mathbb{R}$,

$$H^\psi_{\psi_1,s}(\mathbb{R}^d) \hookrightarrow H^\psi_{\psi_2,r}(\mathbb{R}^d).$$

(10)

if and only if

$$m := (1 + \psi_2)^2(1 + \psi_1)^{-2} \in \mathcal{M}_{p,q}$$

(11)

where, $\mathcal{M}_{p,q}$ is the space of Fourier multipliers of type $(p, q)$ (see Definition 3.4).

**Corollary 3.2** [18].

1. Let $p \in (1, \infty)$ and let $\psi : \mathbb{R}^d \rightarrow \mathbb{R}$ be an unbounded CNDF. Then $H^\psi_{\psi,s}(\mathbb{R}^d) \hookrightarrow H^\psi_{\psi,r}(\mathbb{R}^d)$ if and only if $s \geq r$.

2. Let $p \in (1, \infty)$, $s > 0$ and $\psi_1, \psi_2 : \mathbb{R}^d \rightarrow \mathbb{R}$ be two CNDFs. Then the embedding $H^\psi_{\psi_1,s}(\mathbb{R}^d) \hookrightarrow H^\psi_{\psi_2,s}(\mathbb{R}^d)$ implies that there exists a constant $c > 0$ such that

$$1 + \psi_2(\xi) \leq c(1 + \psi_1(\xi)), \; \xi \in \mathbb{R}^d.$$

If, in particular, $H^\psi_{\psi_1,s}(\mathbb{R}^d) = H^\psi_{\psi_2,s}(\mathbb{R}^d)$, then we have

$$\frac{1}{c}(1 + \psi_1(\xi)) \leq 1 + \psi_2(\xi) \leq c(1 + \psi_1(\xi)), \; \xi \in \mathbb{R}^d.$$

More interestingly, the converse relation holds for $p = 2$.

**Theorem 3.7** (Operator domain associated to $H^\psi_{\psi,s}(\mathbb{R}^d)$) [18]. For $s \geq 0$, $p \in [1, \infty)$ and $\psi : \mathbb{R}^d \rightarrow \mathbb{R}$ a CNDF, we have $H^\psi_{\psi,s}(\mathbb{R}^d) = D((1 - \psi(D))-\hat{f})$, where

$$(1 - \psi(D))\hat{f} u = \hat{\psi}^{-1}[(1 + \psi(\xi))\hat{f} \hat{\xi} u], \; \forall u \in \mathcal{S}(\mathbb{R}^d).$$

### 3.3 From a microscale SDE to a macroscale abstract Cauchy problem

Consider the following simple SDE driven by a Lévy process $N_t$ on $\mathbb{R}^d$ which has $A$ as the IG of the corresponding $C_0$-semigroup (in short as $C_0$-SG) $T_t$.

$$dY_t = dN_t$$

$$Y_0 = 0.$$

Then clearly, $Y_t = N_t$. Now the $C_0$ SG $T_t$ on a Banach space $X$ associated with $N_t$ can be prescribed by $T_t f(y) = \mathbb{E}(f(Y_t)|Y_0 = y)$ for every $f \in X$. Since $A$ is the IG of the $C_0$ SG $T_t$, for all $f \in D(A)$ we have that

$$\frac{d}{dt} T_t f = A T_t f$$

$$\implies \frac{d}{dt} \mathbb{E}(f(Y_t)|Y_0 = y) = A \mathbb{E}(f(Y_t)|Y_0 = y)$$

$$\implies \frac{d}{dt} \int_{\mathbb{R}^d} f(x)p_t(y, dx) = A \int_{\mathbb{R}^d} f(x)p_t(y, dx).$$
Now let \( p_t(\cdot, dx) \ll dx \), then
\[
\frac{d}{dt} \int f(x)p_t(y, x)dx = A \int f(x)p_t(y, x)dx + \int f(x)\partial_t p_t(y, x)dx = \int f(x)Ap_t(y, x)dx.
\]

If this holds for all \( f \in C_c^\infty(\mathbb{R}^d) \) then we get that
\[
\partial_t p_t(y, x) = Ap_t(y, x), \text{ for a.e. } x \in \mathbb{R}^d.
\]

This is nothing but the backward Kolmogorov’s equation.

Similarly, using the identity \( \frac{d}{dt} T_t f = T_t Af \) we get
\[
\frac{d}{dt} T_t f = T_t Af
\]
\[
\Rightarrow \frac{d}{dt} \mathbb{E}(f(Y_t)|Y_0 = y) = \mathbb{E}(Af(Y_t)|Y_0 = y)
\]
\[
\Rightarrow \frac{d}{dt} \int f(x)p_t(y, dx) = \int Af(x)p_t(y, dx)
\]

Now let \( p_t(\cdot, dx) \ll dx \), then
\[
\frac{d}{dt} \int f(x)p_t(y, x)dx = \int Af(x)p_t(y, x)dx + \int f(x)\partial_t p_t(y, x)dx = \int f(x)A^\dagger p_t(y, x)dx
\]

where \( A^\dagger \) is the formal adjoint of the operator \( A \). If this holds for all \( f \in C_c^\infty(\mathbb{R}^d) \) then we get that
\[
\partial_t p_t(y, x) = A^\dagger p_t(y, x), \text{ for a.e. } y \in \mathbb{R}^d.
\]

This is called the forward Kolmogorov equation.

**Example 3.1.** Let \( N_t \) be a Brownian motion with drift on \( \mathbb{R}^d \). It is a Lévy process with characteristics \( (b, a, 0) \). The corresponding IG \( A \) of the \( C_0 \) SG \( T_t \) associated to \( N_t \) is given by
\[
A = \sum_{k} b_k \partial_k + \frac{1}{2} \sum_{k,j} a_{kj} \partial_j \partial_k.
\]

The formal adjoint \( A^\dagger \) takes the form
\[
A^\dagger = - \sum_{k} \partial_k b_k + \frac{1}{2} \sum_{k,j} \partial_j \partial_k a_{kj}.
\]

**Example 3.2.** Let \( N_t \) be a Poisson process on \( \mathbb{R}^d \) with characteristics \( (0, 0, \lambda \delta_1) \). The corresponding IG \( A \) of the \( C_0 \) SG \( T_t \) associated to \( N_t \) is given by
\[
Af(x) = \lambda [f(x + 1) - f(x)].
\]

The formal adjoint \( A^\dagger \) takes the form
\[
A^\dagger f(x) = \lambda [f(x) - f(x - 1)].
\]

**Example 3.3.** Let \( N_t \) be a compound Poisson process on \( \mathbb{R}^d \) with characteristics \( (0, 0, \lambda \mu) \). The corresponding IG \( A \) of the \( C_0 \) SG \( T_t \) associated to \( N_t \) is given by
\[
Af(x) = \lambda \int_{\mathbb{R}^d} [f(x + y) - f(x)] \mu(dy).
\]

The formal adjoint \( A^\dagger \) takes the form
\[
A^\dagger f(x) = \lambda \int_{\mathbb{R}^d} [f(x) - f(x - y)] \mu(dy).
\]
Example 3.4. Let $N_t$ be a Lévy process on $\mathbb{R}^d$ with characteristics $(b, Q, \lambda \nu)$. The corresponding IG $A$ of the $C_0$ $SG$ $T_t$ associated to $N_t$ is given by

$$A f(x) = \sum_k b_k \partial_k f + \frac{1}{2} \sum_{k,j} Q_{kj} \partial_k \partial_j f + \lambda \int_{\mathbb{R}^d} [f(x + y) - f(x)] \nu(dy).$$

The formal adjoint $A^\dagger$ takes the form

$$A^\dagger f(x) = -\sum_k \partial_k b_k f + \frac{1}{2} \sum_{k,j} \partial_k Q_{kj} f + \lambda \int_{\mathbb{R}^d} [f(x) - f(x - y)] \nu(dy).$$

Example 3.5. Let $N_t$ be a symmetrically invariant stable process of index $\alpha \in (0, 2)$ with symbol given by $\psi(\xi) = -|\xi|^\alpha$ for all $\xi \in \mathbb{R}^d$. The corresponding IG $A$ of the $C_0$ $SG$ $T_t$ associated to $N_t$ is given by

$$A = -\left( \sum_k - (\partial_k)^2 \right)^{\alpha/2} = -(-\Delta)^{\alpha/2}.$$

The formal adjoint $A^\dagger$ is the same as the operator $A$. In fact we actually have that $A$ is a self-adjoint operator.

Above we used a very simple SDE to describe the microscopic dynamics. In practical applications, however, one encounters more general equations of the following form:

$$X_t = X_0 + \int_0^t b(X_s) \, ds + \int_0^t g(X_s) \, dW_s + \int_0^t \int_{\mathbb{R}^d} g(s, x) \tilde{N}(ds, dx) + \int_0^t \int_{\mathbb{R}^d} h(s, x) N(ds, dx)$$

$$= X_0 + \dot{X} + \int_0^t \int_{\mathbb{R}^d} g(s, x) \tilde{N}(ds, dx) + \int_0^t \int_{\mathbb{R}^d} h(s, x) N(ds, dx)$$

$$= dX + \int_0^t \int_{\mathbb{R}^d} g(t, x) \tilde{N}(dt, dx) + \int_0^t \int_{\mathbb{R}^d} h(t, x) N(dt, dx)$$

(12)

where $X_t \in \mathbb{R}^d$, $q : \mathbb{R}^d \in \mathbb{R}^d$, $b \in \mathbb{R}^d \in \mathbb{R}^{d \times n}$, $W_t \in \mathbb{R}^n$, $g \in \mathbb{R}^+ \times \mathbb{R}^d \rightarrow \mathbb{R}^d$, $h \in \mathbb{R}^+ \times \mathbb{R}^d \rightarrow \mathbb{R}^d$ and $N_t(K) \in \mathbb{R}^d$ for all $K \in \mathbb{R}^{d \times \{0\}}$.

Since the above SDE is time homogeneous, the solution $X_t$ is a time homogeneous Markov process. Thus we get a $C_0$-$SG$ via the prescription $E(f(X_t)|X_0 = x)$ (details to be provided later). In order to be able to find the associated IG, we need Ito’s formula for Lévy type stochastic integrals.

Theorem 3.8 (Ito-type formula for Lévy integrals [12]). Let $X_t$ be a Lévy type stochastic integral taking the form (12). Then for each $f \in C^2(\mathbb{R}^d)$, $t \geq 0$, with probability 1 we have that

$$f(X_t) - f(X_0) = \int_0^t \sum_{k=1}^d \partial_k f(X_s) \, d\tilde{X}_s + \frac{1}{2} \int_0^t \sum_{k,j=1}^d \partial_k \partial_j f(X_s) \, d[\tilde{X}_s, \tilde{X}_s]_s$$

$$+ \int_0^t \int_{\mathbb{R}^d} f(X_s^- + g(s, x)) - f(X_s^-) \tilde{N}(ds, dx) + \int_0^t \int_{\mathbb{R}^d} f(X_s^- + h(s, x)) - f(X_s^-) N(ds, dx)$$

$$+ \int_0^t \int_{\mathbb{R}^d} [f(X_s^- + g(s, x)) - f(X_s^-) - g(s, x)] \sum_{k=1}^d \partial_k f(X_s) \nu(dx)ds,$$

(13)

where $X_s^- = X_{s-}$ is the left limit point of $X$ at $s$.

Now using the above theorem we would like to determine the generator of a generic Lévy process as given by (12).

Proposition 3.2. Let $T_t f = E(f(X_t)|X_0 = x)$ for $f \in L^p(\mathcal{F})$, $1 \leq p < \infty$ be the $L^p(\mathcal{F})$-$SG$ associated with the Lévy process $X$. Then the IG $A$ associated to $(T_t)_{t \geq 0}$ is given by

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where,

\[ Af(X_s) = \frac{d}{k=1} \partial_k b_k(X_s) f(X_s) + \frac{1}{2} \sum_{k,j=1}^d Q_{kj}(X_s) \partial_k \partial_j f(X_s) + \int_{K'} f(X_s^- + h(s,x)) - f(X_s^-) \nu(dx) \]

\[ + \int_K [f(X_s^- + g(s,x)) - f(X_s^-) - g(s,x) \sum_k \partial_k f(X_s)] \nu(dx), \]

for \( f \in C^2(\mathbb{R}^d) \cap L^p(\mathbb{R}^d). \)

