POLITECNICO DI TORINO
Repository ISTITUZIONALE

On two-boundary first exit time of Gauss-diffusion processes: closed-form results and biological modeling

Original
On two-boundary first exit time of Gauss-diffusion processes: closed-form results and biological modeling / D'Onofrio, G., Pirozzi, E.. - In: LECTURE NOTES OF SEMINARIO INTERDISCIPLINARE DI MATEMATICA. - ISSN 2284-0206. - 12:(2015).

Availability:
This version is available at: 11583/2982902 since: 2023-10-10T15:34:52Z

Publisher:
Università degli Studi della Basilicata

Published
DOI:

Terms of use:

This article is made available under terms and conditions as specified in the corresponding bibliographic description in the repository

Publisher copyright

(Article begins on next page)

10 November 2026

Lecture Notes of
Seminario Interdisciplinare di Matematica
Vol. 12(2015), pp. 111 – 124.

On two-boundary first exit time of Gauss-diffusion processes: closed-form results and biological modeling

Giuseppe D'Onofrio[1] and Enrica Pirozzi[2]

Abstract. The Gauss-Diffusion (GD) processes and their First Exit Time (FET) through a couple of absorbing boundaries are here considered highlighting some specific relations. The corresponding linear stochastic differential equations are re-written specifying the coefficient functions and giving them several theoretical meanings useful for biological modeling. The FET problem is considered in order to present and discuss a protein dynamics model based on Gauss-Diffusion processes in presence of two boundaries. Known closed forms of FET density are specialized for suitable GD processes and thresholds. In the context of biological modeling, relations between threshold values, mean behavior of the protein dynamics and input forces are given for the existence of a closed form result useful to describe the acto-myosin dynamics.

1. Introduction

The theory of Gauss-Markov and Diffusion processes (see [5], [10] and references therein) allows to construct and develop models in many different fields, as molecular biology, financial markets, population dynamics and in the context of neuronal modeling ([3]-[9]). The stochastic Leaky Integrate-and-Fire (LIF) neuronal models are essentially based on specific GD processes such as the Ornstein-Uhlenbeck process and some others (see, for instance, [1], [12]-[14], [18]-[20]). Putting together theoretical, numerical and simulative results about GD processes it is possible to obtain improvements in the theoretical and applicative apparatus jointly to additional understandings of experimental evidences.

In order to show how it is possible to use GD processes and the corresponding FET through suitable boundaries for modeling the acto-myosin dynamics (see, for instance, [2]), we firstly recall their definitions and properties. Essentially, we collect here some main results from some papers (as [4], [5], [10], [11], [16]) and we use them to refine theoretical and applicative aspects of a biological model. We focus the attention on the linear stochastic differential equations (SDEs) used for the biological modeling. Then, we specify the closed form results holding for two-boundary FET densities of some specified GD processes particularly useful in the

[1]G. D'Onofrio, Università degli Studi di Napoli "Federico II", Dipartimento di Matematica e Applicazioni, Monte S. Angelo, 80126 Napoli, Italy; giuseppe.donofrio@unina.it

[2]E. Pirozzi, Università degli Studi di Napoli "Federico II", Dipartimento di Matematica e Applicazioni, Monte S. Angelo, 80126 Napoli, Italy; epirozzi@unina.it

Keywords. Gauss-Markov processes, stochastic differential equations, acto-myosin dynamics.
AMS Subject Classification. 60G15, 60J60, 60J70.

application models, as the Wiener process, the Ornstein-Uhlenbeck (OU) process and the time-inhomogeneous OU process (here, also called generalized OU process). In particular, we point out the key role played by the time-inhomogeneous OU process for modeling phenomena subject to additional (external) time-dependent forces. Finally, a specific biological model is discussed.

1.1. **The Gauss-Diffusion processes.** We consider the real-valued Gauss–Markov process $\{X(t), t \geq 0\}$ having mean $m(t) := E[X(t)]\ \forall t \geq 0$, and covariance $c(s,t) := E\{[X(s) - m(s)]\,[X(t) - m(t)]\} = h_1(s)h_2(t)$, for $0 \leq s \leq t$ with $r(t) = h_1(t)/h_2(t)$ a non-negative monotonically increasing function. The process $\{X(t), t \geq 0\}$ is a GD process if its mean and covariance are differentiable functions in such a way it is also a Diffusion satisfying the Fokker-Planck equation and the associated initial condition

$$\begin{aligned} &\frac{\partial f(x,t|y,\tau)}{\partial t} = -\frac{\partial}{\partial x}[A_1(x,t)\, f(x,t|y,\tau)] + \frac{1}{2}\,\frac{\partial^2}{\partial x^2}[A_2(t)\, f(x,t|y,\tau)]\,, \\ &\lim_{\tau \uparrow t}\ f(x,t|y,\tau) = \delta(x-y)\,, \end{aligned} \tag{1}$$

with the following infinitesimal moments

$$A_1(x,t) = \frac{h_2'(t)}{h_2(t)}x + m'(t) - m(t)\frac{h_2'(t)}{h_2(t)} \quad , \quad A_2(t) = h_2^2(t)\, r'(t) \quad \text{for } t \geq 0\,. \tag{2}$$

Note that, setting

$$a(t) = \frac{h_2'(t)}{h_2(t)} \quad , \quad b(t) = m'(t) - m(t)\,\frac{h_2'(t)}{h_2(t)} \quad , \quad \sigma^2(t) = h_2^2(t)\, r'(t)\,, \tag{3}$$

the infinitesimal moments (2) for the GD process $\{X(t), t \geq 0\}$, alternatively, can be rewritten as space-linear functions as follows:

$$A_1(x,t) = a(t)x + b(t) \quad , \quad A_2(t) = \sigma^2(t) \quad \text{for } t \geq 0\,. \tag{4}$$

Furthermore, the transition probability density function (pdf) $f(x,t|y,\tau)$ is a normal-type density with the following conditional mean and variance:

$$\begin{aligned} &E[X(t)|X(\tau) = y] = m(t) + \frac{h_2(t)}{h_2(\tau)}[y - m(\tau)] \qquad (0 \leq \tau < t) \\ &Var[X(t)|X(\tau)] = h_2(t)\left[h_1(t) - \frac{h_2(t)}{h_2(\tau)}\, h_1(\tau)\right]. \end{aligned} \tag{5}$$

