

PREFACE

Preface: new trends in first-passage methods and applications in the life sciences and engineering

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Preface



Preface: new trends in first-passage methods and applications in the life sciences and engineering

When does a virus infecting a biological cell reach its nucleus, or how long does it take for an epidemic to spread to your town? When does your preferred stock asset cross a threshold price above which you decide to sell it? When will a gambler or an insurance company be ruined? Or finally, when will the next earthquake have a dangerously high magnitude? These and many other questions from science as well as our everyday life can be addressed within the concept of the *first-passage time* (FPT), also known as first-hitting time, first-crossing time, first-encounter time, first-exit time, and so on, depending on the precise context. In mathematical terms, we typically represent the above dynamics by a stochastic process X_t . That is, for lack of more detailed knowledge we view the stock price, the distance to the cell nucleus, the earthquake magnitude, etc, as randomly evolving with time. The first-passage time τ is then the first moment when X_t exceeds a prescribed level x : $\tau = \inf\{t > 0 : X_t > x\}$. Due to the stochastic nature of X_t , the FPT is a random variable itself: one cannot predict precisely the date of the next market crash, but we can introduce a likelihood that the first-passage event does not occur until the end of a given time interval. This likelihood is given by the *survival probability* $S(t) = \Pr\{\tau > t\}$ that the first-passage event has not occurred up to time t . Relations between specific stochastic processes and their first-passage properties have been studied extensively over the last century, with applications in practically all disciplines, including mathematics, physics, chemistry, biology, epidemiology, ecology, geo-sciences, economics, and finances, to name but a few [1–13].

The first systematic derivation of the survival probability is attributed to Smoluchowski, who studied the first-encounter of two diffusing spherical particles [14]. In his solution of the diffusion equation, we recognise the survival probability,

$$S(t) = 1 - \frac{R}{r} \operatorname{erfc} \left(\frac{r - R}{\sqrt{4Dt}} \right), \quad (1)$$

where D is the sum of the diffusion coefficients of the two particles, R is the sum of particle radii, r is the initial distance between two particles, and $\operatorname{erfc}(z)$ is the complementary error function. More generally, for a stochastic process governed by an elliptic second-order differential operator, the survival probability satisfies the associated backward Kolmogorov or Fokker–Planck equation [12, 13]. Explicit closed-form solutions such as equation (1) are, however, quite rare. In favourable cases, the survival probability can be written as a spectral expansion over eigenfunctions of the governing operator which are known explicitly only for a limited number of relatively simple settings. For this reason, most studies focus on the asymptotic properties [15], such as the Sparre-Andersen theorem for Markovian processes with symmetric jump length distributions [16], escape from potential wells in chemical kinetics [17–20], short-time heat kernel expansions [21–24], or Molchan’s result for the long-time tail of the first-passage density of a semi-infinite fractional Brownian motion [25]. Another quantity typically studied is the *mean* (or even the global mean) first-passage time (MFPT) and

its inverse, the reaction rate constant. These are much easier to analyse and provide important information on the system's first-passage properties. Curiously, in Smoluchowski's problem of the diffusive particle encounter, the mean first-encounter time, as well as higher order moments, are infinite. This basic example illustrates that moments of the first-passage dynamics are not always informative.

Considerable progress has also been achieved over two past decades in the analysis of a related process, the so-called narrow escape problem. This scenario pictures a particle diffusing in an Euclidean domain (or on a manifold) and searches for a small escape window on the domain boundary [26, 27]. In chemical physics this problem is equivalent to searching for a reactive patch (target) on the otherwise reflecting (inert) surface. For instance, a particle may diffusively attempt to locate a small channel in a porous medium, to move to the next pore, or a protein could search for a specific receptor on the inside of the plasma membrane of a biological cell. In particular, the asymptotic behaviour of the MFPT to a single or multiple windows or targets was thoroughly investigated [28–35]. One of the interesting recent steps in the understanding of the narrow escape problem is that the escape through such an escape window may be barrier-controlled rather than diffusion-controlled [36–38].

The literature of first-passage phenomena is immense. Thus a Web of Science search for 'first-passage or first-hitting or first-arrival' reveals more than 7000 hits. Nevertheless, our understanding of first-passage dynamics remains incomplete. As said earlier, most former studies we devoted to the MFPT, to some extent suggesting that the MFPT were the only relevant characteristic of the associated first-passage process. While this is indeed true in some cases, especially if one is only interested in the long-time description and for macroscopic chemical concentrations. However, recent works showed that the distribution of the FPT can become very broad and involves different characteristic time scales. For instance, the most probable FPT is many orders of magnitude smaller than the mean value in generic geometries [39–44], compare the example shown in figure 1. Relying only on the mean FPT, one can therefore strongly over-estimate the relevant timescales of search processes, chemical reactions, or biological events. Similarly, one may miss out on the crucial role of the initial distance between the diffusing particle and its target that is of relevance, for instance, in the context of gene regulation [45–47]. The decisive role of the partial reactivity of a target, especially for biochemical reactions, was put forward by Collins and Kimball in 1949 [48], but it still remains largely under-estimated [36, 49]. A finite lifetime of diffusing particles (so-called 'mortal walkers', for instance, bacterial messenger RNA has a typical lifetime of few minutes) also reshapes the distribution of the first-passage times [50–53]. The broad ('defocused') distribution of first-passage times then also implies that two realisations of the process typically result in two very different first-passage times [54, 55]. Moreover, the geometric complexity of confinement such as hierarchical or fractal-like porous media, molecular crowding in the cellular cytoplasm or in membranes, and scale-free structural organisation of networks, are known to considerably alter the first-passage dynamics of diffusing particles [56–58].