**Proof.** First let \( f \in C^2(\mathbb{R}^d) \cap L^p(\mathbb{R}^d). \) Then,

\[ T_{t+h}f - T_{t}f = E \left( f(X_{t+h}) - f(X_{t}) \big| X_{0} = x \right) \]

\[ \mathbb{E} \left( \left[ \int_t^{t+h} \sum_{k=1}^d \partial_k b_k(X_s) dX_s + \frac{1}{2} \sum_{k,j=1}^d \partial_k \partial_j f(X_s) d[X^h,X^j]_s \right. \right. \]

\[ + \int_t^{t+h} \int_K f(X_s^- + h(s,x)) - f(X_s^-) \bar{N}(ds, dx) - \int_t^{t+h} f(X_s^- + g(s,x)) - f(X_s^-) N(ds, dx) \]

\[ + \int_t^{t+h} \int_K [f(X_s^- + g(s,x)) - f(X_s^-) - g(s,x) \sum_k \partial_k f(X_s)] \nu(dx)ds \bigg| X_{0} = x \right) \]

\[ = \mathbb{E} \left( \left[ \int_t^{t+h} \sum_{k=1}^d b_k(X_s) \partial_k f(X_s) ds + \frac{1}{2} \sum_{k,j=1}^d Q_{kj}(X_s) \partial_k \partial_j f(X_s) ds \right. \right. \]

\[ + \int_t^{t+h} \int_{K'} f(X_s^- + h(s,x)) - f(X_s^-) \nu(dx)ds \]

\[ + \int_t^{t+h} \int_K [f(X_s^- + g(s,x)) - f(X_s^-) - g(s,x) \sum_k \partial_k f(X_s)] \nu(dx)ds \bigg| X_{0} = x \right) \]

\[ = \int_t^{t+h} \mathbb{E} \left( \frac{d}{k=1} b_k(X_s) \partial_k f(X_s)ds + \frac{1}{2} \sum_{k,j=1}^d Q_{kj}(X_s) \partial_k \partial_j f(X_s)ds \right. \]

\[ + \int_{K'} f(X_s^- + h(s,x)) - f(X_s^-) \nu(dx)ds \]

\[ + \int_K [f(X_s^- + g(s,x)) - f(X_s^-) - g(s,x) \sum_k \partial_k f(X_s)] \nu(dx)ds \bigg| X_{0} = x \right) \]

\[ = \int_t^{t+h} \mathbb{E} \left( \frac{d}{k=1} \partial_k b_k(X_s) f(X_s) + \frac{1}{2} \sum_{k,j=1}^d Q_{kj}(X_s) \partial_k \partial_j f(X_s) + \int_{K'} f(x^- + h(s,x)) - f(x^-) \nu(dx) \right. \]

\[ + \int_K [f(x^- + g(s,x)) - f(x^-) - g(s,x) \sum_k \partial_k f(x)] \nu(dx) \]

where,

\[ \hat{A}f(x) = \frac{d}{k=1} \partial_k b_k(x) f(x) + \frac{1}{2} \sum_{k,j=1}^d Q_{kj}(x) \partial_k \partial_j f(x) + \int_{K'} f(x^- + h(s,x)) - f(x^-) \nu(dx) \]

\[ + \int_K [f(x^- + g(s,x)) - f(x^-) - g(s,x) \sum_k \partial_k f(x)] \nu(dx) \]

and \((Q_{kj}(x))_{k,j=1}^{d} := a(x)a(x)^T.\)
Therefore, if $A$ is the generator of the $L^p(\mathcal{D})$-SG $T_t$, then
\[ \int_t^{t+h} T_s Af \, ds = \int_t^{t+h} T_s \tilde{A} f \, ds \]
\[ \Rightarrow Af = \tilde{A} f, \quad \text{for all } f \in C^2(\mathbb{R}^d) \cap L^p(\mathcal{D}). \]

Since $C_c^\infty(\mathbb{R}^d) \subset L^p(\mathcal{D})$ is dense and since $D(A) \subset L^p(\mathcal{D})$, in particular it holds that $Af = \tilde{A} f$, for $f \in D(A)$ such that $f_n \overset{n \to \infty}{\to} f$ in $L^p(\mathcal{D})$ with $f_n \in C_c^\infty$. Indeed, since $A$ (the generator of a $C_0$-semigroup) is closed, $Af_n \to Af$ in $L^p(\mathcal{D})$ as $n \to \infty$. But, since $\tilde{A}f_n = \tilde{A}f_n$ we get that the limits coincide. Here $A$ can be seen as the smallest closed extension of $\tilde{A}$.  

**Lemma 3.2.** Let $\psi$ be a negative definite function. Then the pseudo-differential operator defined as
\[ Af = \tilde{\mathfrak{S}}^{-1}[\psi \tilde{\mathfrak{S}} f], \quad \text{for all } f \in \mathcal{S}(\mathbb{R}^d) \]
is closable in $L^2(\mathbb{R}^d)$.

**Proof.** Let $(f_n)_{n \in \mathbb{N}}$ be a sequence in $\mathcal{S}(\mathbb{R}^d)$ such that $f_n \to 0$ in $L^2(\mathbb{R}^d)$, then by Plancherel we have that $\hat{f}_n \to 0$ in $L^2(\mathbb{R}^d)$, in particular $\hat{f}_{nk} \to 0$ a.e. along some subsequence $f_{nk}$. Now, let $Af_n \to g$ in $L^2(\mathbb{R}^d)$ then by Plancherel we get that $\hat{A}f_n \to \hat{g}$ in $L^2(\mathbb{R}^d)$. But the definition of $A$ implies that $\psi f_n \to \hat{g}$ in $L^2(\mathbb{R}^d)$. So by dominated convergence we get that $\psi \hat{f}_n \to 0$ in $L^2(\mathbb{R}^d)$ i.e. $g = 0$ and hence $A$ is closable.

Thus we see that depending on the type of noise acting at the microscale we get different operators at the macroscale.

### 3.4 Examples of transport equations as a particularization of the above generators

Many transport equations that appear in the context of biology takes the following form

\[ \partial_t p_t(x,v) = - v \cdot \nabla p_t(x,v) + \int_V [K(v,v')p_t(x,v') - K(v',v)p_t(x,v)]dv' \]
\[ \int_V K(v,v')dv' = 1, \quad K(v,v') = K(v',v) \quad \text{for all } v,v' \in V \subset \mathbb{R}^3, \]

where $p_t(x,v)$ is the density of the required biological quantity being studied (e.g. population density, chemical concentration, etc.) depending on the time $t$, the space variable $x \in \mathbb{R}^3$ and the velocity variable $v \in V \subset \mathbb{R}^3$. Usually, the velocity state space $V$ is taken to be a finite state space having the form $[v_1,v_2] \times S^2$, where $[v_1,v_2]$ is a finite interval for the magnitude of the velocity vector $v$ and $S^2$ is the two dimensional sphere representing the orientation of the velocity vector $v$. Here we just consider a generic finite state space $V \subset \mathbb{R}^3$. To arrive at the transport equation (14) we employ the following Lévy-type SDE:

\[
\begin{align*}
    dX_t &= V_t dt, \\
    dV_t &= dL_t
\end{align*}
\]

where, $X_t$ and $V_t$ are the position and velocity, respectively, of an individual (e.g. cell) at time $t$, and $X_t$ is a jump type Lévy process. In order to arrive at the particular form of equation given by (14) we assume that $L_t$ is a compound Poisson process with intensity $\lambda$ and symmetric jump probability measure $\mu$ on $\mathbb{R}^d$. Using Lévy-Itô decomposition we can write $X_t$ as

\[ L_t = ct + \int_{|v| < 1} vN(t, dv) + \int_{|v| \geq 1} vN(t, dv) \]

Now using Itô’s formula (see Theorem 3.8) and Proposition 3.2 for $b(x,v) = (v,0)^T$, $a(x,v) = (0,0)$, $g(x,v) = v$, and $h(x,v) = v$ we get that

\[ \frac{d}{dt} p_t(x,v) = -v \cdot \partial_x p_t(x,v) + \lambda \int_{\mathbb{R}^d} [p_t(x,v) - p_t(x,v-v')]\mu(dv') \]

(16)
Similarly, the microscopic equation results in the following macroscopic model:

\[
\frac{d}{dt} p_t(x, v) = -v \cdot \partial_x p_t(x, v) + \lambda \int_{\mathbb{R}^d} [p_t(x, v) - p_t(x, v')] f(v') dv'.
\]

Now if \( \mu \) is dense with respect Lebesgue measure such that \( \frac{d}{dt} (dv) = f(v) dv \) we get that

\[
\frac{d}{dt} p_t(x, v) = -v \cdot \partial_x p_t(x, v) + \lambda \int_{\mathbb{R}^d} [p_t(x, v') - p_t(x, v)] f(v - v') dv'.
\]

Now if \( \mu \) has a finite support \( V \subset \mathbb{R}^d \) then the above equation reduces to

\[
\frac{d}{dt} p_t(x, v) = -v \cdot \partial_x p_t(x, v) + \lambda \int_{V} [p_t(x, v') - p_t(x, v)] f(v - v') dv'.
\]

This can now be written in the form of [14] by letting \( K(v', v) = f(v - v') \).

So [16] can be seen as a general form of the transport equation (at least for the biological applications). Based on the applications the jump measure \( \mu \) can be particularized in the following different forms:

1. \( \mu(dv) = f(v) dv \). This case is feasible when the velocity of individuals is an observed (say by cell or particle tracking in images and/or videos) quantity and its probability or density can be estimated.

2. \( \mu(dv) = (\int_0^1 f(v, \theta) d\theta) dv = (\int_0^1 f(v|\theta) g(\theta) d\theta) dv \). This case is feasible when the velocity is dependent on an additional observable variable \( \theta \) (say orientation data, e.g. fiber orientation, track orientation) which can be estimated.

Similarly, the microscopic equation

\[
dX_t = V_t dt + \sigma(X_t) dW_t,
\]

\[
dV_t = dL_t
\]

results in the following macroscopic model:

\[
\frac{d}{dt} p_t(x, v) = -v \cdot \partial_x p_t(x, v) + \frac{1}{2} \sum_{j,k=1}^{d} \partial_{x_j} \partial_{x_k} \sigma_j^2(x) p_t(x, v) + \lambda \int_{V} [p_t(x, v') - p_t(x, v)] f(v - v') dv'.
\]

To obtain reaction terms, one needs to consider functionals of the process \( Y_t = (X_t, V_t) \). Let \( u(t, y) \) be defined as

\[
\begin{align*}
u(t, y) := \mathbb{E} \left[ \varphi(Y_t) e^{\int_0^t f(s, Y_s) ds} \middle| Y_0 = y \right].
\end{align*}
\]

Now a macroscopic equation associated to \( u \) can be obtained in the following way:

\[
u(t + h, y) = \mathbb{E} \left[ \varphi(Y_{t+h}) e^{\int_0^{t+h} f(s, Y_s) ds} \middle| Y_0 = y \right]
\]

\[
= \mathbb{E} \left[ \mathbb{E} \left[ \varphi(Y_{t+h}) e^{\int_0^{t+h} f(s, Y_s) ds} \middle| F_h \right] \middle| Y_0 = y \right]
\]

\[
= \mathbb{E} \left[ \mathbb{E} \left[ \varphi(Y_{t+h}) e^{\int_0^{t+h} f(s, Y_s) ds} \middle| F_h \right] e^{\int_0^h f(s, Y_s) ds} \middle| Y_0 = y \right]
\]

\[
= \mathbb{E} \left[ \mathbb{E} \left[ u(t, Y_h) e^{\int_0^h f(s, Y_s) ds} \middle| Y_0 = y \right] \right]
\]

\[
\Rightarrow u(t + h, y) - u(t, y) = \mathbb{E} \left[ u(t, Y_h) e^{\int_0^h f(s, Y_s) ds} - u(t, y) \middle| Y_0 = y \right]
\]

\[
\Rightarrow \lim_{h \to 0} \frac{u(t + h, y) - u(t, y)}{h} = \lim_{h \to 0} \mathbb{E} \left[ \frac{1}{h} \left( u(t, Y_h) e^{\int_0^h f(s, Y_s) ds} - u(t, y) \right) \middle| Y_0 = y \right]
\]

\[
= \lim_{h \to 0} \mathbb{E} \left[ \frac{e^{\int_0^h f(s, Y_s) ds}}{h} \partial_y u(t, Y_h) + u(t, Y_h) \partial_t e^{\int_0^h f(s, Y_s) ds} \right. \\
\left. + O(h^2) \right] \left| Y_0 = y \right]
\]

\[
\Rightarrow \partial_t u(t, y) = Au(t, y) + u(t, y) f(s, y), \quad u(0, y) = \varphi(y).
\]

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Analogously, letting \( u(t, y) := \mathbb{E} \left[ \varphi(Y_t) e^{\int_0^t b(s, Y_s) ds + \int_0^t g(s, Y_s) ds} \middle| Y_0 = y \right] \), yields the following macroscopic equation:

\[
\partial_t u(t, y) = Au(t, y) + u(t, y)f(t, y) + g(t, y), \quad u(0, y) = \varphi(y).
\]

Going a step further, taking \( f \) and \( g \) to be functions of \( u \) would yield nonlinear macroscopic equation:

\[
\partial_t u(t, y) = Au(t, y) + u(t, y)f(u) + g(u), \quad u(0, y) = \varphi(y).
\]

Thus we see that, macroscopic equations arise as a result of averaging out the dynamics of a functional of the microscopic dynamics. If the macroscopic functional itself is random then this gives rise to random macroscopic equations. We shall discuss this in more detail in the next section.

### 3.5 Construction of random operators

In this section we provide a framework for the construction of random time dependent operators. The most simplest idea is to use an operator valued process \((A_t)_{t \in (0,T)}\) which, for each fixed \( \omega \in \Omega \), is constant in a given time interval \((t_k, t_{k+1}) \subset (0, T)\) for any \( k \in \mathbb{N} \). More precisely, we have the following:

Let \((\tau_k)_{k \in \mathbb{N}}\) be a sequence of exponentially distributed independent random variables. Let \(N_t\) be the standard Poisson process with intensity \( \lambda \), and let \( t_n = \sum_{k=0}^{N_t} \tau_k \) with \( \tau_0 = 0 \). Here \( \tau_k \) represents the waiting time and \( t_n \) represents the jumping time, for each \( k, n \in \mathbb{N} \), respectively. Then we can define a piecewise constant (w.r.t time) operator \( A_t \) as

\[
A_t(\omega) = A_n \quad \text{for} \quad t \in (t_n(\omega), t_{n+1}(\omega)) \subset (0, T)
\]

where \((A_n)_{n \leq N}, N \in \mathbb{N}\) is a sequence of operators, each generated by a different Lévy process and its associated \(L^p\) semigroup. Based on this, for every fixed \( \omega \in \Omega \) and a given realization of jumping times \((t_n)_{n \in \mathbb{N}}\) we get the following random initial value problem:

\[
\frac{d}{dt} T^a_t f = A_t T^a_t f \quad \text{for} \quad t \in (t_n, t_{n+1})
\]

\[
T^a_0 f = \lim_{t \uparrow t_n} T^{a-1}_t f
\]

\[
T^a_0 f = f.
\]

Now the idea is to generalize this concept for continuously varying operators. To this end we use the relation between characteristic functionals, negative definite functions, and the associated generators to construct random operators. Here we assume that we are given the Lévy symbol \( \psi \) (which in general may be random and time dependent as well) and from this we define the generator via Fourier transform which will be both random and time dependent.