The class of GD processes includes two well-known time-homogeneous processes: the Wiener (W) and the Ornstein–Uhlenbeck (OU) processes. In particular, the Wiener process with the following infinitesimal moments

$$A_{1_W}(x,t) = b_W \quad , \quad A_{2_W}(t) = \sigma_W^2 \quad , \quad \text{for } t \geq 0\,, \tag{6}$$

has the mean $m(t)$ and covariance factors $h_1(t)$, $h_2(t)$ as follows

$$\begin{aligned} &m_W(t) = b_W t + c_W\,, \\ &h_{1_W}(t) = \sigma_W t \quad , \quad h_{2_W} = \sigma_W \quad , \quad (b_W, c_W \in \mathbb{R},\ \sigma_W \in \mathbb{R}^+)\,. \end{aligned} \tag{7}$$

Its coefficient functions $a(t), b(t), \sigma^2(t)$, for $t \geq 0$, from (3) and (7), are such that

$$a(t) \equiv 0 \quad , \quad b(t) \equiv b_W \quad \text{and} \quad \sigma^2(t) \equiv \sigma_W^2\,. \tag{8}$$

The well-known diffusion Ornstein-Uhlenbeck (OU) process $\{U(t), t \geq 0\}$ has the infinitesimal moments for $t \geq 0$

$$A_{1_U}(x,t) = -a_U x + b_U \quad , \quad A_{2_U}(t) = \sigma_U^2 \ , \tag{9}$$

and mean and covariance factors:

$$\begin{aligned} m_U(t) &= \frac{b_U}{a_U} + \left(c_U - \frac{b_U}{a_U}\right) e^{-a_U t} \ , \\ h_{1_U}(t) &= \frac{\sigma_U}{2a_U}\left(e^{a_U t} - e^{-a_U t}\right) \quad , \quad h_{2_U}(t) = \sigma_U e^{-a_U t} \ , \end{aligned} \tag{10}$$

with $a_U, \sigma_U \in \mathbb{R}^+, b_U, c_U \in \mathbb{R}$. In this case the coefficient functions $a(t), b(t), \sigma^2(t)$, for $t \geq 0$, from (3) and (10), are such that

$$a(t) \equiv -a_U \quad , \quad b(t) \equiv b_U \quad \text{and} \quad \sigma^2(t) \equiv \sigma_U^2. \tag{11}$$

The class of GD processes includes also the time-inhomogeneous process Ornstein-Uhlenbeck $\{V(t), t \geq 0\}$ having the infinitesimal moments for $t \geq 0$

$$A_{1_V}(x,t) = -a_V x + b_V(t) \quad , \quad A_{2_V}(t) = \sigma_V^2 \ , \tag{12}$$

and the following mean and covariance factors

$$\begin{aligned} m_V(t) &= \left[c_V + B_V(t)\right] e^{-a_V t} \ , \quad \text{with } B_V(t) = \int_0^t b_V(\tau) e^{a_V \tau}\, d\tau \ , \\ h_{1_V}(t) &= \frac{\sigma_V}{2a_V}(e^{a_V t} - e^{-a_V t}) \ , \quad h_{2_V}(t) = \sigma_V e^{-a_V t} \ , \end{aligned} \tag{13}$$

with $a_V, \sigma_V \in \mathbb{R}^+, c_V \in \mathbb{R}$, and $b_V(t)$ a time continuous function. Note that $h_{1_V}(t) = h_{1_U}(t)$ and $h_{2_V}(t) = h_{2_U}(t)$ for $a_V = a_U$ and $\sigma_V = \sigma_U$. Now, the coefficient functions $a(t), b(t), \sigma^2(t)$, for $t \geq 0$, from (3) and (13), are such that

$$a(t) \equiv -a_V \quad , \quad b(t) = b_V(t) \quad \text{and} \quad \sigma^2(t) \equiv \sigma_V^2 \ . \tag{14}$$

We also refer to the $V(t)$ process as the generalized OU process.

Note that when the Wiener, the OU and the time-inhomogeneous OU processes are characterized as Gauss-Markov processes, by (7), (10) and (13), respectively, an additional constant (c_W for Wiener, c_U for OU, c_V for V) is required: it specifies the starting point of the corresponding process.

Furthermore, we stress that identify the process $X(t)$ only as a diffusion process means to take into account its differential behavior, whereas consider it as a Gauss-Diffusion process means to take into account also its integral (mean) behavior.

2. The linear stochastic differential equations

Let $W(t)$ be the standard Wiener process, i.e., with $b_W = c_W = 0$ and $\sigma_W = 1$, also called the standard Brownian motion. Given the following SDE

$$dX(t) = A_1(X,t)\, dt + \sqrt{A_2(t)}\, dW(t) \tag{15}$$

with initial condition $X(0) = x_0$, it is well-known that it admits as solution a diffusion process with infinitesimal moments $A_1(x,t)$ and $A_2(t)$ (see for instance [15]). It means that a GD process, using (4), solves the following linear SDE

$$dX = \left[a(t)X(t) + b(t)\right] dt + \sigma(t)\, dW \quad \text{with} \quad X(0) = x_0 = m(0) \ . \tag{16}$$

In particular, a Wiener process solves the following SDE

$$dX = b_W dt + \sigma_W \, dW \quad \text{with} \quad X(0) = c_W \ , \tag{17}$$

a time-homogeneous OU process solves the following SDE

$$dX = [-a_U X(t) + b_U] \ dt + \sigma_U \, dW \quad \text{with} \quad X(0) = c_U \ , \tag{18}$$

and a time-inhomogeneous process $V(t)$ solves the following SDE

$$dX = [-a_V X(t) + b_V(t)] \ dt + \sigma_V \, dW \quad \text{with} \quad X(0) = c_V \ . \tag{19}$$

The SDEs (18) and (19) are used in the stochastic LIF and in the time-inhomogeneous LIF neuronal models, respectively, (see, for instance, [1], [4] ,[6]-[9], [18]).

We remark that the GD process $X(t)$ solution of (15) is alternatively identified by its infinitesimal moments that have the following expression:

$$A_1(X,t) = m'(t) + h_2'(t) W(r(t)) \quad , \quad A_2(t) = h_1'(t) h_2(t) - h_1(t) h_2'(t) \ , \tag{20}$$

with $r(t) = h_1(t)/h_2(t)$. In particular, $A_1(X,t) \equiv \mathbb{E}[dX(t)]$.

