Some results for fractional stochastic modelling in biomathematics

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This research is partially supported by the project PRIN-MUR 2022XZSAFN, the project PRIN-PNRR P2022XSF5H, and INdAM-GNCS.

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Introduction

The interaction between myosin and actin proteins inside the sarcomere is the basis of the muscle contraction process.

We propose two stochastic models for the interaction between the myosin head and the actin filament, the physio-chemical mechanism triggering muscle contraction and that is not yet completely understood.

We make use of the fractional calculus approach with the purpose of constructing non-Markov processes for models with *memory*.

A time-changed process and a fractionally integrated process are proposed for the two models. Each of these includes memory effects in a different way.

The investigation of the dwell time of such phenomenon is carried out by means of density estimations of the first exit time (FET) of the processes from a strip; this mimics the times of the Steps of the myosin head during the sliding movement outside a potential well due to the interaction with actin.

For the case of time-changed diffusion process, we specify an equation for the probability density function of the FET from a strip. The schemes of two simulation algorithms are provided and performed. All such results, some numerical and simulation results are given and discussed in

[Nikolai Leonenko, E P. The time-changed stochastic approach and fractionally integrated processes to model the actin-myosin interaction and dwell times. Mathematical Biosciences and Engineering, 2025, 22(4): 1019-1054. doi: 10.3934/mbe.2025037]

A stochastic model

The modeling scheme of the actin-myosin interaction

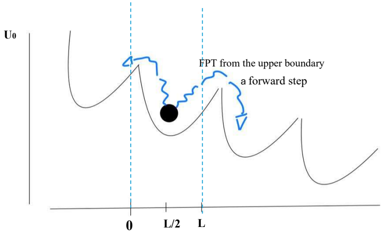


Figure: A simplified drawing: the black ball stands for the myosin head, whereas the periodic tilted structure represents the actin filament. The particle can jump on the right performing a forward step. The time of occurrence of such step is modeled by means of FPT of the particle through the upper boundary in L.

We start by considering the stochastic model proposed in
[G. D'Onofrio, E. P., Two-boundary first exit time of Gauss-Markov processes for stochastic modeling of acto-myosin dynamics, *J. Math. Biol.*, (2017)]
for modeling the actin-myosin interaction, based on the following

SDE:

$$dX = -\left[\frac{1}{\theta}\left(X - \frac{L}{2}\right) - \frac{F(t)}{\beta}\right]dt + \sqrt{\frac{2\kappa_B T}{\beta}}dW, \qquad X(0) = x_0. \quad (1)$$

The above model born by the corresponding Langevin equation

Langevin equation

$$\dot{x} = -\frac{1}{\beta} V'(x) + \sqrt{\frac{2\kappa_B T}{\beta}} \Lambda(t) \quad (2)$$

widely adopted for describing the over-damped motion of a particle subject to a tilted potential

$$V(x) = U(x) - Fx,$$

with $U(x)$ the potential and F the constant tilting force.

Specifically, we list all above functions and parameters and the corresponding modeling meaning:

- F the tilting force: it is the sum of an internal force F_i and an external load F_e, i.e. we have $F = F_i - F_e$,
- $U(x)$ the potential assumed to be a space periodic function with period L (we assume $L = 5.5$ nm equal to the myosin step size).
- β the drag coefficient equal to 90 pN ns/nm,
- T $= 293$ **K** the environmental temperature,
- κ_B the Boltzmann constant.[1]

[1] Note that ($\prime$) is used to indicate the derivative of the function with respect to its own argument; in particular, in (2) ($\prime$) is for the space derivative and ($\cdot$) denotes the time derivative.

In order to include time-varying effects of the tilting force, a time-depending force $F(t)$ was considered in the SDE (1) that corresponds to the Langevin equation (2) by choosing a parabolic potential $U(x)$ such that

$$U(X) = \frac{U_0}{L^2/4}\left(X - \frac{L}{2}\right)^2 \tag{3}$$

where U_0 is the depth of the potential well.

Hence, due to the form of $V(x) = U(x) - F(t)x$ we also have

$$V'(X) = U'(X) - F(t) = \frac{8U_0}{L^2}\left(X - \frac{L}{2}\right) - F(t).$$

Hence, by setting the parameter θ as follows

$$\theta = \frac{\beta L^2}{8U_0} \tag{4}$$

we finally obtain

$$dX = -\left[\frac{U'(X) - F(t)}{\beta}\right] dt + \sqrt{\frac{2\kappa_B T}{\beta}} dW, \tag{5}$$

with W is the standard Brownian motion, and the initial condition is $X(0) = x_0$. For the chosen functions and parameters, the last equation is the same of (1): it constitutes the corresponding Itô version of the Langevin equation (2).

A time-non-homogeneous Ornstein-Uhlenbeck (OU) process $X(t)$ is the solution of SDE (1), that exists under suitable assumptions on the tilting force.

The theory and properties of Gaussian Diffusion (GD) processes can be exploited for the considered case of equation (1).

The dwell time and the first exit time

By setting the starting point $x_0 = L/2$ (that means in the well of the potential), it is possible to model the dwell time of the myosin as the first exit time (FET) random variable

$$T_X = \inf\{t \geq 0 : X(t) \leq 0 \quad \text{or} \quad X(t) \geq L\} \tag{6}$$

through the constant boundaries located at the origin (the lower one) and at L (the upper one).