**Definition 3.6.** Let \( \Theta = (\Theta_t)_{t \in [0,T]} \) be a stochastic process taking values in \( CN(\Xi) \), the convex cone of continuous negative definite functions on \( \Xi \), where \( \Xi = \mathbb{R}^d \). Then for such \( \Theta \) we define an operator valued process \( A = (A_t)_{t \in [0,T]} \) as

\[
A_t f = \delta^{-1}[\Theta_t \delta f], \quad \text{for} \quad f \in S(\mathbb{R}^d) \quad \text{and} \quad t \geq 0
\]

Here we can apply Theorem 3.3 and represent \( \Theta_t \) as \((a_t, b_t, Q_t, \nu_t)\) for each \( t \in [0, T] \), respectively. The elements are such that \( a_t \in \mathbb{R}^+, b_t \times \mathbb{R}, Q_t \in \mathbb{R}^{d \times d} \) and \( \nu_t \in \Sigma(\Xi) \), where \( \Sigma(\Xi) \) is the space of Levy measures on \( \Xi \). In the light of Lemma 3.2 the operator family \( A \) defined via (21) consists of a set of closable operators \( A_t \) on \( L^p(\mathbb{R}) \) for each \( t \in [0, T] \). In order to be able to deduce a differential equation associated to the time dependent operators defined above, we need to construct, for each \( \omega \in \Omega \), an evolution operator \( (U_{t,s})_{t \geq s} \) associated with the process \( A \). To this end we make the following ansatz:

**Ansatz 1.**

1. \( \mathfrak{A} = (A_t)_{t \in [0,T]} \) is a family of sectorial operators for each \( \omega \in \Omega \).

2. The family \( \mathfrak{A} \) of sectorial operators satisfies the following Assumption 2 for each \( \omega \in \Omega \).
Properties 3.1 (Evolution operator). Let $\Upsilon = \{(t, s) \in (\mathbb{R}^+)^2 : 0 \leq s < t \leq T\}$, then $U(t, s)$ satisfies the following properties:

1. Semigroup property:

$$U(t, s) = U(t, r)U(r, s), \quad \text{for all } 0 \leq s \leq r \leq t \leq T,$$

$$U(t, t) = 1, \quad \text{for all } t \in [0, T].$$

2. The mapping $(t, s) \mapsto U(t, s)$ belongs to $C(\Upsilon; L(X))$ and satisfies the estimate

$$\|U(t, s)\|_{L(X)} \leq k_s, \quad \text{for some arbitrary constant } k_s > 0.$$

3. The mapping $(t, s) \mapsto A_tU(t, s)$ belongs to $C(\Upsilon; L(X))$ and satisfies the estimate

$$\|A_tU(t, s)\|_{L(X)} \leq k_s(t - s)^{-1}, \quad (t, s) \in \Upsilon.$$

4. The mapping $(t, s) \mapsto U(t, s)$ satisfies the following initial value problem:

$$\frac{\partial}{\partial t}U(t, s) = -A(t)U(t, s), \quad s \leq t \leq T,$$

$$U(s, s) = 1,$$

and

$$\frac{\partial}{\partial t}U(t, s) = U(t, s)A(t), \quad s \leq t \leq T,$$

$$U(s, s) = 1.$$

Based on this we can construct a two parameter evolution operator $\Omega := (U_{t,s})_{t \geq s}$ on $L^2(\mathbb{R}^d)$ associated to $\Omega$, for every $\omega \in \Omega$ fixed. We shall now illustrate this process.

Let $A$ be a sectorial operator of angle $\kappa_A$ and let $\psi_A$ be a real valued CNDF associated with the operator $A$. Let
ψ_S : \mathbb{R}^+ \to \mathbb{R} be another CNDF, then due to Theorem 3.4, we can compose \psi_S with \psi_A to get another real valued CNDF \psi_Z which is given as \psi_Z := \psi_S \circ \psi_A. Now applying the sector mapping theorem (11) we get that \psi_Z is also a sectorial operator of angle \kappa_{\psi_Z} \leq \kappa_A. Thus one may compose different CNDF to generate new sectorial operators. Now in order to get time dependent random operators, we let \psi_t = \beta_t \psi_Z, where is a real valued bounded continuous stochastic process. Letting \beta_t \subset [\beta_1, \beta_2] for 0 < \beta_1 < \beta_2, we see that (1 + \beta_1 \psi_Z) \leq (1 + \beta_2 \psi_Z). Thus applying the embedding result in Corollary 3.2 we get that \mathcal{H}^{\beta_2 \psi_Z}（\mathbb{R}^d） \supset \mathcal{H}^{\beta_1 \psi_Z}（\mathbb{R}^d） for all r \in \mathbb{R}. Now based on Theorem 3.7 for each t \in [0, T] and \omega \in \Omega we can associate an operator \mathcal{A}_t = (1 - \psi_t(D))^\frac{1}{2}, such that \mathcal{D}(\mathcal{A}_t) = \mathcal{H}^{\psi_t}（\mathbb{R}^d）. Letting \Theta_t = (1 + \psi_t)^\frac{1}{2} we get the desired continuous negative definite function. Note that since \psi_t(A) is a sectorial operator of angle \kappa_{\psi_t} \leq \kappa_A we also get that \mathcal{A}_t is a sectorial operator of angle \kappa_{\mathcal{A}_t} \leq \frac{\kappa}{2} \kappa_{\psi_t}. These considerations can be summarized in the following lemma.

**Lemma 3.3.** Let \((\Theta_t)_{t \in [0, T]} \) be defined as \((1 + \psi_t)^\frac{1}{2} \) with \psi_t = \beta_t \psi where \beta_t \subset [\beta_1, \beta_2], 0 < \beta_1 < \beta_2 is a bounded stochastic process and \psi is a real-valued CNDF generated by a Lévy process. Correspondingly, let \((\mathcal{A}_t)_{t \in [0, T]} \) be the family of differential operators given by \mathcal{A}_t = (1 - \psi_t(D))^\frac{1}{2}. Then we have:

1. \(\mathcal{A}_t = (1 + \psi_t)^\frac{1}{2} \) is a stochastic process such that for every fixed \(t \in [0, T]\) and \(\omega \in \Omega\), \(\mathcal{A}_t(\omega)\) is a real valued CNDF.

2. The operator \(\mathcal{A}_t\) generated by \(\Theta_t\) is a sectorial operator of angle \(\kappa_{\mathcal{A}_t} \leq \frac{\kappa}{2} \kappa_{\psi_t}\).

3. \(D(\mathcal{A}_t) = H^{\psi_t}（\mathbb{R}^d） \supset H^{\beta_t \psi_t}（\mathbb{R}^d） \supset H^{\beta_t \psi_t}（\mathbb{R}^d） = D((\mathcal{A}_t)^\nu)\) for \(s > r > 0, \nu = \frac{s}{2} < 1, \text{ and all } t_1, t_2 \in [0, T].\)

The only thing that needs to be checked is that \(\|A_t[A_t^{-1} - A_t^{-1}]\| \leq C|t - s|^\mu \) with \(1 < \mu + \nu\), which we shall establish now.

Since \(A_t u = \mathfrak{F}^{-1}[\Theta_t u] \) for all \(u \in \mathcal{S}(\mathbb{R}^d), \) we see that \(\mathfrak{F}^{-1}[\Theta_t^{-1} \mathfrak{F} A_t u] = u.\) By letting \(A_t u = v\) and \(u = A_t^{-1} v \in \mathcal{S}(\mathbb{R}^d),\) (since \(A_t\) is a sectorial operator and \(0 \in \sigma(A_t)\) for every \(t \in [0, T]\)), we observe that \(\mathfrak{F}^{-1}[\Theta_t^{-1} \mathfrak{F} v] = A_t^{-1} v.\) Thus (in general, by replacing \(v\) by \(u\)) we have that \(\mathfrak{F}[A_t^{-1} - A_t^{-1}]u = [\Theta_t^{-1} - \Theta_t^{-1}]\mathfrak{F} u\) for all \(u \in \mathcal{S}(\mathbb{R}^d).\) Now for \(t_1, t_2 \in [0, T], \) \(\beta_1' \in [\beta_3, \beta_4], \beta_3 \leq \beta_4,\) we can estimate \(\Theta_t^{-1} - \Theta_s^{-1}\) in the following way:

\[
|\Theta_t^{-1} - \Theta_s^{-1}| = |(1 + \psi_t)^{-\frac{1}{2}} - (1 + \psi_s)^{-\frac{1}{2}}| = \frac{|(1 + \psi_t)^{-\frac{1}{2}} - (1 + \psi_s)^{-\frac{1}{2}}|}{(1 + \psi_t)^{-\frac{1}{2}}(1 + \psi_s)^{-\frac{1}{2}}}
\]

\[
\leq \frac{|1 + \beta_t \psi_Z - (1 + \beta_s \psi_Z)|}{(1 + \beta_t \psi_Z)^{\frac{1}{2}}(1 + \beta_s \psi_Z)^{\frac{1}{2}}}
\]

\[
\leq \frac{1}{(1 + \beta_t \psi_Z)^{\frac{1}{2}}} |\beta_t - \beta_s| \psi_Z, \text{ for } t \in (t_1, t_2),
\]

\[
\leq \frac{C|\beta|_t}{(1 + \beta_t \psi_Z)^{\frac{1}{2}}} |\beta_t - \beta_s|, \text{ for } \beta_1' \in [\beta_3, \beta_4]
\]

\[
\leq \frac{C|\beta|_t}{(1 + \beta_t \psi_Z)^{\frac{1}{2}}} |\beta_t - \beta_s|, \text{ since } \beta_1 > 0
\]

\[
\leq \frac{C|\beta|_t}{(1 + \beta_t \psi_Z)^{\frac{1}{2}}} |\beta_t - \beta_s| = \frac{|\beta_t|_t}{(1 + \beta_t \psi_Z)^{\frac{1}{2}}} |\beta_t - \beta_s|
\]

\[
= \frac{C|\beta|_1}{(1 + \beta_t \psi_Z)^{\frac{1}{2}}} |\beta_t - \beta_s|, \text{ for } 1 < r \leq s
\]
Recalling that \((A_t)_{\nu} = (1 - \psi_t(D)) \tilde{\xi} \), \(\mathcal{F}[(A_t)_{\nu} u] = (1 + \psi_t) \tilde{\xi} F u\) and applying Lemma 3.1, we see that
\[
\|A_{t_2}^{-}(A_{t_1}^{-1} - A_{t_2}^{-1})u\|_2 = \|\mathcal{F}[A_{t_2}^{-}(A_{t_1}^{-1} - A_{t_2}^{-1})u]\|_2 = \|\mathcal{F}[(1 + \psi_t) \tilde{\xi} F (A_{t_1}^{-1} - A_{t_2}^{-1})u]\|_2
\leq \|(1 + \psi_t) \frac{C|\beta_2|}{\beta_1} (1 + \beta_1 \psi_Z) \tilde{\xi} \| |\beta_1 - \beta_2\|_2
\leq \frac{C|\beta_2|}{\beta_1} |\beta_1 - \beta_2| \|(1 + \beta_2 \psi_Z) \tilde{\xi} (1 + \beta_1 \psi_Z) \frac{\tilde{\xi}}{\beta_1} F u\|_2
\leq \frac{C|\beta_2|}{\beta_1} |\beta_1 - \beta_2| \|(1 + \beta_2 \psi_Z) \tilde{\xi} (1 + \beta_1 \psi_Z) \frac{\tilde{\xi}}{\beta_1} F u\|_2
\leq \frac{C|\beta_2|}{\beta_1} |\beta_1 - \beta_2| \|(1 + \beta_2 \psi_Z) \tilde{\xi} (1 + \beta_1 \psi_Z) \frac{\tilde{\xi}}{\beta_1} F u\|_2
\leq \frac{C|\beta_2|}{\beta_1} |\beta_1 - \beta_2| \|(1 + \beta_2 \psi_Z) \tilde{\xi} (1 + \beta_1 \psi_Z) \frac{\tilde{\xi}}{\beta_1} F u\|_2
\leq \frac{C|\beta_2|}{\beta_1} |\beta_1 - \beta_2| \|(1 + \beta_2 \psi_Z) \tilde{\xi} (1 + \beta_1 \psi_Z) \frac{\tilde{\xi}}{\beta_1} F u\|_2
\leq \frac{C|\beta_2|}{\beta_1} \left|\frac{\beta_2}{\beta_1} \right| \beta_1 \|\tilde{\xi} u\|_2 |t_1 - t_2| \leq \frac{C|\beta_2|}{\beta_1} \left|\frac{\beta_2}{\beta_1} \right| \beta_1 \|\tilde{\xi} u\|_2 |t_1 - t_2|
(32)