In order to clarify how expressions (20) have been obtained, we recall that being $X(t)$ a Gauss-Markov process, with mean $m(t)$ and covariance factors $h_1(t)$, $h_2(t)$, the following Doob-representation formula, by a standard Wiener process W, is valid (see, for instance, [10]):

$$X(t) = m(t) + h_2(t) W(r(t)) \ . \tag{21}$$

Note that applying the Itô differentiation rule on both sides of (21), the SDE (16) is obtained with the coefficient functions $a(t), b(t), \sigma^2(t)$, for $t \geq 0$, as specified in (3). Indeed, from (21), by differentiating according to Itô lemma

$$dX(t) = m'(t) \, dt + h_2'(t) W(r(t)) \, dt + h_2(t) \sqrt{r'(t)} \ dW(t) =$$

$$= [m'(t) + h_2'(t) W(r(t))] \ dt + h_2(t) \sqrt{r'(t)} \ dW(t) \ . \tag{22}$$

From (21), $W(r(t)) = [X(t) - m(t)]/h_2(t)$; recalling (2) and (15), one has

$$m'(t) + h_2'(t) W(r(t)) = m'(t) + h_2'(t) \ \frac{[X(t) - m(t)]}{h_2(t)} = A_1(X,t) \ ,$$

$$h_2(t) \ \sqrt{r'(t)} = \sqrt{A_2(t)} \ .$$

Finally, the (20) hold.

Conversely, given the SDE (16), the solution is the GD process having the mean and covariance functions obtained as follows (see [5])

$$\begin{aligned} m(t) &= \left[x_0 + \int_0^t b(\tau) \, e^{-\int_0^\tau a(s) \, ds} \, d\tau \right] e^{\int_0^t a(s) \, ds} \qquad (t \geq 0) \\ c(\tau,t) &= \left[\int_0^t \sigma^2(\xi) \, e^{-2\int_0^\xi a(s) \, ds} \, d\xi \right] e^{\int_0^t a(s) \, ds} \, e^{\int_0^\tau a(s) \, ds} \qquad (0 \leq \tau \leq t) \ . \end{aligned} \tag{23}$$

2.1. **About the OU and generalized OU processes.** From (21), we firstly note that the OU process $U(t)$ can be written as (see, also, [17])

$$U(t) = m_U(t) + \sigma_U e^{-a_U t} W\left(\frac{e^{2a_U t}-1}{2a_U}\right) \tag{24}$$

recalling that in this case $r(t) = (e^{2a_U t}-1)/2a_U$.

Whereas the generalized OU process $V(t)$, having the mean $m_V(t)$ and the same covariance factors of OU process, can be written as follows

$$V(t) = m_V(t) + \sigma_V e^{-a_V t} W\left(\frac{e^{2a_V t}-1}{2a_V}\right) = m_V(t) + [U(t) - m_U(t)] \tag{25}$$

where the time homogeneous OU process $U(t)$ has $a_U = a_V$ and $\sigma_U = \sigma_V$. From (24) and (25) one has

$$dV = m'_V(t)\,dt + d\,[U(t) - m_U(t)]\ . \tag{26}$$

Note that, from (15), the GD process $[U(t) - m_U(t)]$, having zero mean ($b(t) = 0$), is solution of the following SDE

$$d\,[U(t) - m_U(t)] = -a_U\,[U(t) - m_U(t)]\,dt + \sigma_U dW \quad \text{with} \quad U(0) = m_U(0)\ , \tag{27}$$

hence, for the process $V(t)$ as in (25), and from (26) and (27), one has

$$dV = m'_V(t)\,dt + d\,[U(t) - m_U(t)] = m'_V(t)\,dt - a_U\,[U(t) - m_U(t)]\,dt + \sigma_U\,dW \tag{28}$$

and, finally, being $[U(t) - m_U(t)] = [V(t) - m_V(t)]$ from (25), we can write that $V(t)$ is solution of the following SDE

$$dV = \{-a_V\,[V(t) - m_V(t)] + m'_V(t)\}\,dt + \sigma_V dW \quad , \quad V(0) = m_V(0)\ , \tag{29}$$

with $a_V = a_U$ and $\sigma_V = \sigma_U$.

Finally, we stress that the generalized OU process $V(t)$ is solution of SDE (19) and from (29) it is such that

$$A_1(V,t) = a(t)V + b(t) = -a_V\,[V(t) - m_V(t)] + m'_V(t)\ ,$$

with

$$a(t) \equiv -a_V \quad , \quad b(t) = m'_V(t) + a_V m_V(t)\ . \tag{30}$$

In the modeling context, the $V(t)$ is the GD process obeying the dynamics based on SDE (29) in which $a_V m_V(t)$ preserves the meaning of the equilibrium state for $V(t)$, a_V is related to the characteristic time, i.e. the time constant of $V(t)$ for relaxation over the equilibrium level, and $m'_V(t)$ can be interpreted as the time-dependent external input signal (force). The relations (30) specify the meaning of diffusion coefficients: in particular, $a(t)$ is related to the relaxation time, whereas the $b(t)$ identifies the overall effect of the driving term $m'_V(t)$ and of the attractive equilibrium level $a_V m_V(t)$.

2.1.1. *An example of application.* We can find a direct application of the last sentence and of (30) considering the following SDE, used by us in [11] to model the acto-myosin dynamics ([2]),

$$dX = -\frac{1}{\beta}\,[X(t) - F(t)]\,dt + \gamma\,dW \quad \text{with} \quad X(0) = x_0\ , \tag{31}$$

where β is the drag coefficient, $F(t)$ is a driving force and γ is dependent on the environmental temperature, the Boltzmann constant and the drag coefficient (better specified in the last section).

Remark 2.1. The GD process solving (31) is the generalized OU process $V(t)$ with the mean $m_V(t)$ that solves the following ordinary differential equation (ODE):

$$m'(t) + \frac{1}{\beta}\, m(t) = \frac{F(t)}{\beta} \quad \text{with} \quad m(0) = x_0 \,. \tag{32}$$

Note that the (31) is the same of the SDE (19) with $a_V = 1/\beta$, $b_V(t) = F(t)/\beta$. Referring to the generalized OU process $V(t)$, the (30) becomes $m'_V(t) + a_V m_V(t) = F(t)/\beta$. Hence, the Remark 2.1 follows.

Similarly, referring to (23), we can specify that only the first of them has to be evaluated, providing the solution of (32),

$$m(t) = x_0 e^{-t/\beta} + e^{-t/\beta} \int_0^t \frac{F(\tau)}{\beta}\, e^{\tau/\beta}\, d\tau \,. \tag{33}$$

Note that here it is evident that the generalized process solution of (31) is a time-inhomogeneous OU process because its mean function (33) integrates the input force $F(t)$ over time until t.