Yet another challenge for our understanding of first-passage processes is the parallel search by multiple diffusing particles. This could be relevant for the large number of spermatozoa searching for an egg cell [59], or for the case of a large number of calcium ions diffusing in the synaptic bouton to release neurotransmitters for inter-neuron communication. In this setting, either the smallest FPT (i.e., the FPT of the fastest particle) [52, 60–63], or the collective effect of several particles [64, 65] controls biological events.

This special issue combines several new perspectives in the understanding of first-passage processes and their applications. Thus, an important ongoing research direction consists in exploring first-passage properties of various stochastic processes beyond ordinary Brownian

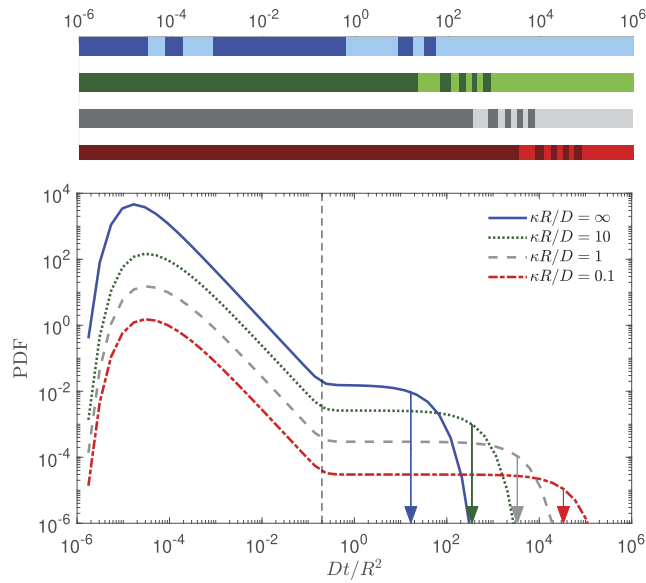


Figure 1. Probability density of the first-reaction time on a spherical target of radius $\rho/R = 0.01$, surrounded by a concentric reflecting sphere of radius R , for four progressively decreasing (from top to bottom) values of the dimensionless reactivity $\kappa R/D$ indicated in the plot. The particle starts close to the target at $r/R = 0.02$. The coloured vertical arrows indicate the mean first-passage times for these cases. The vertical black dashed line indicates the crossover time $t_c = 2(R - \rho)^2 / (D\pi^2)$ to a plateau region with equiprobable realisations of the FPT, terminated by an exponential tail. Note the extremely broad range of relevant reaction times (the horizontal axis) spanning over 12 orders of magnitude. The coloured bar-codes on the top indicate the cumulative depths corresponding to four considered values of $\kappa R/D$ in decreasing order from top to bottom. Each bar-code is split into ten regions of alternating brightness, representing ten 10%-quantiles of the distribution (e.g., the first dark blue region of the top bar-code in panel indicates that 10% of reaction events occur till $Dt/R^2 \simeq 1$). Adapted from [43].

motion. Mangeat *et al* [66] further investigate first-passage dynamics for heterogeneous diffusion [67–70], and Grebenkov [71] reports new findings for first-passage in diffusing-diffusivity processes [72–74] and switching diffusion [75–77]. Lanoiselée and Grebenkov address the first-passage dynamics in subordinated diffusion processes [78]. Ben-Zvi *et al* report an extension of diffusion-reaction dynamics in two-dimensional velocity fields and discuss applications in disordered media [79]. The paper by Pal *et al* [80] provides new results for local diffusion times in the context of stochastic resetting [81, 82]. Durang *et al* [83] further generalise the parameters in resetting models. First-passage times in the context of mean-reverting processes [84] are studied in the paper by Martin *et al* [85]. Hartich and Godec present novel connections between functionals of first-passage times and extreme value statistics of confined stochastic processes [86]. The papers by Padash *et al* [87] and Giona *et al* [88] add new results to the field of Lévy flight and Lévy walk search processes [89–91] important, inter alia, for the spreading of diseases such as SARS following multi-scale human mobility networks [92–94]. A quantum application of first-passage time theory is presented by Meidan *et al* [95]. Finally, the spreading of genetic modifications along DNA is analysed in the paper by Sandholtz *et al* [96].

From Bernoulli’s studies of a gambler’s ruin [97] over the timing of biochemical signalling in gene regulation [98] to the multi-scale spreading of diseases in the modern world [93]

first-passage processes occur on all time and length scales. Despite this ubiquity, the exploration of first-passage dynamics is far from complete. This special issue provides new perspectives and results for various systems and scenarios. We hope that the papers compiled here will be useful for the scientific community applying first-passage theories in their fields, as well as that they will inspire scientists working in the field of first-passage modelling.

Denis S Grebenkov 

Laboratoire de Physique de la Matière Condensée (UMR 7643), CNRS—Ecole Polytechnique, IP Paris, 91128 Palaiseau, France

David Holcman

Applied Mathematics and Computational Biology, Ecole Normale Supérieure, 46 rue d’Ulm, 75005 Paris, France

Ralf Metzler 

Institute of Physics & Astronomy, University of Potsdam, D-14476 Potsdam-Golm, Germany

E-mail: denis.grebenkov@polytechnique.edu, david.holcman@ens.fr and rmetzler@uni-potsdam.de

ORCID iDs

Denis S Grebenkov  <https://orcid.org/0000-0002-6273-9164>

Ralf Metzler  <https://orcid.org/0000-0002-6013-7020>

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