Based on (32) and (30) we get the following result:

**Lemma 3.4.** Let \((\beta_t)_{t \in [0,T]}\) be a bounded stochastic process that is continuous and has bounded derivatives, i.e., \(\beta_t \in [\beta_1, \beta_2]\) and \(\beta_t' \in [\beta_3, \beta_4]\) for all \(t \in [0,T]\), with \(\beta_1 > 0\). Moreover, let \(s \in \mathbb{R}^+,\ 0 < r < s\). Then for \(\nu = \frac{r}{s}\) we get that
\[
\|A_{t_2}^{-}(A_{t_1}^{-1} - A_{t_2}^{-1})u\|_2 \leq \frac{C|\beta_2|}{\beta_1} \left|\frac{\beta_2}{\beta_1} \right| \beta_1 \|\tilde{\xi} u\|_2 |t_1 - t_2|
(33)

**Theorem 3.10.** Let \((\Theta_t)_{t \in [0,T]}, \mathfrak{A} := (A_t)_{t \in [0,T]} \), \(\mathfrak{A} := (A_t)_{t \in [0,T]} \) be as in Lemma 3.3 and Lemma 3.4. Then, for every \(\omega \in \Omega\) fixed, there exists a unique two parameter evolution operator \(\Omega := (U_{t,s})_{t \geq s, t \geq 0}\) on \(L^2(\mathbb{R}^d)\) associated to \(\mathfrak{A}\), such that for every \(\omega \in \Omega\) fixed, and \(f \in D((A_t)_{\nu}) \subset L^2(\mathbb{R}^d)\) we get the following random abstract Cauchy problem
\[
\frac{d}{dt} U_{t,0}(\omega) f = -A_t(\omega) U_{t,s}(\omega) f, \quad \text{in } L^2(\mathbb{R}^d)
U_{0,0} f = f.
(34)

**Proof.** Follows from Lemma 3.2 Lemma 3.3 Lemma 3.4 and Theorem 3.9

The preceding discussion gives an abstract method for constructing random operators that satisfy the Ansatz 1 and thus generate a two parameter evolution semigroup which establishes the abstract Cauchy problem which is stochastic by construction. The source of randomness stems from the switching noises operating at the microscopic level. Figure 7 illustrates the mathematical framework used for this construction.

Now we provide some concrete examples.
Example 3.6. Let $(\beta_t)_{t \in [0,T]}$ be a bounded continuous process defined in the following way:

$$\beta_t := \beta_1 + \frac{\beta_2 I_t}{1 + I_t}, \quad \text{with} \quad I_t := \int_0^t \sin(B^{\beta_3, \beta_4}_s)^2 ds,$$

where

$$B^{\beta_3, \beta_4}_t = \frac{1}{T} \left( (T-t) \beta_3 + TW_t + t(\beta_4 - W_T) \right), \quad \text{for} \ t \in [0, T]$$

is the Brownian bridge process starting at $\beta_3$ and ending at $\beta_4$ and $(W_t)_{t \in [0,T]}$ is the standard Wiener process. Let $\psi_A(\xi) = |\xi|^2$, $\psi_S(\lambda) = \lambda^\alpha$ for $\alpha \in (0, 1)$. Then $\psi_t = \beta_t(\psi_S \circ \psi_A) = \beta_t |\xi|^{2\alpha}$. Then $\Theta_t$ is given as

$$\Theta_t(\xi) = (1 + \beta_t |\xi|^{2\alpha})^2$$

where $s \in (0, 2)$, $\beta_1 > 1$, $\beta_2 > \beta_1$ and $0 < \beta_3 < \beta_4$.

Example 3.7. Let $\beta_t$ and $\psi_A$ be defined as in Example 3.6, letting $\psi_S = 1$ we get

$$\Theta_t(\xi) = (1 + \beta_t |\xi|^2)^2.$$

This operator is nothing but the fractional Laplacian.

Example 3.8. In this example we use a more direct approach and define $\Theta_t$ as

$$\Theta_t(\xi) = |\xi|^{2\alpha_t}$$

where $\alpha_t = \frac{\alpha_1 + \alpha_2 I_t^2}{1 + I_t^2}$, such that $\alpha_t \in [\alpha_1, \alpha_2] \subset (0, 1)$. The fact that the operator associated to $\psi_t = \alpha_t$ satisfies the Ansatz will be established by Lemma 53 in Section 4.

Next we provide a generalization of the above procedure and consider a general Banach space valued random equation and deduce an analogous functional equation.
Let \((U_{t,s})_{t,s \geq s \in [0,T]}\) be the two parameter semigroup on \(L^2(\mathbb{R}^d)\) constructed in Theorem 3.10 and \(\mathfrak{A} = (A_t)_{t > 0}\) the corresponding family of sectorial operators. Then we have that, \(U_{t,s}\) fulfills the following (operator) equations

\[
\frac{\partial}{\partial t} U_{t,s} = -A_t U_{t,s} \quad \text{and} \quad \frac{d}{ds} U_{t,s} = U_{t,s} A_s
\]

In particular, for any \(f \in D((A_t)^r) \subset L^2(\mathbb{R}^d)\) we have that

\[
\frac{d}{dt} U_{t,0} f = -A_t U_{t,0} f \quad \text{in} \ L^2(\mathbb{R}^d)
\]

\[U_{0,0} f = f\]

**Proposition 3.3.** Let us assume that there exists a unique solution \(u_t = U_{1,0} f\) to the non-autonomous abstract Cauchy problem \((35)\). Then we get that \(u = (u_t)_{t \geq 0}\) is a \(L^2(\mathbb{R}^d)\) valued Markov process.

**Proof.** Without loss of generality, let \(t > s > r\). Since \(u_t = U_{t,0} f = U_{t,s} U_{s,r} U_{r,0} f\), for some given value of \(u_s\) say \(g\) (i.e. \(u_s = U_{s,0} f = g\)) we have that \(u_t = U_{t,s} g\) which implies that

\[(u_t)_{t > s} \prod_{u_r = g, r < s},\]

i.e. given \(g, u_t\) for \(t > s\) is independent of the values of \(u_r\) for all \(r < s\). Since \(u_t \in L^2(\mathbb{R}^d)\), altogether we get that \(u_t\) is an \(L^2(\mathbb{R}^d)\) valued Markov process.

With this we want to define a semigroup on \(C_b(L^2(\mathbb{R}^d))\) via the prescription \(T_{s,t} f = \mathbb{E}(f(u_t)|u_s)\) for all \(f \in C_b(L^2(\mathbb{R}^d))\) and \(t \geq s \geq 0\).

**Proposition 3.4.** Let \(u_t = U_{t,0} f\) be a unique solution to the non-autonomous abstract Cauchy problem \((35)\), then \(T_{s,t} f(u_s) = \mathbb{E}(f(u_t)|u_s)\), for \(0 \leq s \leq t < \infty\) is a bounded linear operator on \(C_b(L^2(\mathbb{R}^d))\) and is a \(C_0\)-SG.

**Proof.** Let \(f \in C_b(L^2(\mathbb{R}^d))\) and let \(\| \cdot \|_0\) denote the norm on \(C_b(L^2(\mathbb{R}^d))\) i.e.

\[
\| f \|_0 = \sup_{x \in L^2(\mathbb{R}^d)} |f(x)|, \quad \forall f \in C_b(L^2(\mathbb{R}^d)),
\]

then we have the following assertions:

1. \(T_{s,t} \in \mathcal{L}(C_b(L^2(\mathbb{R}^d))):\) Let \(t \geq s \geq 0\), then

\[
\| T_{s,t} f \|_0 = \| \mathbb{E}(f(u_t)|\cdot) \|_0 \overset{\text{Jensen's inequality}}{\leq} \mathbb{E}(\| f(u_t) \|_0|u_s) \leq \| f \|_0.
\]

Thus \(T_{s,t}\) is a contraction operator.

2. \(T_{r,s} = T_{r,t} T_{t,s}:\) Let \(0 \leq r \leq s \leq t < \infty\), then

\[
T_{r,s} f(u_r) = \mathbb{E}(f(u_t)|u_r) \overset{\text{Tower property}}{=} \mathbb{E}(\mathbb{E}(f(u_t)|F_s)|u_r) \overset{\text{Markov property}}{=} \mathbb{E}(\mathbb{E}(f(u_t)|u_s)|u_r)
\]

\[= \mathbb{E}(T_{s,t} f)(u_r) = T_{r,s} T_{s,t} f(u_r).
\]

3. \(\lim_{t \to s} T_{s,t} f - f \|_0 = 0:\) For this we make use of the fact that for a.e. \(\omega \in \Omega\) the evolution operator \(U_{t,s}\) is strongly continuous w.r.t \((t,s)\). Thus \(u_t = U_{t,0} f\) is continuous w.r.t \(t\) in \(L^2(\mathbb{R}^d)\), i.e. \(\lim_{t \to s} \| u_t - u_s \|_{L^2(\mathbb{R}^d)} = 0\) for \(0 \leq s \leq t\).

\[
\| T_{s,t} f - f \|_0 = \| \mathbb{E}(f(u_t)|\cdot) - f(u_s) \|_0 = \| \mathbb{E}(f(u_t) - f(u_s)) \|_0
\]

\[\leq \mathbb{E}(\| f(u_t) - f(u_s) \|_0 u_s) \leq \| f(u_t) - f(u_s) \|_0
\]

Since \(u_t \to u_s\) as \(t \to s\) for a.a. \(\omega \in \Omega\) and \(f \in C_b(L^2(\mathbb{R}^d))\) we have that \(f(u_t) \to f(u_s)\) as \(t \to s\). As a result we get that \(T_{s,t} \to I\) strongly as \(t \to s\). In fact, since \(U_{t,s}\) is strongly continuous in \((s,t) \in \mathbb{R}^+ \times \mathbb{R}^+\), i.e. \(U_{t,s} \to I\) as \((t,s) \to (r,r)\), it holds that \((s,t) \to T_{s,t}\) is strongly continuous as well.

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In order to establish a Cauchy problem associated to the (time inhomogeneous) semigroup \((T_{s,t})_{0 \leq s < t}\), we find it convenient to make \(T\) time homogeneous. This is possible by augmenting the state space of the Markov process \((u_t)_{t \geq 0}\) (defined in Proposition 3.3) with the time state space, i.e. by converting the nonautonomous ODE to an autonomous ODE by taking the deterministic time variable to be a part of the state space.

\[
\frac{d}{dt} u_t = A_t u_t,
\]

\[u_0 = f\]  \[\implies \frac{d}{dt} v_t = A_t v_t\] (36)

Following this transformation we should also change the probability transition function to incorporate the augmented deterministic time variable. It turns out that the new probability transition function is time homogeneous in some sense, as shown in the proposition below.

**Proposition 3.5.** Let \((E, \| \cdot \|_E)\) be a Banach space and \(B\) the Borel sigma algebra on \(E\) induced by its norm \(\| \cdot \|_E\).

Let \((u_t)_{t \geq 0}\) be an \((E, B)\) valued Markov process (given by the LHS of (36)) with the probability transition function \(p_{\tau_1, \tau_2}(x, B)\) for \(0 \leq \tau_1 \leq \tau_2\) and \(x \in E\) and \(B \in B\). Then the process \((\hat{u}_t)_{t \geq 0} = (\tau_t, u_t)\) (given by the RHS of (36)) with the probability transition function \(\hat{p}_{s,t}\) defined as

\[
\hat{p}_{s,t}(\hat{x}, \hat{B}) = \mathbb{P}(u_t \in B | u_s = x) \otimes \delta_0(I | \tau_s = s)
\]

with \(\hat{x} = (s, x), \hat{B} = B \times I, I\) a Borel subset of \(\mathbb{R}^+\) is a time homogeneous Markov process.

**Proof.** For \((\hat{u}_t)_{t \geq 0} = (\tau_t, u_t)\), and \(\hat{x} = (s, x)\) we have that

\[
\hat{p}_{s,t}(\hat{x}, \hat{B}) = \mathbb{P}(\hat{u}_t \in \hat{B} | \hat{u}_s = \hat{x}) = \mathbb{P}\left( \left(\tau_t, u_t \right) \in I \times B \mid \left(\tau_0, u_0 \right) = (s, x) \right)
\]

and

\[
\hat{p}_{0,t-s}(\hat{x}, \hat{B}) = \mathbb{P}\left( \left(\tau_{t-s}, u_{t-s} \right) \in I \times B \mid \left(\tau_0, u_0 \right) = (0, x) \right)
\]

Since the initial condition \(\hat{x} = (s, x)\) is fixed and \(\tau_t = t - \tau_0\), we see that \(\tau_t = t - s\) if \(\tau_0 = s\) and \(\tau_{t-s} = t - s\) if \(\tau_0 = 0\). Thus the evolution of \(A_{\tau_t}\) and hence of \(u_{\tau_t}\) in the time interval \((s, t]\) and \((0, t - s]\) remains the same. Consequently, we get that \(\hat{p}_{s,t}(\hat{x}, \hat{B}) = \hat{p}_{0,t-s}(\hat{x}, \hat{B})\).

Now if \((u_t)_{t \geq 0}\) satisfies the Cauchy problem we get that \((\hat{u}_t)_{t \geq 0}\) is a \((\mathbb{R}^+ \times L^2(\mathbb{R}^d))\) valued homogeneous Markov process. From now on we drop the hat and refer \((u_t)_{t \geq 0}\) to be our newly constructed homogeneous Markov process \((\hat{u}_t)_{t \geq 0}\).