In this context some theoretical results on GD processes can be useful: for instance, we can specify for which kind of driving force $F(t)$ it is possible to provide a closed-form function useful to model the dwell-time of the myosin head in a potential well.

In order to obtain answers to this kind of question, we have to give some further definitions and recall some main theoretical results.

3. The first exit time

Here, we recall definitions and main results of [16]. We now focus our attention on the random variable FET $\mathcal{T}_{x_0}$ from a strip with absorbing boundaries $S_1(t)$, $S_2(t)$ of a GD process $X(t)$ starting from x_0. Specifically, let $S_1(t)$ and $S_2(t)$ be a $C^1([0,+\infty))$-class functions such that $S_1(t) < S_2(t)$, $\forall t$, $S_1(0) < X(0) \equiv x_0 < S_2(0)$. For all $t \geq 0$, we shall now focus our attention on the random variables:

$$\begin{aligned}
&\mathcal{T}^{(1)}_{x_0} = \inf_{t\geq 0} \{t \,:\, X(t) < S_1(t);\ X(\vartheta) < S_2(\vartheta),\ \forall \vartheta \in (0,t)\} \,,\ X(0) = x_0 \\
&\qquad\qquad \text{(first-passage time through the lower boundary)} \\
&\mathcal{T}^{(2)}_{x_0} = \inf_{t\geq 0} \{t \,:\, X(t) > S_2(t);\ X(\vartheta) > S_1(\vartheta),\ \forall \vartheta \in (0,t)\} \,,\ X(0) = x_0 \\
&\qquad\qquad \text{(first-passage time through the upper boundary)} \\
&\mathcal{T}_{x_0} = \inf_{t\geq 0} \{t \,:\, X(t) \notin (S_1(t), S_2(t))\} \,,\ X(0) = x_0 \\
&\qquad\qquad \text{(first-exit time)}
\end{aligned} \tag{34}$$

and denote by $g_1(t \mid x_0, 0)$, $g_2(t \mid x_0, 0)$ and $g(t \mid x_0, 0)$, respectively, their pdf's:

$$\begin{aligned}
g_1(t \mid x_0, 0) &= \frac{\partial}{\partial t} P\left(\mathcal{T}^{(1)}_{x_0} < t\right) , \\
g_2(t \mid x_0, 0) &= \frac{\partial}{\partial t} P\left(\mathcal{T}^{(2)}_{x_0} < t\right) , \\
g(t \mid x_0, 0) &= \frac{\partial}{\partial t} P\left(\mathcal{T}_{x_0} < t\right) \equiv g_1(t \mid x_0, 0) + g_2(t \mid x_0, 0) \,.
\end{aligned} \tag{35}$$

Hence, $P(\mathcal{T}^{(1)}_{x_0} < t)$ $[P(\mathcal{T}^{(2)}_{x_0} < t)]$ is the probability that $X(t)$ crosses for the first time $S_1(t)$ $[S_2(t)]$ at some time preceding t before crossing $S_2(t)$ $[S_1(t)]$, whereas

$P(\mathcal{T}_{x_0} < t)$ is the probability that $X(t)$ crosses for the first time either $S_1(t)$ or $S_2(t)$ before time t.

Here, from [16], we recall that, the FPT pdfs $g_1[t|x_0, 0]$ and $g_2[t|x_0, 0]$ solve the following system of nonsingular second-kind Volterra integral equations:

$$
\begin{aligned}
g_1(t \mid x_0, 0) &= 2\Psi_1(t \mid x_0, 0) - \\
&-2\int_0^t \{g_1(\tau \mid x_0, 0)\, \Psi_1[t \mid S_1(\tau), \tau] \; + g_2(\tau \mid x_0, 0)\, \Psi_1[t \mid S_2(\tau), \tau]\}\, d\tau \,, \\
g_2(t \mid x_0, 0) &= -2\,\Psi_2(t \mid x_0, 0) + \\
&+2\int_0^t \{g_1(\tau \mid x_0, 0)\, \Psi_2[t \mid S_1(\tau), \tau] \; + g_2(\tau \mid x_0, 0)\, \Psi_2[t \mid S_2(\tau), \tau]\}\, d\tau \,,
\end{aligned}
\tag{36}
$$

where

$$
\begin{aligned}
\Psi_j(t \mid y, \tau) &= \\
&= \left\{ \frac{S_j'(t) - m'(t)}{2} - \frac{S_j(t) - m(t)}{2}\; \frac{h_1'(t)\, h_2(\tau) - h_2'(t)\, h_1(\tau)}{h_1(t)\, h_2(\tau) - h_2(t)\, h_1(\tau)} - \right. \\
&\left. - \frac{y - m(\tau)}{2}\; \frac{h_2'(t)\, h_1(t) - h_2(t)\, h_1'(t)}{h_1(t)\, h_2(\tau) - h_2(t)\, h_1(\tau)} \right\} f[S_j(t), t \mid y, \tau] \quad (j = 1, 2) \,.
\end{aligned}
\tag{37}
$$

3.0.2. *Reduction to a single integral equation.* First of all, under suitable assumptions on the boundaries of the GD process, it is possible to prove that the first-exit time $g(t \mid x_0, 0)$ is the solution of a single non singular Volterra integral equation in place of the system (36). We recall that, again from [16], under all above assumptions, if

$$
\lim_{t \to +\infty} r(t) = +\infty \quad , \quad P\{S_1(t) \le X(t) < S_2(t) \mid X(0) = x_0\} \neq 1 \,,
$$

one has:

$$
\int_0^{+\infty} g(t \mid x_0, 0)\, dt = 1 \,. \tag{38}
$$

Furthermore, if $S_1(t)$ and $S_2(t)$ are such that

$$
S_1(t) + S_2(t) = 2\, m(t) + 2\, c\, h_2(t) \quad , \quad (c \in \mathbb{R}) \,, \tag{39}
$$

for all $t \ge 0$, then

$$
\begin{aligned}
g(t \mid x_0, 0) &= 2\,[\Psi_1(t \mid x_0, 0) - \Psi_2(t \mid x_0, 0)] - \\
&-2\int_0^t g(\tau \mid x_0, 0)\; \{\Psi_1[t \mid S_1(\tau), \tau] - \Psi_2[t \mid S_1(\tau), \tau]\}\, d\tau \,.
\end{aligned}
\tag{40}
$$

Finally, if $S_1(t)$ and $S_2(t)$ are such that (39) holds for all $t \ge 0$ and if x_0 is such that

$$
x_0 = m(0) + c\, h_2(0) \quad , \quad (c \in \mathbb{R}) \,, \tag{41}
$$

then

$$
g_1(t \mid x_0, 0) = g_2(t \mid x_0, 0) \,, \tag{42}
$$

and as consequence

$$g(t \mid x_0, 0) \equiv 2\, g_1(t \mid x_0, 0) \equiv 2\, g_2(t \mid x_0, 0) \tag{43}$$

satisfies the single integral equation (40).

