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ABSTRACT

Stochastic diffusion processes with jumps for cancer growth and neuronal activity models

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Abstract

In the last decades, great attention has been paid to the description of biological, physical and engineering systems subject to various types of jumps. A jump, or catastrophe, is considered as a random event that shifts the state of an evolutionary process in a certain level from which the process can restart. A catastrophe can represent the extinction or reduction of elements in a biological population (due to virus infection or external agent) or of customers in a queue system (due to power failure, reset or system bug).
In literature, some results have been obtained for continuous-time Markov chains and stochastic diffusion processes subject to catastrophes occurring at exponential rate.
In this thesis we propose to study further evolutionary processes subject to jumps and we consider various applications of interest in different areas.
In particular, we introduce the effect of jumps in:

- deterministic models for rumor spreading,
- time non-homogeneous Markov chains,
- stochastic diffusion processes with particular attention to the Gompertz model for cancer evolution and to the non-homogeneous Ornstein-Uhlenbeck process for neuronal activity.

Specifically, we analyze firstly rumor spreading mechanisms, during which one can consider the effect of an external entity that denies the rumor so that the process is reset to the initial state consisting in a unique spreader that renews the spreading process. This study is provided in the subsection of the Introduction *Rumor spreading with denials*.

The denials, or jumps, are random and they occur according to a Poisson process with parameter ξ. Two rumor spreading models with denials are studied. In both models the population is divided into three groups: the spreaders (who know and transmit the rumor), the ignorants (who do not know the rumor) and the stiflers (who know the rumor but do not transmit it). The rumor spreads through pair-wise contacts, occurring with rate λ, between spreaders and the other people.

We consider a model A based on the well-known DK where denials are introduced and we study an alternative model, model B, in which denials occur and each spreader can transmit the rumor at most k times. For both models, we write the system of ordinary differential equations describing the rumor spreading mechanism and we study its steady state solution focusing on the asymptotic percentage of ignorants to identify the density of the population that knows the rumor. A scrutinized numerical analysis is performed to study the effect of denials on varying parameters and to compare the proposed models.

We note that, in both cases the asymptotic percentage of ignorants increases when the rate of the denials grows respect to the rate of the contacts; in particular, if the size of the population is large and $\xi \geq \lambda$, the rumor does not spread at all.

For the model B, the density of individuals that knows the rumor increase with k, since the rumor has more chance to spread. Moreover, the model B behaves like the model A when k increases, in particular a good match is found already for $k = 6$. Finally, in both models we obtain that at most the half of the population can be informed about the rumor.

Concerning the time non-homogeneous Markov chains, we consider a queueing system subject to catastrophes which occur at random times and that empty instantaneously the system reducing to zero the number of customers. This study is shown in the subsection of the Introduction *Time non-homogeneous adaptive queue with catastrophes.*

Catastrophes occur according to a time non-homogeneous Poisson process; in particular, the catastrophe's rates depend on time and on the number of

customers in the queue.
We analyze the system by studying the transition probabilities and the moments of the number of customers in the system. We focus on the problem of the first visit time (FVT) to zero state with particular attention to busy period of the service center, i.e the time interval during which at least one server is busy. Specifically, we pay attention to the case in which the catastrophe intensity is a periodic function of time obtaining some properties of asymptotic distribution and of the FVT density. We study the $M/M/1$ queueing systems to perform an example of the obtained results.

After a brief study of deterministic models and of Markov chains subject to jumps, the thesis is focused especially on stochastic diffusion processes with jumps. In Chapter 1, *Stochastic diffusion processes with random jumps*, we construct diffusion processes with jumps by supposing that catastrophes occur at time interval following a general distribution and the return points are randomly chosen. Moreover, we consider the possibility that, after each jump, the process can evolve with a different dynamics respect to the previous processes; we also suppose that the inter-jump intervals and the return points are not identically distributed. For this type of process, we analyze the probability density function (pdf), its moments and the first passage time (FPT) problem. We also study the Wiener process with jumps, as example. In the remaining chapters of the thesis, we focus on the effect of jumps in stochastic diffusion processes of interest in neurobiology.