Now letting \(D_u f\) denote the Fréchet derivative of \(f\) at point \(u\), applying Taylor’s Theorem (which yields us the remainder term \(R_{u,e}\)) we can deduce the result.

**Proposition 3.6.** Let \((T_t)(f)(u_0) := \mathbb{E}(f(u_t)|u_0 = u_0)\) be a \(C_0\)-SG on \(C_0(\hat{L}^2(\mathbb{R}^d))\), where \(\hat{L}^2(\mathbb{R}^d) := \mathbb{R}^+ \times L^2(\mathbb{R}^d)\).

Let \(e = u_{t+h} - u_t\), then for sufficiently smooth \(f\), we have that

\[
\frac{d}{dt} T_t f = T_t(G f), \quad \text{with } G f = (D_u f)(A_t u_t).
\]

**Proof.**

\[
\frac{T_{t+h} f - T_t f}{h} = \frac{1}{h} \mathbb{E}\left[f(u_{t+h}) - f(u_t) \mid u_0\right] = \frac{1}{h} \mathbb{E}\left[f(u_t + e) - f(u_t) \mid u_0\right] = \frac{1}{h} \mathbb{E}\left[(D_u f)(e) + (R_{u,t,e})(e) \mid u_0\right] = \mathbb{E}\left[(D_u f)\left(\frac{e}{h}\right) + (R_{u,t,e})(e)\left(\frac{e}{h}\right) \mid u_0\right] = \mathbb{E}\left[(D_u f)\left(\frac{u_{t+h} - u_t}{h}\right) + (R_{u,t,e})(\frac{u_{t+h} - u_t}{h}) \mid u_0\right]
\]

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Moreover, the remainder term \( R_{u_t,e} \) is given as:

\[
\lim_{h \downarrow 0} \frac{u_{t+h} - u_t}{h} \quad \text{as} \quad h \to 0
\]

Analogously, for the first term we get

\[
\lim_{h \downarrow 0} \frac{u_{t+h} - u_t}{h} \quad \text{as} \quad h \to 0
\]

Therefore, the mapping \( \hat{u}_t \) converges to \( u_t \) in \( L^2(\mathbb{R}^d) \) and \( D_u f \in L^2(\mathbb{R}^d) \) is continuous in \( u \).

Moreover, the remainder term \( R_{u_t,e} \) is \( o(\varepsilon^2) \) and \( R_{u_t,e} \to 0 \) in \( L^2(\mathbb{R}^d) \) as \( \varepsilon \to 0 \). Since, \( u \in C([0,T]; L^2(\mathbb{R}^d)) \) we have that \( e = u_{t+h} - u_t \) converges to 0 in \( L^2(\mathbb{R}^d) \) as \( h \to 0 \).

This completes the general multiscale framework for deducing stochastic equations at the macroscopic level. Next we formally apply this method and propose a macroscopic stochastic equation for the dynamics of cancer invasion under the influence of tissue acidity.

4 Numerical examples

In this section we shall provide some numerical examples that illustrate the methodology for modeling diversity of a complex biological systems. Here we choose cancer as a prototypical example of such a system, and we specifically focus on modeling the diverse invasion capability of cancer cells under the influence of tissue and cellular acidity. To this end we provide two approaches: namely microscopic and macroscopic approaches. In the first approach we consider the dynamics at the cell-level interactions while in the second approach we consider the dynamics at the tissue-level interactions.

4.1 Microscopic modeling:

In this section we consider the modeling of invasive dynamics of cancer cells under the influence of acidity while keeping in mind to take into account diversity aspect. Based on this the main quantities under considerations are \( H_i \) which capture the intra- and extra-cellular concentration of protons. The motion of cancer cells itself is modeled via first order Newtonian dynamics, namely in terms of velocity variable \( V \) and position variable \( X \). Finally, the structure or the density of the underlying tissue structure is modeled by \( N \). Based on this, the microscopic dynamics is given as:

\[
\begin{align*}
&dV_t = \nabla N_i dt + dL_t \\
&dX_t = V dt \\
&\frac{dH_i}{dt}(t,X_t) = -T(H_e) + S_1(H_i) + Q(H_i) \\
&\frac{dH_e}{dt}(t,X_t) = T(H_i) + S_2 \\
&\frac{dN_i}{dt}(t,X_t) = -\gamma N_i H_e
\end{align*}
\]

The intra-cellular proton dynamics is affected by: (i) production of protons due to glycolysis \( Q(H_i) \), (ii) buffering of protons due to intracellular and organellar buffer \( S_1(H_i) \) and (iii) efflux of intracellular protons due to membrane proton transporters \( T_1, T_2 \) and \( T_3 \). These terms are summed up and represented by a single term \( T \). Similarly, the extra-cellular proton dynamics is affected by: (i) influx of protons by membrane transporters \( T \) and (ii) sequestering of excess protons by the tissue vasculature \( S_2 \). The effect of excess protons in the extra-cellular region accelerate...
the activity protolytic activity of matrix-degrading enzymes because of which there is a loss of extra-cellular tissue. Thus \( N \) is just modeled by a decay term. Lastly, the movement of cancer cells is specified (in general) by a jump velocity model where in the velocity process \( V \) is given by the SDE \((37d)\) and the position process \( X \) is simply the integral of the velocity term \((37a)\). Additionally, the mean velocity of the cancer cell is assumed to be specified by the fiber orientation \( \nabla N \) of the underlying tissue structure. Altogether the model is as given in \((37)\). Since, \( N \) and \( H_e \) are typically macroscopic variables, their dynamics is affected only at the position of the cancer cells, thus in the equation we see that \( N \) and \( H_e \) are written as a function \( X_t \). Their macroscopic version \( N(t, x) \) and \( H_e(t, x) \), respectively, are obtained simply by convolving \( N(t, X_t) \) and \( H_e(t, X_t) \) by the density function of \( X_t \).

\[
H_e(t, x) = \int_{\mathcal{D}} f(x - y)H_e(t, x)dy, \quad N(t, x) = \int_{\mathcal{D}} f(x - y)N(t, x)dy
\]

We now perform some numerical experiments for the above model. We consider a 2D spatial domain \( \mathcal{D} = [0, 1] \times [0, 1] \) and discretize it uniformly. Similarly, the temporal component is discretized into \( N \) steps with time step \( \tau = .05 \). Since we are interested in microscopic simulation, we consider \( M \) different cancer cells which are idealized as particles. Each particle undergoes motion as per \((37a)\) and \((37b)\) while exhibiting intra-cellular dynamics (for \( H_i \)). Due to the coupling between \( H_i(., X_t) \) and \( H_e(., X_t) \), the macroscopic extracellular proton concentration \( H(t, x) \) is affected along the path of the particles. Analogously, the macroscopic normal tissue density is \( N(t, x) \) is also affected. Based on this, the initial condition for the above SDE as shown in Figure 3. We now run three different simulations with \( M = 2500 \) and \( N = 25 \), each with a different type of noise processes \( dL_t \) for the velocity equation \((37a)\). The different types of processes used for the simulation are as defined in \((38)\). In order to understand the effect of these different types of noise distribution, we compute a macroscopic quantity at the end of the simulation and compare it for all different cases. The macroscopic variable here is the mean survival percentage of cancer cells. To enable this we incorporate a condition based on which we kill the particle process \( X_i \). To be more precise, all the particles \( X_i \), with either \( H_i(t, X_i) < h_1 \) or \( H_i(t, X_i) > h_2 \) or \( H_e(t, X_i) > h_3 \) are killed, i.e. are removed from the system. The remaining percentage of particles (cells) determine the survival percentage of the population.

\[
S_{H_i} := \left\{ j \in \mathbb{N}, j \leq M : H_i(t, X_i^j) < h_1 \right\}, \quad S_{H_2} := \left\{ j \in \mathbb{N}, j \leq M : H_i(t, X_i^j) > h_2 \right\}, \quad S_{H_e} := \left\{ j \in \mathbb{N}, j \leq M : H_e(t, X_i^j) > h_3 \right\}, \quad S_0 := \left\{ j \in \mathbb{N}, j \leq M \right\}, \quad S := \frac{\#S}{M},
\]

\[
S_1 := S_{H_i} \cup S_{H_2} \cup S_{H_e}, \quad \hat{S} := S_0 - S_1 \quad dL_t \sim N(0, 1) \quad \text{(38a)}
\]

\[
dL_t \sim \begin{cases} N(0, 1) & \text{if } U \in [0, 0.3), U \in U(0, 1) \\ \text{Laplace}(0, 1) & \text{else if } U \in [0.3, 0.5), \\ \text{Triangular}(-4, 0, 8) & \text{else} \end{cases} \quad \text{(38b)}
\]

\[
dL_t \sim 10 \sin(\sigma_t)N(0, 1), \quad \sigma_t \sim \text{Cauchy}(0, 1) \quad \text{(38c)}
\]

Based on the mean survival percentage \( S \) and the final distribution of cells obtained for the three different cases, we can infer that the migration pattern generated by type-3 noise process \((38c)\) is the most invasive while the pattern generated by type-1 noise process \((38a)\) is least invasive. Even though one could also generate a highly invasive migration pattern by simply choosing a high variance parameter for the Type-1 noise, it fails to take into account the intracellular and extracellular disturbances leading to a change in the distribution types such as from uni-modal to multi-modal, thin-tailed to heavy-tailed and so on. Such switching in the distribution types results in switch in the migration regime consequently exhibiting a diverse migration regime. Based on the discussion from Section 3.3 we can infer that Type-2 and Type-3 noise processes induce random operators at the macroscopic levels while Type-1 noise does not, thus make it unsuited for modeling diverse behaviors. Motivated by this and due to the tight coupling, offered by the modeling framework (cf. Fig. 1), between the micro and macro level, we shall now consider a macroscopic model for acid mediated cancer invasion involving random operators.

### 4.2 Macroscopic modeling:

In this section we provide an example of continuous negative definite functions that satisfy Ansatz and based on this example we propose a macroscopic model for the acid-mediated tumor invasion.
Figure 8: Initial condition for the microscopic model \([17]\). Starting from the left, the first plot shows the directional vector field generated by underlying tissue structure in gray background. The blue dots show different cell particles and their velocity vectors are indicated by red arrow. Second plot from the left shows the initial concentration of intra-cellular protons \(H_i\) of all \(M = 2500\) particles arranged in a 2D grid. Third plot from the left shows the concentration of extra-cellular protons \(H_e\). The fourth plot from the right shows the density of normal cells i.e. the structure of the underlying tissue.
Figure 9: Simulation results for the microscopic model at time $T = 2.5\text{s}$ when taking $dL_t$ as per (38a). The resulting mean survival percentage $S \approx 35\%$. 

(a) $X_T$ and $\nabla N_T$

(b) $H_i(T, X_T)$

(c) $H_i(T, x)$

(d) $N_i(T, x)$
Figure 10: Simulation results for the microscopic model (37) at time $t = 2.5s$ when taking $dL_t$ as per (38). The resulting mean survival percentage $S \approx 40\%$
Figure 11: Simulation results for the microscopic model (37) at time $t = 2.5s$ when taking $dL_t$ as per (38c). The resulting mean survival percentage $S \approx 50\%$
To be precise, in this section we explore the properties of the operator whose symbol is given by \( \eta(\xi) = |\xi|^{2\alpha} \), for \( \xi \in \mathbb{R}^d \) and \( \alpha \in (0, 1) \). The function \( |\xi|^{2\alpha} \) appears as a symbol of the Lévy process \( (Z_t)_{t \geq 0} \) obtained by the subordination of the Wiener process \( W = (W_t)_{t \geq 0} \) with respect to the \( \alpha \)-subordinator \( S = (S_t)_{t \geq 0} \), whose characteristics is given as \( (0, \lambda) \), with \( \lambda(dx) = \frac{\alpha}{\Gamma(1 - \alpha)} \frac{d^\alpha}{2} \). Consequently, the subordinated process \( Z = W_S = (W_{S_t})_{t \geq 0} \). Correspondingly, as a consequence of the Phillips theorem we find that the generator \( A^Z \) of the subordinated process \( Z \) is given by the fractional Laplacian \( (-\Delta)^\alpha \) for \( \alpha \in (0, 1) \) (as shown in example 3.5). In order to specify a time dependent random operator, we just let \( \alpha \) be a bounded stochastic process with values in \( (0, 1) \). First we shall recall the definition and properties of the fractional Laplacian \( (-\Delta)^\alpha \).

**Definition 4.1 (Fractional Laplacian).** Let \( f \in L^p(\mathbb{R}^d), p \in \{1, 2\} \). Then the operator \( A \) defined on \( L^p(\mathbb{R}^d) \) as

\[
(\mathcal{F}A)f(\xi) = -|\xi|^{2\alpha}(\mathcal{F}f)(\xi) \quad \alpha \in (0, 1)
\]

is called the fractional Laplacian on \( L^p(\mathbb{R}^d) \) with \( A = (-\Delta)^\alpha \).

Though this is an easy and convenient way of defining the fractional Laplacian, one can find in the literature various different definitions, namely - Balakrishnan's definition, singular integral definition, Dynkin's definition, and so on. We now state a very nice theorem, due to [32], that establishes an equivalence relation between these various definitions:

**Theorem 4.1.** Let \( \mathcal{B} \) be any of the spaces \( L^p(\mathbb{R}^d), C_0 \) or \( C_b, \ p \in [1, \infty] \). Let \( f \in \mathcal{B} \) and \( \alpha \in (0, 2) \). Then the following definitions of the fractional Laplacian \( A = (-\Delta)^\alpha \) are equivalent:

(a) **Fourier definition:**

\[
(\mathcal{F}A)f(\xi) = -|\xi|^{\alpha}(\mathcal{F}f)(\xi) \quad \alpha \in (0, 1)
\]

if \( \mathcal{B} = L^p(\mathbb{R}^d), p \in [1, 2] \).