3.1. **Closed form for FET density.** Here, we briefly recall Theorems 4.1 and 4.2 of [16]. Let $S_1(t)$ and $S_2(t)$ be such that

$$S_1(t) = m(t) + b\, h_1(t) + c_1\, h_2(t) \quad , \quad S_2(t) = m(t) + b\, h_1(t) + c_2\, h_2(t)\ , \tag{44}$$

with $S_1(t) < S_2(t)$ for all $t \geq 0$, and let x_0 be such that

$$x_0 = m(0) + b\, h_1(0) + c\, h_2(0)\ , \tag{45}$$

with $b, c, c_1, c_2 \in \mathbb{R}$ and $S_1(0) < x_0 < S_2(0)$. Then, the closed form for the following FET density holds:

$$\begin{aligned} g(t \mid x_0, 0) = {} & \frac{h_2(t)}{r(t) - r(0)}\, \frac{dr(t)}{dt} \sum_{n=-\infty}^{+\infty} \exp\left\{ -\frac{2\, n^2\, (c_2 - c_1)^2}{r(t) - r(0)} \right\} \times \\ & \times \left\{ [c - c_1 + 2\, n\, (c_2 - c_1)] \exp\left\{ -\frac{2\, n\, (c_2 - c_1)\, (c - c_1)}{r(t) - r(0)} \right\} f[S_1(t), t \mid x_0, 0] + \right. \\ & \left. + [c_2 - c - 2\, n\, (c_2 - c_1)] \exp\left\{ \frac{2\, n\, (c_2 - c_1)\, (c_2 - c)}{r(t) - r(0)} \right\} f[S_2(t), t \mid x_0, 0] \right\}\ . \end{aligned} \tag{46}$$

We point out that in Theorem 4.3 of [16] is reported also the particular case of two Daniels-type boundaries for which the FET density admits a closed form. We do not consider this case here.

We remark that when the conditions for the existence of a closed form for FET density are not satisfied, it is possible to obtain evaluations of FET density by means of numerical quadrature of the integral equations (36).

3.1.1. *The FET closed form for specified processes.* Let us make explicit the (46) in specific cases of particular interest for stochastic modeling.

- The Wiener process. We consider the Wiener process $W(t)$ with $m_W(t)$, $h_{1_W}(t)$ and $h_{2_W}(t)$ as in (7) and satisfying the (17). Then, from (44) and (45), for this kind of process the closed form (46) holds for boundaries and initial condition as follows

$$S_{1_W}(t) = Bt + C_1 \quad , \quad S_{2_W}(t) = Bt + C_2 \quad , \quad x_0 = c_W + C \tag{47}$$

  with $B = b_W + b\sigma_W$, $C_1 = c_W + c_1\sigma_W$, $C_2 = c_W + c_2\sigma_W$ and $C = c\sigma_W$ are such that $S_{1_W}(t) < S_{2_W}(t)$ for all t and $S_{1_W}(0) < x_0 < S_{2_W}(0)$. Hence, the closed form FET (46) for the Wiener process is

$$\begin{aligned} g_W(t \mid x_0, 0) = {} & \frac{1}{t} \sum_{n=-\infty}^{+\infty} \exp\left\{ -\frac{2n^2 L^2}{\sigma_W^2 t} \right\} \times \\ & \times \left\{ (l_1 + 2nL) \exp\left\{ -\frac{2n\, l_1 L}{\sigma_W^2 t} \right\} f_W[S_{1_W}(t), t \mid x_0, 0] + \right. \\ & \left. + (l_2 - 2nL) \exp\left\{ \frac{2n l_2 L}{\sigma_W^2 t} \right\} f_W[S_{2_W}(t), t \mid x_0, 0] \right\} \end{aligned} \tag{48}$$

where $L = S_{2_W}(0) - S_{1_W}(0) = \sigma_W(c_2 - c_1)$ and $l_1 = x_0 - S_{1_W}(0) = \sigma_W(c - c_1)$ and $l_2 = S_{2_W}(0) - x_0 = \sigma_W(c_2 - c)$, respectively.
Note that for $c_1 \to -\infty$ in (48), i.e. moving away the lower boundary $S_{1_W}(t)$, only the term with $n = 0$ gives a non-zero contribution, so that the FET density (48) tends to the well-known Inverse Gaussian-type density for the first passage time through the linear upper boundary $S_{2_W}(t)$:

$$\frac{S_{2_W}(0) - x_0}{\sqrt{2\pi t^3}} \exp\left\{-\frac{(S_{2_W}(t) - x_0)^2}{2t}\right\} .$$

Furthermore, as particular case, we can put together (44) and (45) assuming

$$S_{1_W}(t) = Bt + x_0 - \tilde{c} \quad , \quad S_{2_W}(t) = Bt + x_0 + \tilde{c} \tag{49}$$

with the values $B, \tilde{c} \in \mathbb{R}^+$. It can be easily verified that, in this case, one has that $L = 2\tilde{c}$ and $l_1 = l_2 = \tilde{c}$. For $B = b_W, x_0 = c_W, c = 0$ the conditions (39) and (41) hold and so we can use (43) to obtain $g_1(t \mid x_0, 0)$ and $g_2(t \mid x_0, 0)$ with the following expression for FET density provided by (48):

$$g(t \mid x_0, 0) = \frac{\tilde{c}}{t}\left\{f_W[Bt - \tilde{c}, t \mid 0, 0] + f_W[Bt + \tilde{c}, t \mid 0, 0]\right\} +$$

$$+\frac{2\tilde{c}}{t}\sum_{n=1}^{+\infty}\exp\left\{-\frac{8n^2\tilde{c}^2}{\sigma_W^2 t}\right\}\left\{f_W[Bt - \tilde{c}, t \mid 0, 0]\left[\cosh\left(\frac{4n\tilde{c}^2}{\sigma_W^2 t}\right) - 4n\sinh\left(\frac{4n\tilde{c}^2}{\sigma_W^2 t}\right)\right] +\right.$$

$$\left. + f_W[Bt + \tilde{c}, t \mid 0, 0]\left[\cosh\left(\frac{4n\tilde{c}^2}{\sigma_W^2 t}\right) - 4n\sinh\left(\frac{4n\tilde{c}^2}{\sigma_W^2 t}\right)\right]\right\} . \tag{50}$$