In Chapter 2, *A Gompertz model with jumps for an intermittent treatment in cancer growth*, we construct a Gompertz process with jumps to analyze the effect of a therapeutic program that provides intermittent suppression of cancer cells. In this context, a jump represents an application of the therapy. Firstly, we consider a simple model in which the Gompertz process has the same characteristics between two consecutive jumps, the return points and the inter-jump intervals are independent and identically distributed. For this model, we study the transition pdf, the average state of the system (representing the mean size of the tumor) and the number of therapeutic applications to be carried out in time intervals of fixed amplitude. We consider the degenerate and the exponential distribution for the inter-jump intervals and we study three different distributions of the return point (degenerate, uniform and bi-exponential). We note that the obtained results for different distribution are comparable, so, in the following studies, we consider only the degenerate.

After this first step, we construct a more realistic model. Specifically, we assume: the therapeutic program has a deterministic scheduling, so that jumps occur at fixed and conveniently chosen time instants; the return points are deterministic; therapeutic treatments weaken an ill organism and when a therapy is applied there is a selection event in which only the most aggressive clones survive (for example this perspective could be applied to targeted drugs that have a much lower toxicity for the patient).

Taking into consideration these aspects, we construct the deterministic and stochastic processes with jumps.

Since each therapeutic application involves a reduction of the tumor mass, but it also implies an increase of the growth speed, the problem of finding a compromise between these two aspects raises. Two possible scheduling are proposed in order to control the cancer growth.

In the first scheduling, we assume that inter-jump intervals have equal size. We also suppose that the return points are all equal after each jump. In this case, we obtain interesting properties which allow to choose the most appropriate application times, when the toxicity of the drug is fixed.

In the second scheduling, we suggest to apply the therapy just before the cancer mass reaches a fixed control threshold S. To this aim, we study the FPT problem through S and we provide information on how to choose the application times so that the cancer size remains bounded during the treatment. The goodness of the obtained results is measured via the increase of the mean FPT of the process through S. The performed analysis shows that better results are obtained when the therapy is applied as later as possible, for higher control thresholds and smaller weakening rates.

Moreover, we compare the deterministic and stochastic approaches noting that, for both scheduling, the mean FPT through S increases as the ampli-

tude of random fluctuations increases.
We also provide a comparison between the two proposed scheduling and we conclude that the second strategy is the best, i.e. it is preferable to apply the therapy just before the cancer mass crosses the control threshold.

In Chapter 3, *Return process with refractoriness for a non-homogeneous Ornstein-Uhlenbeck neuronal model*, we consider a diffusion stochastic process with jumps for the neuronal activity.
To describe the input-output behavior of a single neuron subject to a diffusion-like dynamics, we model the neuronal membrane potential via the Ornstein-Uhlenbeck (OU) diffusion process. We assume that inputs, while remaining a constant amplitude, are characterized by time-dependent rates. In particular, we consider an OU process characterized by a time-dependent drift in which appears a periodic function $m(t)$ representing some oscillatory effects of the environment acting on the neuron.
To describe a neuronal train spike, a return process is constructed on such time non-homogeneous OU process as follows. Starting from the value representing the resting potential, the neuronal membrane potential follows the non-homogeneous OU process as long as a threshold (the action threshold) is reached for the first time. In correspondence to the reaching of this peak, a neuronal spike occurs resetting the process to the resting potential. Then, the membrane potential evolves as before until the threshold is reached again causing another neuronal spike, and so on.
In order to study the interspike intervals (ISI) distribution, we analyze the FPT random variable of the non-homogeneous OU process because it represents the theoretical counterpart of the neuronal firing time, so that the FPT's pdf describes the pdf of the firing time. In this regard, we make use of an asymptotic behavior of exponential type for the FPT pdf .
Concerning this return process, we study the ISI distribution and the number of firings occurring until a fixed time.
Moreover, we take into account the effect of the refractoriness on the model. A refractory period is a time interval following each spike and during which the neuron is completely or partially unable to respond to stimuli. Hence,

we introduce random downtimes which delay spikes, simulating the effect of refractoriness. We provide the expression of the ISI distribution also for the process with refractoriness. This distribution is conditioned by the time in which the last fire occurs.
A theoretical and numerical analysis of the return process in the presence of constant and exponential refractoriness is performed.
Some similarities between the ISI pdf with refractoriness and without refractoriness are observed. In particular, our analysis shows that the ISI pdf in the presence of refractoriness is shifted respect to the ISI pdf in the absence of refractoriness, provided the latter is suitably conditioned. This observation supports the proposed model.

The thesis ends with conclusions on the obtained results and with some possible future developments.