(b) **Distributional definition:**

\[
\int_{\mathbb{R}^d} A_f(y)\phi(y)dy = \int_{\mathbb{R}^d} f(x)A\phi(x)dx
\]

for all \( \phi \in \mathcal{S}(\mathbb{R}^d) \) and with \( A\phi \) defined as in (39).

(c) **Bochner’s definition:**

\[
A_f = \frac{1}{\Gamma(-\frac{d}{2})} \int_0^\infty (e^{t\Delta}f-f)t^{-1-\frac{d}{2}}dt,
\]

where the integral is Bochner’s integral for \( \mathcal{B} \)-valued functions.

(d) **Balakrishnan’s definition:**

\[
A_f = \frac{1}{\pi} \int_0^\infty \Delta(s-\Delta)^{-1}s^{-\frac{d+\alpha}{2}}ds,
\]

where the integral is Bochner’s integral for \( \mathcal{B} \)-valued functions.

(e) **Singular integral definition:**

\[
A_f(x) = \lim_{r \to 0^+} \frac{2^\alpha \Gamma(\frac{d+\alpha}{2})}{\pi^{d/2} \Gamma(-\frac{d}{2})} \int_{\mathbb{R}^d \setminus B(x, r)} \frac{f(x+z)-f(x)}{|z|^{d+\alpha}}dz,
\]

with the limit in \( \mathcal{B} \).

(f) **Dynkin’s definition:**

\[
A_f(x) = \lim_{r \to 0^+} \frac{2^\alpha \Gamma(\frac{d+\alpha}{2})}{\pi^{d/2} \Gamma(-\frac{d}{2})} \int_{\mathbb{R}^d \setminus B(x, r)} \frac{f(x+z)-f(x)}{|z|^{d+\alpha}}dz,
\]

with the limit in \( \mathcal{B} \).
(g) Quadratic form or Dirichlet form definition: \( \langle Af, \phi \rangle = \mathcal{E}(f, \phi) \) for all \( \phi \) in the Sobolev space \( H^2 \), where
\[
\mathcal{E}(f, g) = \frac{2\pi^2 \Gamma\left(\frac{d+\alpha}{2}\right)}{\pi^{d/2} |\Gamma(-\frac{\alpha}{2})|} \int_{\mathbb{R}^d} \int_{\mathbb{R}^d} \frac{(f(x) - f(y)) (g(x) - g(y))}{|x - y|^{d+\alpha}} \, dx \, dy,
\]
when \( \mathcal{B} = L^2(\mathbb{R}^d) \).

(h) Semigroup definition:
\[
Af = \lim_{t \to 0^+} \frac{T_t f - f}{t},
\]
with \( T_t f = f \ast p_t \) and \( (\tilde{\mathcal{F}} p_t)(\xi) = e^{-|\xi|^\alpha} \).

(i) Inverse Riesz potential definition:
\[
-f(x) = \frac{2^{-\alpha} \Gamma\left(\frac{d-\alpha}{2}\right)}{\pi^{d/2} |\Gamma(-\frac{\alpha}{2})|} \int_{\mathbb{R}^d} Af(x + z) |z|^{d-\alpha} \, dz
\]
if \( \alpha < d \) and \( \mathcal{B} = L^p(\mathbb{R}^d) \), \( p \in [1, \frac{d}{\alpha}) \).

(j) Harmonic extensions’ definition:
\[
\Delta_y u(x, y) + \alpha^2 c\alpha^2 y^{-2/\alpha} \partial^2_y u(x, y) = 0 \quad \text{for } y > 0,
\]
\[
u(x, 0) = f(x), \quad \partial_y \nu(x, 0) = Af(x),
\]
where \( c_\alpha = \frac{2^{-\alpha} \Gamma\left(\frac{\alpha}{2}\right)}{\Gamma\left(\frac{d-\alpha}{2}\right)} \) and \( u(\cdot, y) \) is a function of class \( \mathcal{B} \) which depends continuously on \( y \in [0, \infty) \) and \( \|u(\cdot, y)\|_{L^2} \) is bounded in \( y \in [0, \infty) \).

In addition, in (c), (e), (f), (h) and (j), the convergence in the uniform norm can be relaxed to pointwise convergence to a function in \( \mathcal{B} \) when \( \mathcal{B} = C_{0} \) or \( \mathcal{B} = C_{b} \). Finally, for \( \mathcal{B} = L^p(\mathbb{R}^d) \), with \( p \in [1, \infty) \), the norm convergence in (e), (f), (h) or (j) implies pointwise convergence for almost all \( x \).

Proof. Refer to [32]

We now collect some properties of the operator \((-\Delta)^\alpha\).

**Theorem 4.2.** If the IG of the \(L^2\)-Markov semigroup induced by the Lévy process \( X \) is the fractional Laplacian \((-\Delta)^\alpha\), for \( \alpha \in (0, 1) \), then its domain \( D(A) \) is given by \( H^{2\alpha}(\mathbb{R}^d) \equiv W^{2\alpha, 2}(\mathbb{R}^d) \).

Proof. Refer to [33, 47].

**Theorem 4.3.** Let \( A \) be a sectorial operator of angle \( \kappa_A \) then for \( \alpha \in (0, 1) \) the operator \( A^\alpha \) is a sectorial operator of angle \( \alpha \kappa_A \).

Proof. Refer to [11, 52].

**Example 4.1.** Let \( A = -\Delta \), then we know that \(-\Delta\) is sectorial operator of angle \( 0 \), thus \((-\Delta)^\alpha\), for \( \alpha \in (0, 1) \), is also a sectorial operator of angle \( 0 \).

Now by letting \( \alpha \) to be a bounded stochastic process, such that \( \alpha(\omega) : [0, T] \to (0, 1) \) for every \( \omega \in \Omega \) fixed, we can specify a stochastic, time dependent Fourier multiplier \( \xi^\alpha \). Then due to [40] and Theorem 4.2 we readily observe that, for each fixed \( \omega \) and \( t \), we get \( \langle A_{t}(\omega), D(A_{t}(\omega)) \rangle = ((-\Delta)^{\alpha_{t}(\omega)}, H^{\alpha_{t}(\omega), 2}(\mathbb{R}^d)) \). Additionally, Example 4.1 yields that for every \( \omega \in \Omega \) and \( t \in [0, T] \), \( A_t(\omega) \) is a sectorial operator of angle \( 0 \). Thus for every \( \omega \) and \( t \) fixed we have that \( A_t(\omega) \) generates a bounded analytic semigroup of angle \( \frac{\pi}{2} \). Thus we are now in a good position to check the existence of the two parameter semigroup for time dependent operator \( A_t(\omega) \) with \( \omega \in \Omega \) being fixed. To this end we need to check that \( (A_{t}(\omega))(\tau \in [0, T]) \) satisfies Assumption 1. The only tricky part is to check the condition [24], which is established by Lemma 4.2 in Section 4.2.1.
4.2.1 A model for acid mediated cancer invasion

Based on the above discussion we now propose a macroscopic model for cancer invasion which is mediated by tissue acidity. In this model the main variables of interest are: (i) cancer cell density \( C \), (ii) normal cell density \( N \), and (iii) the shifted ratio between extracellular and intracellular proton concentrations \( H_e \) and \( H_i \), respectively, called the proton ratio index or simply proton index \( H = H_e/H_i - 1 \). Next we describe the dynamics for each of the aforementioned quantities.

Proton dynamics: Since we intend to propose just a macroscopic models, the proton dynamics is modeled via the changes in the ratio of intracellular and extracellular protons. Cancer cells exhibit a reversed pH gradient \( x \), where \( H_e \) is greater than \( H_i \). This relationship is captured by the shift, by a constant of value 1, in the definition of \( H \).

Cancer cell dynamics: According to [36, 46, 50, 51] many animals exhibit Lévy flight type movements in order to gather food or to avoid predators. As discussed at the end of the previous subsection, Lévy flight processes can be constructed using a CTRW process and it generates a fractional Laplacian operator at the macroscopic level. Moreover, because we are interested in modeling diverse kinds of movements at the macroscopic level, in order to describe the movement of cancer cells through fibrous tissue and crowded cells, we use a time dependent random fractional Laplacian operator \( -(-\Delta)^{\alpha_t} \). The exponent \( \alpha_t \) is a bounded stochastic process which is a function of the proton index \( H \). Apart from this we also model movement of cells via the pH-taxis and haptotaxis mechanisms. The former models the movement of cells in the direction of a high proton index or simply proton index \( H = H_e/H_i - 1 \). Next we describe the dynamics for each of the aforementioned quantities.

Normal cell dynamics: The dynamics of normal cell density \( N \) is simply given by an ODE which describes the decay of healthy cells due to their interaction with cancer cells and protons.

\[
\begin{align*}
\frac{dH_t}{dt} &= \sigma_H A H_t dt + R_1(H_t) dt + f(H_t, C_t) \nabla H_t \cdot \nabla C_t dt + H_t dW_t \\
\frac{dC_t}{dt} &= \sigma_C A C_t dt + R_2(C_t) dt + \nabla \cdot (g(H_t, C_t) \nabla N_t) dt - \nabla \cdot (h(H_t, C_t) \nabla H_t) dt \\
\frac{dN_t}{dt} &= R_3(C_t, H_t) dt.
\end{align*}
\]

where \( \alpha_t \) is an \( \mathbb{R} \) valued, bounded and continuous (w.r.t time \( t \)) process such that:

\[
\sup_{t,x,\omega} \alpha_t = a_2 \in (0, 1), \quad \inf_{t,x,\omega} \alpha_t = a_1 \in (0, 1),
\]

and \( \frac{1}{2} < a_1 < a_2 < 1 \). Let \( \gamma \in (0,1) \) be such that

\[
\gamma a_2 = \eta \in (0, 1), \quad \gamma a_1 = \delta \in (0, 1)
\]

and \( \delta < \eta \). Based on this, we let \( \alpha_t \) take the following form:

\[
\alpha_t := a_1 + (a_2 - a_1) \frac{a H_t}{1 + a H_t}, \quad a, a_1, a_2 \in \mathbb{R} \text{ and } a_1 < a_2.
\]

Since \( a_1 > \frac{1}{2} \) there exists \( \nu > 0 \) such that \( (1 - \nu)a_1 > \frac{1}{2} \).

**Lemma 4.1.** The operator \((-A_t, D(-A_t)) = ((-A)^{\alpha_t}, H^{\alpha_t}(\mathbb{R}^d))\) is a closed and densely defined operator in \( L^2(\mathbb{R}^d) \).
Lemma 4.2. For $u \in H^\gamma(\mathbb{R}^d)$, $\|(A_t)^\gamma u\|_{L^2(\mathbb{R}^d)} \leq M_{A^\gamma}$ uniformly in $t$, where $M_{A^\gamma} < \infty$ is a fixed constant.

Proof. Firstly, we note that $(-A_t)^\gamma = (-A)^{\gamma \alpha_t}$, so $D(A_t^\gamma) = H^{\gamma \alpha_t}$. Since $H^{s_1}(\mathbb{R}^d) \subseteq H^{s_2}(\mathbb{R}^d)$ for $s_1 \geq s_2$ we have that $H^\gamma(\mathbb{R}^d) \subseteq D((-A_t)^\gamma)$ i.e. $H^\gamma(\mathbb{R}^d) \subseteq H^{\gamma \alpha_t}(\mathbb{R}^d)$ (since $\gamma \alpha_t \in [\delta, \eta] \subset (0, 1)$ and continuous w.r.t. $t$).

\[
\sup_{u \in H^\gamma(\mathbb{R}^d), \|u\| = 1} \|(-A_t)^\gamma u\| \leq \sup_{u \in D((-A_t)^\gamma), \|u\| = 1} \|(-A_t)^\gamma u\| = \|(-A_t)^\gamma\|.
\]

Thus

\[
\sup_{t \in \mathbb{R}, u \in H^\gamma(\mathbb{R}^d), \|u\| = 1} \|(-A_t)^\gamma u\| \leq \sup_{t \in \mathbb{R}, \omega \in \Omega, \|u\| = 1} \|(-A_t)^\gamma u\| < M_{A^\gamma},
\]

with $M_{A^\gamma} < \infty$ being a fixed constant. \hfill \blacksquare

Lemma 4.3. For a bounded process $\alpha_t$ defined as in (50), we have that

\[
\|(-A_t)^{-1} - (-A_s)^{-1} u\|_{H^\gamma(\mathbb{R}^d)} \leq k(\eta, \delta)\|\alpha_t - \alpha_s\|_{H^{2}(\mathbb{R}^d)} \|u\|_{L^2(\mathbb{R}^d)}, \quad \forall u \in L^2(\mathbb{R}^d).
\]