- The OU process. For the $U(t)$ process with $m_U(t)$, $h_{1_U}(t)$ and $h_{2_U}(t)$ as in (10), from (44) and (45), the closed form (46) holds for the hyperbolic-type boundaries and initial condition as follows

$$\begin{gathered} S_{1_U}(t) = A_1 e^{a_U t} + B_1 e^{-a_U t} + C_1 \quad , \quad S_{2_U}(t) = A_1 e^{a_U t} + B_2 e^{-a_U t} + C_1 , \\ x_0 = c_U + C \end{gathered} \tag{51}$$

where

$$\begin{gathered} A_1 = \frac{b\sigma_U}{2a_U} , \\ B_1 = c_U - \frac{b_U}{a_U} - \frac{b\sigma_U}{2a_U} + c_1\sigma_U \quad , \quad B_2 = c_U - \frac{b_U}{a_U} - \frac{b\sigma_U}{2a_U} + c_2\sigma_U , \\ C_1 = \frac{b_U}{a_U} \quad , \quad C = c\,\sigma_U , \end{gathered} \tag{52}$$

such that $S_{1_U}(t) < S_{2_U}(t)$ for all $t \geq 0$ and $S_{1_U}(0) < x_0 < S_{2_U}(0)$. Specifically, the closed form FET (46) for the OU process is

$$g_U(t \mid x_0, 0) = \frac{2a_U e^{a_U t}}{e^{2a_U t} - 1} \sum_{n=-\infty}^{+\infty} \exp\left\{-\frac{2n^2 L^2}{\sigma_U^2(e^{2a_U t} - 1)}\right\} \times$$

$$\times \left\{(l_1 + 2nL)\exp\left\{-\frac{2nl_1 L}{\sigma_U^2(e^{2a_U t} - 1)}\right\} f_U[S_{1_U}(t), t \mid x_0, 0] +\right.$$

$$+(l_2 - 2nL)\exp\left\{\frac{2nl_2L}{\sigma_U^2(e^{2a_U t}-1)}\right\} f_U[S_{2_U}(t), t \mid x_0, 0]\Bigg\} \tag{53}$$

where $L = S_{2_U}(0) - S_{1_U}(0) = \sigma_U(c_2 - c_1)$, $l_1 = x_0 - S_{1_U}(0) = \sigma_U(c - c_1)$ and $l_2 = S_{2_U}(0) - x_0 = \sigma_U(c_2 - c)$.
Note that it is possible to obtain (53) from (48) by means of the Doob-transformation rule between Wiener and OU process, i.e. by exploiting the following transformation (cf. [16])

$$g_U(t \mid x_0, t_0) = \frac{dr(t)}{dt}\, g_W\left[r(t) \mid x_0^*, r(t_0)\right] \ , \tag{54}$$

where $r(t) = (e^{2a_U t} - 1)/2a_U$, $g_W\left[r(t) \mid x_0^*, r(t_0)\right]$ is the FET pdf of $W(\vartheta)$ from $(S_1^*(\vartheta), S_2^*(\vartheta))$, with

$$x_0^* = \frac{x_0 - m_U[r^{-1}(\vartheta_0)]}{h_{2_U}[r^{-1}(\vartheta_0)]} \ , \ S_j^*(\vartheta) = \frac{S_j[r^{-1}(\vartheta)] - m_U[r^{-1}(\vartheta)]}{h_{2_U}[r^{-1}(\vartheta)]} \quad (j = 1, 2) \ . \tag{55}$$

- The generalized OU process. Let $V(t)$ be the generalized OU process with mean and covariance as in (13). From (44) and (45), the closed form (46) holds for boundaries and initial condition as follows

$$S_{1_V}(t) = A_1 e^{a_V t} + B_1(t) e^{-a_V t} \ , \ S_{2_V}(t) = A_1 e^{a_V t} + B_2(t) e^{-a_V t} \ , \ x_0 = c_V + C \tag{56}$$

where $A_1 = b\sigma_V/2a_V$, $C = c\sigma_V$, and

$$B_1(t) = c_V + c_1\sigma_V - \frac{b\sigma_V}{2a_V} + B_V(t) \ , \ B_2(t) = c_V + c_2\sigma_V - \frac{b\sigma_V}{2a_V} + B_V(t) \ , \tag{57}$$

such that $S_{1_V}(t) < S_{2_V}(t)$ for all $t \geq 0$ and $S_{1_V}(0) < x_0 < S_{2_V}(0)$. We note that now $B_1(t), B_2(t)$ are functions of time, since they depend on $B_V(t)$, specified in (13).
From these positions we obtain a closed form FET pdf that is the same of (53) with $a_U = a_V$, $\sigma_U = \sigma_V$, $L = S_{2_V}(0) - S_{1_V}(0) = \sigma_V(c_2 - c_1)$, $l_1 = x_0 - S_{1_V}(0) = \sigma_V(c - c_1)$ and $l_2 = S_{2_V}(0) - x_0 = \sigma_V(c_2 - c)$, whereas the transition normal densities $f_U[S_{1_U}(t), t \mid x_0, 0]$ and $f_U[S_{2_U}(t), t \mid x_0, 0]$ are substituted by $f_V[S_{1_V}(t), t \mid x_0, 0]$ and $f_V[S_{2_V}(t), t \mid x_0, 0]$, respectively.