Proof. For $-\alpha_t$, due to Equation 2.108 of [52] we have that:

\[
(-A_t)^{-1} = \frac{-\sin(\pi \alpha_t)}{\pi} \int_0^\infty \rho^{-\alpha_t}(\rho + A)^{-1} d\rho.
\]

\[
\|(-A_t)^{-1} - (-A_s)^{-1} u\|_{H^\gamma} = \left\| \frac{\sin(\pi \alpha_t)}{\pi} \int_0^\infty \rho^{-\alpha_t}(\rho + A)^{-1} u d\rho - \frac{\sin(\pi \alpha_s)}{\pi} \int_0^\infty \rho^{-\alpha_s}(\rho + A)^{-1} u d\rho \right\|_{H^\gamma}
\]

\[
= \frac{1}{\pi} \left( \int_0^\infty \left\| (\sin(\pi \alpha_t) - \sin(\pi \alpha_s)) \rho^{-\alpha_t}(\rho + A)^{-1} u \right\|_{H^\gamma} d\rho
\]

\[
+ \left| \sin(\pi \alpha_s) \right| \int_0^\infty \left\| \rho^{-\alpha_s} - \rho^{-\alpha_t} \right\|_{H^\gamma} d\rho
\]

\[
\leq \frac{1}{\pi} \int_0^\infty \rho^{-\alpha_t} \left\| \alpha_t - \alpha_s \right\|_{L^\infty} \left\| (\rho + A)^{-1} u \right\|_{H^\gamma} d\rho
\]

\[
+ \int_0^\infty \ln(\rho) \rho^{-\alpha_s} \left\| \alpha_t - \alpha_s \right\|_{L^\infty} \left\| (\rho + A)^{-1} u \right\|_{H^\gamma} d\rho
\]

\[
\leq \frac{1}{\pi} \int_0^\infty \rho^{-\alpha_t} \left\| \alpha_t - \alpha_s \right\|_{L^\infty} \left\| (\rho + A)^{-1} u \right\|_{H^\gamma} d\rho
\]

\[
\leq \int_0^\infty \ln(\rho) \rho^{-\alpha} \left\| \alpha_t - \alpha_s \right\|_{L^\infty} \left\| (\rho + A)^{-1} u \right\|_{H^\gamma} d\rho
\]

\[
\leq \int_0^\infty \ln(\rho) \rho^{-\alpha} \left\| \alpha_t - \alpha_s \right\|_{L^\infty} \left\| (\rho + A)^{-1} u \right\|_{H^\gamma} d\rho
\]
This implies that

$$\|(A_t^{-1} - (-A_s)^{-1})u\|_{H^\alpha} \leq 2\pi \|\alpha_t - \alpha_s\|_{H^2} \int_0^\infty (\rho^{-\eta} + |\ln(\rho)|\rho^{-\eta})((\rho + A)^{-1}u)\|_{H^\alpha} d\rho$$

$$\leq 2\pi \left( \int_0^\infty \frac{2\rho^{-\eta}}{(1 + \rho)} d\rho + \int_1^\infty \frac{\ln(\rho)\rho^{-\eta}}{(1 + \rho)} d\rho + \int_1^\infty \frac{\ln(\rho)\rho^{-\eta}}{(1 + \rho)} d\rho \right) \|\alpha_t - \alpha_s\|_{H^2} \|u\|_{L^2}$$

$$\leq 2\pi \left( \int_1^\infty 2\rho^{(1-\eta)-1}(1-\rho)^{1-1} d\rho + \int_1^\infty 2\rho^{-\eta-1} d\rho + \int_0^1 \frac{ze^{(1-\eta)z}}{1 + e^z} dz + \int_0^\infty \frac{ze^{(1-\eta)z}}{1 + e^z} dz \right) \|\alpha_t - \alpha_s\|_{H^2} \|u\|_{L^2}$$

This further implies that

$$\|(A_t^{-1} - (-A_s)^{-1})u\|_{H^\alpha} \leq 2\pi \left( \beta(1-\eta,1) + \frac{2}{\eta} + \int_0^\infty \frac{-ze^{-(1-\eta)z}}{1 + e^z} dz + \int_0^\infty \frac{ze^{(1-\eta)z}}{1 + e^z} dz \right)$$

$$\|\alpha_t - \alpha_s\|_{H^2} \|u\|_{L^2}$$

$$\leq 2\pi \left( \beta(1-\eta,1) + \frac{2}{\delta} + \int_0^\infty \frac{ze^{-(1-\eta)z}}{1 + e^z} dz + \int_0^\infty \frac{ze^{(1-\eta)z}}{1 + e^z} dz \right) \|\alpha_t - \alpha_s\|_{H^2} \|u\|_{L^2}$$

$$\leq 2\pi \left( \beta(1-\eta,1) + \frac{2}{\delta} + \int_0^\infty \frac{ze^{-(1-\eta)z}}{1 + e^z} dz + \int_0^\infty \frac{ze^{(1-\eta)z}}{1 + e^z} dz \right) \|\alpha_t - \alpha_s\|_{H^2} \|u\|_{L^2}$$

$$\leq 2\pi \left( \beta(1-\eta,1) + \frac{2}{\delta} + \frac{1}{(1-\eta)^2} + \frac{1}{\eta^2} \right) \|\alpha_t - \alpha_s\|_{H^2} \|u\|_{L^2}$$

$$\leq k(\eta, \delta) \|\alpha_t - \alpha_s\|_{H^2} \|u\|_{L^2}.$$

Lemma 4.4. Let $H \in C^\mu([0,T]; H^2(\mathbb{R}^d))$ and $\alpha_t$ as defined in (50). Then we get that

$$\|(A_t^{-1} - (-A_s)^{-1})u\|_{L^2(\mathbb{R}^d)} \leq k|t-s|^{\mu} \|u\|_{L^2(\mathbb{R}^d)}$$

(53)

Proof. Because $A_t^{-1}$ maps $D(A^\gamma)$ into $L^2(\mathbb{R}^d)$ and $D(A_t^{-1} - (-A_s)^{-1}) \subset D(A^\gamma)$ for all $t \in [0,T]$, we are only left to show that $\|\alpha_t - \alpha_s\|_{H^2(\mathbb{R}^d)}$ is H"older continuous, uniformly with respect to $t$ and $s$. This follows easily due to (50) and $H \in C^\mu([0,T]; H^2(\mathbb{R}^d))$, as shown below

$$\|\alpha_t - \alpha_s\|_{H^\alpha} \leq k\left| \frac{H_t - H_s}{(1 + aH_t)(1 + aH_s)} \right|$$

$$\leq k\|H_t - H_s\|_{H^\alpha}$$

$$\leq k\|H_t - H_s\|_{H^2}$$

$$\leq k|t-s|^{\mu}, \ \text{since} \ H \in C^\mu([0,T]; H^2(\mathbb{R}^d)).$$

Thus due to (51) and (52) we get the required result.

Thus we have verified that $A_t$ and $A$ satisfy Assumption (1) and consequently generate the corresponding semigroup. Thus for sufficiently regular data, following the lines of (52), one can prove the local existence of a mild solution to (49).

Properties of the coefficient functions $g, f, h$

1. $g \in C^2(\mathbb{R} \times \mathbb{R}; \mathbb{R})$. There exist constants $m_g, M_g > 0$ such that $m_g \leq g + g' + g'' \leq M_g$.  

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2. \( f \in C^2(\mathbb{R} \times \mathbb{R}; \mathbb{R}) \). There exist constants \( m_f, M_f > 0 \) such that \( m_f \leq f + f' + f'' \leq M_f \).

3. \( h \in C^2(\mathbb{R} \times \mathbb{R}; \mathbb{R}) \). There exist constants \( m_h, M_h > 0 \) such that \( m_h \leq h + h' + h'' \leq M_h \).

4. \( g, f, h \) such that \( C, H \) and \( N \) are in \( L^2(\mathcal{D}) \) and \( \nabla C, \nabla N \) and \( \nabla H \) are in \( L^4(\mathcal{D}) \).

5. \( N \in H^2_D, p \geq \frac{12}{5} \).

6. \( R_1, R_2 \) and \( R_3 \) are of sub-polynomial growth.

### 4.3 Numerical simulations

In this section we perform numerical simulations for the proposed model \([49]\). We assume periodic boundary conditions and restrict ourselves to the finite 2D domain \( \mathcal{D} \). Let \( L^2_p(\mathcal{D}) \) denote the subspace of \( L^2 \) functions on \( \mathcal{D} \) that are not constants and are even. We let \( \mathcal{D} := [a_1, b_1] \times [a_2, b_2] \); \( a_1 < b_1, a_2 < b_2 \); \( a_1, a_2, b_1, b_2 \in \mathbb{R} \). Let \( M_x, M_y \) be the number of partitions of the \( x \)-axis and the \( y \)-axis of \( \mathcal{D} \). Thus we have \( \delta_x := \frac{b_1-a_1}{M_x}, \delta_y := \frac{b_2-a_2}{M_y} \).

The spatial grid points at which the solution to our problem will be computed are represented as \( (\sqrt{\frac{2}{L_x}} \cos \left( \frac{2 \pi n x}{L_x} \right))_{n \in \mathbb{N}} \) and \( (\sqrt{\frac{2}{L_y}} \cos \left( \frac{2 \pi m y}{L_y} \right))_{m \in \mathbb{N}} \) be the ONB of \( L^2_p([a_1, b_1]) \) and \( L^2_p([a_2, b_2]) \), respectively. Now if we let \( \lambda_k = \frac{1}{(1+k^2)^{1/2}} \) for \( k \in \{m, n\} \) with \( m, n \in \mathbb{N} \). Then by Proposition 2.1.6 and Proposition 2.1.10 of \([43]\), the Q-Wiener process on \( L^2_p([a_1, b_1]) \) and \( L^2_p([a_2, b_2]) \) can be represented as

\[
\begin{align*}
w_1(x) &= \sum_{n=1}^{\infty} \xi_n(t) \lambda_n e_n(x) \\
w_1(y) &= \sum_{m=1}^{\infty} \xi_m(t) \lambda_m e_m(y),
\end{align*}
\]

where \( (\xi_k)_{k \in \mathbb{N}} \) for \( k = m \) or \( k = n \) is an sequence of independent real valued Brownian motions. Since \( L^2_p([a_1, b_1] \times [a_2, b_2]) \) is isomorphic to \( L^2_p([a_1, b_1]) \times L^2_p([a_2, b_2]) \), we get that

\[
W_t(x, y) = \sum_{m,n=1}^{\infty} \xi_{m,n}(t) \lambda_{m,n} e_n(x) \otimes e_m(y)
\]

which, for \( \lambda_{m,n} = \lambda_m \lambda_n \), is equivalent (in the distributional sense) to \( w_1(x) \times w_1(y) \), i.e.

\[
W_t(x, y) \overset{\text{Law}}{=} w_1(x) \times w_1(y) = \sum_{n=1}^{\infty} \xi_n(t) \lambda_n e_n(x) \times \sum_{m=1}^{\infty} \xi_m(t) \lambda_m e_m(y).
\]
Thus the increments of the $Q$-Wiener process are given as

$$dW_t(x, y) = \sum_{m,n=1}^{\infty} d\xi_{m,n}(t)\lambda_{m,n} e_n(x) \otimes e_m(y).$$

Letting $W^n_{k,j} = W_{t_n}(x_k, y_j)$ we get the following discretization

$$dW^n_{k,j} = dW_{k,j} = \sum_{m,n=1}^{\infty} \sqrt{T} z_{m,n} \lambda_{m,n} e_n(x_k) \otimes e_m(y_j),$$

(54)

where $(z_{m,n})_{m,n\in\mathbb{N}}$ is a sequence of independent random variables having standard Gaussian distribution.

### 4.3.2 Simulating the fractional Laplacian

For numerical simulation, we use the singular representation of $(-\Delta)^{\frac{\alpha}{2}}$ for $\alpha \in (0, 2)$, which, based on (43), is given as

$$I f(x) = (-\Delta)^{\frac{\alpha}{2}} f(x) = \lim_{\varepsilon \to 0^+} \frac{-2^\alpha \Gamma(\frac{\alpha+2}{2})}{\pi^{\frac{\alpha}{2}} |\cdot|^{\frac{\alpha+2}{2}}} \int_{|x|/\varepsilon \leq |y|} \int_{B(x, r)} f(z) - f(x) \frac{\sqrt{T} z_{m,n} \lambda_{m,n} e_n(x_k) \otimes e_m(y_j)}{|z|^{\alpha+2}} dz$$

(55)

Letting

$$c_{d,\alpha} := \frac{-2^\alpha \Gamma(\frac{\alpha+2}{2})}{\pi^{\frac{\alpha}{2}} |\cdot|^{\frac{\alpha+2}{2}}} \frac{\alpha^{\alpha-1} \Gamma(\frac{\alpha+2}{2})}{\pi^{\frac{\alpha}{2}} |\cdot|^{\frac{\alpha+2}{2}}}$$

and $h < 1$, following [27], the integral $I$ in (55) can be split into the singular part and the tail part as follows:

$$I_s f(x) = c_{d,\alpha} \int_{|y| \leq h} \frac{f(x) - f(x-y)}{|x-y|^{\alpha+2}} dy$$

(56)

$$I_t f(x) = c_{d,\alpha} \int_{|y| \geq h} \frac{f(x) - f(x-y)}{|x-y|^{\alpha+2}} dy.$$  

(57)

The singular integral (56) is implemented using the finite difference scheme described in [27], which for $d = 1$ is given as

$$I_s^h f(x_k) = -\frac{c_{1,\alpha}}{(2-\alpha)} \left[ f(x_{k+1}) - 2f(x_k) + f(x_{k-1}) \right] + O(\delta_k^{1-\alpha}).$$

(58)

The tail integral (57) is implemented using a simple quadrature rule, which for $d = 1$ is as follows:

$$I_t^h f(x_k) = c_{1,\alpha} \sum_{i=1}^{N} \frac{f(x_i) - f(x_{i+1})}{(ih)^\alpha}, \quad \text{for } N < \infty \text{ large enough.}$$

(59)

Based on this we have the following discretization scheme for the system (49).