3.1.2. *An inverse question.* Now we are able to answer the applicative question proposed at the end of subsection 2.1.1. With this aim, we consider a GD process with infinitesimal moments

$$A_1(x, t) = a(t)x + b(t) \quad , \quad A_2(t) = \sigma^2(t) \ . \tag{58}$$

Given the boundaries $S_1(t), S_2(t)$, by adding side-by-side the conditions in (44), we can write the following condition on the mean of the process

$$m(t) = \frac{S_1(t) + S_2(t)}{2} - bh_1(t) - \frac{c_1 + c_2}{2} h_2(t) \ . \tag{59}$$

From (3) we know that, with $a(t) = h_2'(t)/h_2(t)$,

$$b(t) = m'(t) - a(t)m(t) \ . \tag{60}$$

Using (59) in (60), we obtain

$$b(t) = \frac{S_1'(t) + S_2'(t)}{2} - bh_1'(t) - \left[\frac{S_1(t) + S_2(t)}{2} - bh_1(t)\right] \frac{h_2'(t)}{h_2(t)} \ . \tag{61}$$

For constant boundaries S_1 and S_2, we have

$$b(t) = -bh_1'(t) - \left[\frac{S_1+S_2}{2} - bh_1(t)\right]\frac{h_2'(t)}{h_2(t)}\,. \tag{62}$$

This expression for $b(t)$ ensures that, for the GD process solution of the SDE $dX = [a(t)X + b(t)]dt + \sigma dW$ with $X(0) = x_0$, $S_1 < x_0 < S_2$ in presence of constant boundaries S_1 and S_2, the FET density admits the closed form (46) for suitable values of the involved parameters. Specifically, for the generalized OU process $V(t)$ solution of

$$dV = [-a_V V + b_V(t)]\,dt + \sigma_V\,dW \quad , \quad S_1 < V(0) = v_0 < S_2 \tag{63}$$

the FET density has a closed form of type (53) if

$$b_V(t) = -b\sigma_V e^{a_V t} + \left(\frac{S_1+S_2}{2}\right)a_V \tag{64}$$

with $a_U = a_V$, $S_{1_U}(t) = S_1$, $S_{2_U}(t) = S_2$, $\sigma_U = \sigma_V$, $c = 0$ and for $\sigma_V(c_1 + c_2) = S_1 + S_2 - 2x_0$. Furthermore, if $S_2 = S = -S_1$ the condition (64) becomes $b_V(t) = -b\sigma_V e^{a_V t}$. Finally, the FET density admits a closed form if $V(t)$ is solution of

$$dV = [-a_V V - b\sigma_V e^{a_V t}]\,dt + \sigma_V\,dW \quad , \quad -S < V(0) = v_0 < S\,. \tag{65}$$

3.1.3. *About the example of application.* Concerning the application presented in subsection 2.1.1, we can say that for an input force of type: $F(t)/\beta = -b\gamma e^{t/\beta}$ in (31), the corresponding FET pdf from $(-S, S)$ admits a closed form. Specifically, the time inhomogeneous OU process $X(t)$ with the following mean and covariance factors:

$$\begin{aligned} m_X(t) &= x_0 e^{-t/\beta} - b\,\frac{\gamma\beta}{2}\left(e^{t/\beta} - e^{-t/\beta}\right), \\ h_{1_X}(t) &= \frac{\gamma\beta}{2}\left(e^{t/\beta} - e^{-t/\beta}\right) \quad , \quad h_{2_X}(t) = \gamma e^{-t/\beta} \end{aligned} \tag{66}$$

with $-S < x_0 < S$, is solution of (31) with $F(t)/\beta = -b\gamma e^{t/\beta}$ and it admits the following FET closed form in presence of constant boundaries $(-S, S)$:

$$\begin{aligned} g_X(t \mid x_0, 0) \;=\; & \frac{2\,e^{t/\beta}}{\beta(e^{2t/\beta}-1)} \sum_{n=-\infty}^{+\infty} \exp\left\{-\frac{8n^2S^2}{\gamma^2(e^{2t/\beta}-1)}\right\} \times \\ & \times \left\{(S + x_0 + 4nS)\exp\left\{-\frac{4nS(S+x_0)}{\gamma^2(e^{2t/\beta}-1)}\right\} f_X[-S, t \mid x_0, 0] + \right. \\ & \left. + (S - x_0 - 4nS)\exp\left\{\frac{4nS(S-x_0)}{\gamma^2(e^{2t/\beta}-1)}\right\} f_X[S, t \mid x_0, 0]\right\}\,. \end{aligned} \tag{67}$$

The form (67) is obtained from (53) with $a_U = 1/\beta$, $\sigma_U = \gamma$, $c = 0$, $\gamma c_1 = -S - x_0$, $\gamma c_2 = S - x_0$, $L = 2S = \gamma(c_2 - c_1)$, $l_1 = x_0 + S = -\gamma c_1$ and $l_2 = S - x_0 = \gamma c_2$, whereas the transition normal densities $f_U[S_{1_U}(t), t \mid x_0, 0]$ and $f_U[S_{2_U}(t), t \mid x_0, 0]$ are substituted by $f_X[-S, t \mid x_0, 0]$ and $f_X[S, t \mid x_0, 0]$, respectively.

4. A stochastic model for protein dynamics

In [11] we propose a model that essentially exploits the theory of GD processes and of the corresponding FET from a strip. Indeed, we consider the interaction between myosin and actin proteins responsible of the muscle contraction in skeletal muscles. By successive steps of myosin head along the actin filament, the chemical energy released by ATP hydrolysis is converted in mechanical work. In our model these steps are modeled as exit events from a strip; the exit from the upper (lower) boundary of the strip stands for a forward (backward) step. For detailed and extensive readings on molecular motors see [2] and references therein.

In the proposed model, we assume that the diffusive dynamics takes place in a symmetric one-well parabolic potential (the binding site) tilted by a time-dependent force (driving the particle motion). The acto-myosin dynamics is described as an over-dumped motion (disregarding the inertial force) and confined to only one space-period (with length $\mathcal{L}$) of the periodical morphology of the actin filament. A parabolic profile is considered for the potential of the myosin head; this allows to use a suitable time inhomogeneous OU process, substantially the process $X(t)$ solution of an SDE of type (31). In this context the myosin steps are escapes from the potential well: the escape occurs when the particle attains a local maximum of the potential. Hence, by means of the FET of the process $X(t)$ from the strip, we are able to provide evaluations of the dwell time, i.e., the time elapsed in the potential well before escaping from it.

We consider the case of a time-increasing force acting in the dynamics and also the case of a time-decreasing force. Discretizing the considered SDE, we simulate particle paths and we obtain statistical approximations of FET density. We compare these results with evaluations of FET density obtained by numerical quadrature of the two corresponding integral equations (of type (36)) and also with some experimental data.

The simulation strategy and the numerical approach is mandatory because no closed form results hold for the specified case.

The model in [11] is based on a SDE of the following type

$$dX = -\left[\frac{\alpha}{\beta}\left(X - \frac{\mathcal{L}}{2}\right) - \frac{F(t)}{\beta}\right] dt + \sqrt{\frac{2\mathrm{K}_B\mathrm{T}}{\beta}}\, dW \quad , \quad X(0) = \frac{\mathcal{L}}{2} \tag{68}$$

in presence of two absorbing boundaries $S_1 = 0$ and $S_2 = \mathcal{L}$, with α proportional to the space-period $\mathcal{L}$ of the potential and to the depth of the potential well, β the drag coefficient, K_B the Boltzmann constant, T the environmental temperature.

Again in [11] for SDE (68) an increasing exponential force

$$F(t) = k\beta(1 - e^{-t/\vartheta}) \tag{69}$$

is considered with k positive real number to model an attractive force to the next actin monomer (i.e., the upper boundary) rising during the interaction between the proteins. Note that here the time constant ϑ characterizes the time that the force takes to assume its maximum value $k\beta$.

We also consider in (68) the following decreasing exponential force

$$F(t) = k\beta e^{-t/\vartheta} \tag{70}$$

with k positive real number to model a quasi-impulsive force that rapidly decays. This could be the case of an initial strong impact between the myosin head and the

actin filament that may cause the so-called conformational change in the myosin neck. Here, ϑ is the decaying time of the force.

For both above considered forces, the GD process solution of (68) is a time inhomogeneous OU process with mean (33) and covariance factors as in (13), with the suitably specified involved functions and parameters; the corresponding FET is solution of integral equations (36). If the force

$$F(t) = -b\beta\sqrt{\frac{2\mathrm{K}_B\mathrm{T}}{\beta}}\, e^{(\alpha/\beta)t} \tag{71}$$

obtained from $b_V(t)$ of (64) for $a_V = \alpha/\beta$, $\sigma_V = \sqrt{2\mathrm{K}_B\mathrm{T}/\beta}$, $S_1 = 0$ and $S_2 = \mathcal{L}$, is used in SDE (68), the solution is a generalized OU process $X(t)$ and it admits a closed form for the FET density. Note that the case (71) is different from the cases considered previously, because it has a positive exponential behavior. It can be used in this model to describe some phenomena in which a force with an unbounded increasing intensity is involved, although most of the times these cases are of a limited interest from a biological point of view.

References

[1] A.N. Burkitt, *A review of the integrate-and-fire neuron model: I. Homogeneous synaptic input*, Biological Cybernetics, 95(2006), 1–19.

[2] A. Buonocore, L. Caputo, Y. Ishii, E. Pirozzi, T. Yanagida & L.M. Ricciardi, *On Myosin II dynamics in the presence of external loads*, Biosystems, 81(2005), 165–177.

[3] A. Buonocore, L. Caputo & E. Pirozzi, *On the evaluation of firing densities for periodically driven neuron models*, Mathematical Biosciences, 214(2008), 122–133.

[4] A. Buonocore, L. Caputo, E. Pirozzi & L.M. Ricciardi, *On a stochastic leaky integrate-and-fire neuronal model*, Neural Computation, 22(2010), 2558–2585.

[5] A. Buonocore, L. Caputo, E. Pirozzi & L.M. Ricciardi, *The first passage time problem for Gauss-diffusion processes: algorithmic approaches and applications to LIF neuronal model*, Methodol. Comput. Appl. Prob., 13(2011), 29–57.

[6] A. Buonocore, L. Caputo, E. Pirozzi & M.F. Carfora, *Gauss-diffusion processes for modeling the dynamics of a couple of interacting neurons*, Math. Biosci. Eng., 11(2014), 189–201.

[7] A. Buonocore, L. Caputo, A.G. Nobile & E. Pirozzi, *Gauss-Markov processes in the presence of a reflecting boundary and applications in neuronal models*, Applied Mathematics and Computation, 232(2014), 799–809.

[8] A. Buonocore, L. Caputo, A.G. Nobile & E. Pirozzi, *Restricted Ornstein-Uhlenbeck process and applications in neuronal models with periodic input signals*, Journal of Computational and Applied Mathematics, 285(2015), 59–71.

[9] A. Buonocore, L. Caputo, A.G. Nobile & E. Pirozzi, *Gauss-Markov Processes for neuronal models including reversal potentials*, Advances in Cognitive Neurodynamics (IV), 11(2015), 299–305.

[10] E. Di Nardo, A.G. Nobile, E. Pirozzi & L.M. Ricciardi, *A computational approach to first passage-time problems for Gauss-Markov processes*, Adv. Appl. Prob., 33(2001), 453–482.

[11] G. D'Onofrio & E. Pirozzi, *Two-boundary first exit time of Gauss-Markov processes for stochastic modeling of acto-myosin dynamics*, Submitted.

[12] V. Giorno & S. Spina, *On the return process with refractoriness for a non-homogeneous Ornstein-Uhlenbeck neuronal model*, Math. Bios. Eng., (2)11(2014).

[13] P. Lánský & S. Ditlevsen, *A review of the methods for signal estimation in stochastic diffusion leaky integrate-and-fire neuronal models*, Biol. Cybern., 99(2008), 253–262.

[14] P. Lánský, *Sources of periodical force in noisy integrate-and-fire models of neuronal dynamics*, Physical Review E, (2)55(1997), 2040–2043.

[15] B. Oksendal, *Stochastic differential equations*, Springer, 5th edition, (2000).

[16] A.G. Nobile, E. Pirozzi & L.M. Ricciardi, *On the two-boundary first-passage-time problem for Gauss-Markov processes*, Scientiae Mathematicae Japonicae, (2)64(2006), 421–442.

[17] A.G. Nobile, E. Pirozzi & L.M. Ricciardi, *On the estimation of first-passage time densities for a class of Gauss-Markov processes*, LNCS, 4739, Berlin, Springer-Verlag, 2007, 146–153.

[18] L. Sacerdote & M.T. Giraudo, *Stochastic integrate and fire models: a review on mathematical methods and their applications*, in Stochastic biomathematical models with applications to neuronal modeling, Lecture Notes in Math., 2058, Springer, 2013, 99–142.

[19] S. Shinomoto, Y. Sakai & S. Funahashi, *The Ornstein-Uhlenbeck process does not reproduce spiking statistics of cortical neurons*, Neural Computation, 11(1997), 935–951.

[20] T. Taillefumier & M.0. Magnasco, *A fast algorithm for the first-passage times of Gauss-Markov processes with Holder continuous boundaries*, J. Stat. Phys., (6)140(2010), 1130–1156.