### 4.3.3 Discretization scheme

For the normal cell density equation (49c), we use the following straightforward discretization:

$$N_{k,j}^{n+1} = N_{k,j}^n + \tau R_3(C_{k,j}^n, H_{k,j}^n),$$

where, $N_{k,j}^{n+1} := N_{t_{n+1}}(x_k, y_j), C_{k,j}^{n+1} := C_{t_{n+1}}(x_k, y_j)$, $H_{k,j}^{n+1} := H_{t_{n+1}}(x_k, y_j)$ and $R_3(C_{k,j}^n, H_{k,j}^n) = \gamma_3(C_{k,j}^n + H_{k,j}^n) N_{k,j}^n$. 

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For discretizing the proton equation \([49a]\) we use an implicit finite difference scheme for the advection and diffusion terms, while an explicit scheme is employed for the reaction term. The noise term is discretized using \([54]\). After letting

\[
R_{1,k,j}^n := \gamma_1 H_{k,j}^n (1 - H_{k,j}^n), \quad f_{k,j} := \frac{C_{k,j}}{\tau + C_{k,j}}
\]

we get

\[
H_{k,j}^{n+1} = H_{k,j}^n + \frac{\tau R_{1,k,j}^n + H_{k,j}^n dW_{k,j}}{\delta_x^2 (H_{k-1,j}^{n+1} + H_{k+1,j}^{n+1} - 2H_{k,j}^{n+1})} + \frac{\tau \sigma H_{k,j}^{n+1} + H_{k,j+1}^{n+1} - 2H_{k,j}^{n+1}}{\delta_y^2 (H_{k,j}^{n+1} + H_{k,j+1}^{n+1} - 2H_{k,j}^{n+1})}
\]

\[
\gamma_f \frac{\tau}{\delta_x^2} [R_{1,k,j}^n (H_{k,j+1}^{n+1} - H_{k,j-1}^{n+1})(C_{k,j+1}^{n+1} - C_{k,j-1}^{n+1})]
\]

\[
\gamma_f \frac{\tau}{\delta_y^2} [R_{1,k,j}^n (H_{k,j+1}^{n+1} - H_{k,j-1}^{n+1})(C_{k,j+1}^{n+1} - C_{k,j-1}^{n+1})]
\]

For the cancer cell population dynamics equation \([49b]\) we use \([58]\) and \([59]\) to discretize the fractional Laplacian implicitly, while the taxis terms and the reaction term are discretized explicitly. Altogether, after letting

\[
R_{2,k,j}^{n+1} := \gamma_2 C_{k,j}^n (1 - C_{k,j}^n), \quad g_{1,k,j}^{n+1} := \gamma_g \frac{N_{k,j}^{n+1} C_{k,j}^n}{1 + (C_{k,j}^n + N_{k,j}^n)^2}, \quad h_{2,k,j}^{n+1} := \gamma_h \frac{H_{k,j}^{n+1} C_{k,j}^n}{1 + (C_{k,j}^n + H_{k,j}^n)^2}
\]

we get

\[
C_{k,j}^{n+1} = C_{k,j}^n + \frac{\tau R_{2,k,j}^{n+1} + H_{k,j}^n dW_{k,j}}{(2 - \alpha)\delta_x^2} (C_{k-1,j}^{n+1} + C_{k+1,j}^{n+1} - 2C_{k,j}^{n+1}) + \frac{\tau \sigma C_{k,j}^{n+1}}{(2 - \alpha)\delta_y^2} (C_{k,j-1}^{n+1} + C_{k,j+1}^{n+1} - 2C_{k,j}^{n+1})
\]

\[
\gamma_f \frac{\tau}{\delta_x^2} [(g_{1,k,j-1}^{n+1} + g_{1,k,j+1}^{n+1})(H_{k,j}^{n+1} - H_{k,j}^n)]
\]

\[
\gamma_f \frac{\tau}{\delta_y^2} [(g_{1,k,j-1}^{n+1} + g_{1,k,j+1}^{n+1})(H_{k,j}^{n+1} - H_{k,j}^n)]
\]

\[
\gamma_f \frac{\tau}{\delta_x^2} [(h_{2,k,j}^{n+1} - h_{2,k,j}) (N_{k,j}^{n+1} - N_{k,j}^n) + (h_{2,k,j+1} + h_{2,k,j})(N_{k,j+1}^n - N_{k,j}^n)]
\]

\[
\gamma_f \frac{\tau}{\delta_y^2} [(h_{2,k,j}^{n+1} - h_{2,k,j}) (N_{k,j}^{n+1} - N_{k,j}^n) + (h_{2,k,j+1} + h_{2,k,j})(N_{k,j+1}^n - N_{k,j}^n)]
\]

### 4.3.4 Numerical simulation of the system \([49]\)

In this section we provide the results obtained from the above numerical discretization scheme. In order to highlight the effectiveness of the model we illustrate the simulations just for the 2D case.

| Phenomenological relevance | Numerical parameters |
|---------------------------|----------------------|
| N | # time steps | 150 |
| M | # Monte Carlo simulations | 500 |
| \(\tau\) | temporal step size | .1 |
| \(h_{x1}\) | spatial step size along \(x_1\) | .1 |
| \(h_{x2}\) | spatial step size along \(x_2\) | .1 |
| \(N_{x1}\) | grid resolution along \(x_1\) | 21 |
| \(N_{x2}\) | grid resolution along \(x_2\) | 21 |

Figure 12 depicts the time snapshots of solution to a simple standalone fractional and standard diffusion equation with periodic boundary conditions. For the fraction diffusion equation, the fraction \(\alpha\) is set to value 0.75. Both the
Table 2: Model parameters

| Phenomenological relevance | Growth and decay parameters $\Xi_R$ |
|----------------------------|-------------------------------------|
| $\gamma_1$                 | growth rate for cancer cells        |
| $\gamma_2$                 | growth rate for proton index value  |
| $\gamma_3$                 | decay rate of normal cells          |
| $\sigma_W$                 | intensity of noise for the proton index |

| Phenomenological relevance | Migration parameters $\Xi_M$ |
|----------------------------|-----------------------------|
| $\sigma_H$                 | diffusion coefficient for the proton index |
| $\gamma_C$                 | diffusion coefficient for cancer cells |
| $\gamma_g$                 | speed of cell movement due to hapto-taxis |
| $\gamma_h$                 | speed of cell movement due to chemo-taxis |
| $\gamma_f$                 | speed of advection for the proton index |

Figure 12: Time snapshots of solutions to a fractional diffusion and a standard diffusion equation. The blue curve with dots represents the solution to the fractional diffusion equation, while the green curve with bars represents the solution to the standard diffusion equation.

Equations have the same initial condition and same diffusion coefficient of 0.025. Based on the figure we see that the speed of the spread is much lower for the fractional diffusion, for the same diffusion coefficient. Thus for a crowded environment, such as cancerous tissue, it makes more sense to use a fractional diffusion operator. Following this we now proceed with the simulation of the stochastic fractional diffusion model (49). The numerically obtained results are shown in Figures 13-17. They depict 5 different sample solutions, randomly chosen from a set of 500 sample solutions. The numerical and model parameters chosen for the simulations are given in Table 1 and Table 2 respectively. Each of the figures consist of 2D-plots representing snapshots at four different time points. Each 2D-plot depicts the concentration distribution of $H$, $C$, and $N$ overlayed on each other. The concentration distribution of $N$ is displayed as a shaded contour plot which is seen as a patchy layer on the background. The concentration distributions of $H$ and $C$ are represented as contour lines, where the former is represented by thin lines while the latter is represented as thick lines. The color bars on the right side of each plot show the values of the respective contour levels. The leftmost color bar indicates the contour levels of $N$, while the rightmost color bar indicates the contour levels of $H$. The center color bar indicates the contour levels of $C$. Based on these figures we
Figure 13: Time snapshots of the sample solution number 10.

Figure 14: Time snapshots of the sample solution number 77.
Figure 15: Time snapshots of the sample solution number 328.

Figure 16: Time snapshots of the sample solution number 427.
Figure 17: Time snapshots of the sample solution number 456.

Figure 18: Time snapshots of the numerical expectation.
observe the following:

1. Starting from a deterministic initial condition, we obtain various different patterns for the spread of cancer. These invasion patterns share the following similarities:

   1a. In all sample paths, the majority of the tumor mass has the tendency to spread to the upper half of the tissue. This can be confirmed by observing the expected behavior of the sample solutions (as shown in Figure 18). This behavior is due to the haptotaxis term which has a negative velocity, meaning that the cancer tends to move away from high density regions of the tissue. The initial condition is chosen such that the upper part of the central region of the tissue is relatively less dense compared to that of the lower part of the central region of the tissue.

   1b. A second factor that influences the direction of the invasion is the value of the proton index $H$. Recall that in our model (i.e. (49)) $H$ represents the ratio of extracellular and intracellular proton concentration, which provides a measure for the RpHG of the cell. Since a higher value of the latter promotes cell movement, this feature is captured by the pH taxis term and serves as the primary source of direction for the movement of cells. The advection term in the $H$ equation facilitates propagation of the RpHG along the tumor edge i.e. away from the dense core and towards the periphery of the tumor. Thus the advection term in (49a) and the pH-taxis term in (49b) together form a positive feedback which pushes the cancer wave.

   1c. In the regions of relatively low or negligible proton index value, the spread of cancer is mainly governed by haptotaxis, fractional diffusion, and proliferation.

2. Apart from the above similarities, the stochasticity of the model induces the following interesting patterns:

   2a. In Figure 14 and Figure 16 we observe that at time $t = 49$, at the lower left part of the tumor core, there is an island-like patch being formed, which is not seen in the expectation plot (Figure 18), hence indicates that this is a rare event.

   2b. More interestingly, in Figure 13 and Figure 14 for time $t = 25.0$, we observe that the tumor has an opening on its lower side. However, looking at the expectation plot at time $t = 25$ we see that the opening is not present. From this we can infer that this is a rare event, as well.

Altogether we get a diverse spread of cancer, in the sense that the invasion pattern is irregular, on the one hand due to the less regular fractional operator and on the other hand due to the randomness of the model and the heterogeneity of the tissue.

5 Summary

In this article we have looked at the problem of modeling diversity in complex living systems, such as cancer, from a very fundamental level. We began with motivation from evolutionary biology which provided an intuitive motivation to interpret cancer as a selfish organism. Based on a novel axiomatic formulation of a very generic living system we highlighted the fundamental reason for living systems to diversify. We further justified this reasoning and demonstrated using an illustrative example (see Figures 6a and 6b) that a diversifying living system has better chances of survival compared to non-diversifying systems. This is evident in competitive games such as football, cricket, volleyball, handball, etc. wherein a team having a set of diverse players has a better chance of winning the game. To be more precise a team having only right handed (legged) players has lower chances of winning when competing against a team that has good a mix of both right and left handed (legged) players. For a more biological example one can consider the cases of diseases and epidemics. It is clear that a population with diversified immune systems has better chances of surviving epidemic breakouts compared to a population having identical immune systems for all individuals.

Motivated by these observations and having considered cancer as a selfish organism that is playing a game of survival against the host, we posed the question: how can one model diverse behavior of an organism as observed at the macroscopic scale starting from the microscopic level? This question was answered by Theorem 3.10 in Section 3.3 where we used a functional analytic machinery (see Figure 7) to introduce a framework through which one is able to construct random equations at the macroscopic level. It should be noted here that the equation thus obtained at the macroscopic level is a random abstract Cauchy equation. As a result, in general, the obtained macroscopic equation need not have pointwise evaluation and even worse the operator need not have an explicit computable representation.

This is one of the drawbacks of the approach and requires further investigation in order to make it more practical. Nonetheless, it is suitable for applications that involve periodic solutions at the macroscopic level, where one can solve the Cauchy equation in Schwartz space (i.e. on Fourier domain) via Fourier transform.

For the deduced abstract random Cauchy equation, we formulated Theorem 3.10 which was able to establish the
existence of a unique solution which enabled us to go ahead with numerical simulations. Nonetheless, we believe that the current approach for proving the existence of unique solution is not the most elegant approach. An alternative approach would be to either introduce an appropriate norm ∥·∥_N on the set of continuous negative definite functions N such that (N, ∥·∥_N) is a Banach space or to introduce a metric on the set N so that the notion of continuity on between the elements of N could be established. Then the task would be to find a closed subspace M ⊂ N which can generate sectorial operators. Once the existence of such a subspace M is established, then the task of constructing random operators would involve specifying an appropriate M valued stochastic process.

In Section 4.3 we provided simulations for the dynamics of cancer-invasion at two different levels namely the microscopic and macroscopic levels. In the microscopic simulations we modeled the intrinsic diversification signal by means of switching distribution of the noise term which consequentially conferred better odds for survival for cancer cells. This also provided the motivation for a direct macroscopic simulation where in the random fractional diffusion operator was used to model diverse invasive behavior of cancer cells. Since the micro to macro modeling framework is bidirectional, one has the flexibility to either start at the macro or the micro level. Starting at a macroscopic equation one could in principle deduce the stochastic process acting at the microscopic level, by making use of potential theory and the theory of Dirichlet forms [34]. Altogether the framework addresses the fundamental problem of diversification of living systems and introduces some new challenging mathematical problems.
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