The FET pdf is:

$$g_X(t|x_0, 0) = \frac{d}{dt} P\{T_X \leq t\}, \quad \text{with} \quad x_0 = L/2. \tag{7}$$

The random variable dwell time plays a key role to model the sliding of the myosin head along the actin filament and the consequent production of ATP energy.

The study of the dwell time and of its distribution is fundamental for the description and the comprehension of the mechanism triggering the muscle contraction. Indeed, such study is also extremely useful to predict pathological effects of drugs or diseases on muscles.

Beyond very few cases for which the pdf of FET is known in closed form, at the moment it is possible to construct approximations of such pdf.

For the stochastic process $X(t)$ evaluations of the pdf of the first passage time through a constant level can be obtained by solving with numerical procedures an integral equation or by some transformation methods or by simulation techniques. In what follows we give specific details for the considered cases.

A time-changed stochastic model

In order to construct a time-changed fractional model, we adopt the stochastic process $\{X(t), t \geq 0\}$ solution of (1) as the parent process, and we compose it with a stochastic time.

The time-change is obtained by substituting the time with the positive non-decreasing process $E_\alpha(t)$ that is the inverse of an α-stable subordinator process $\sigma_\alpha(t)$. We finally consider in place of $X(t)$ the following process:

$$Y_\alpha(t) = X(E_\alpha(t)).$$

By adopting such a model many theoretical results of

[N. Leonenko, E. P., First passage times for some classes of fractional time-changed diffusions, *Stochast. Anal. Appl.*, (2021)]

can be exploited and contribute to enrich the description of this biological phenomenon. With this in mind, we recall some mathematical essentials about the time-changed fractional process Y_α.

Essentials on processes for the time-change

For $\alpha \in (0,1)$, an α-stable subordinator $\sigma_\alpha(t)$ [M. M. Meerschaert, P. Straka, (2013), Bertoin (1996)] is a strictly increasing positive Lévy process that for $\lambda > 0, t > 0$ has the Laplace transform:

$$\mathbb{E}[e^{-\lambda \sigma_\alpha(t)}] = e^{-t\lambda^\alpha},$$

with Laplace exponent λ^α and $\mathbb{E}$ being the expectation operator.

A particular property of the subordinator process is the scaling property

$$\sigma_\alpha(t) \stackrel{d}{=} t^{1/\alpha}\sigma_\alpha(1),$$

which is extremely useful in simulation algorithms.

(Note that the notation $\stackrel{d}{=}$ establishes the equality between finite dimensional distributions of the involved processes.)

The inverse α-stable subordinator $E_\alpha(t)$ is defined as follows

$$E_\alpha(t) := \inf\{r > 0 : \ \sigma_\alpha(r) > t\}, \tag{8}$$

For any $t > 0$, the random variables $\sigma_\alpha(t)$ and $E_\alpha(t)$ are absolutely continuous ([M. M. Meerschaert, P. Straka, (2013)]).

Then, the Laplace-Stieltjes transform of $E_\alpha(t)$ is the following Mittag-Leffler function

$$\mathbb{E}[e^{-zE_\alpha(t)}] = \mathcal{E}_\alpha(-zt^\alpha), \tag{9}$$

where the one-parameter Mittag-Leffler function is defined as

$$\mathcal{E}_\alpha(y) = \sum_{k=0}^{\infty} \frac{y^k}{\Gamma(1+\alpha k)}, y, \alpha \in C, \mathbb{R}(\alpha) > 0, \tag{10}$$

The inverse of α-stable subordinator $E_\alpha(t)$ is a self-similar processes, i.e.,

$$E_\alpha(t) \overset{d}{=} b^{-\alpha} E_\alpha(bt) \quad \forall t \geq 0,\ b > 0, \tag{11}$$

The $E_\alpha(t)$ process has mean

$$\mathbb{E}[E_\alpha(t)] = \frac{t^\alpha}{\Gamma(\alpha+1)}, \tag{12}$$

and the covariance function (cf. [N. Leonenko et al. (2014)] and [N. Leonenko, E.P. (2021)]) for $0 < s \leq t$:

$$cov[E_\alpha(s), E_\alpha(t)] = \frac{[\alpha s^{2\alpha} B(\alpha, \alpha+1) + F(\alpha; s, t)]}{(\Gamma(\alpha+1))^2}, \tag{13}$$

Equation (13) involves special functions: the *Beta function* $B(a, b)$, the *hypergeometric function*

$$F(\alpha; s, t) = \alpha t^{2\alpha} B(\alpha, \alpha+1; s/t) - (st)^\alpha$$

and the *incomplete beta function* $B(a, b; x)$, which for $x \in [0, 1]$, is defined as

$$B(a, b; x) = \int_0^x u^{a-1}(1-u)^{b-1} du,$$

with $B(a, b) = B(a, b; 1)$.

It is immediately available from (13) the expression of the variance:

$$var[E_\alpha(t)] = t^{2\alpha}\left[\frac{2}{\Gamma(2\alpha+1)} - \frac{1}{(\Gamma(\alpha+1))^2}\right], \qquad (14)$$

It is important to recall the asymptotic power law behavior of the covariance ([N. Leonenko, et al. (2014)]), that is

$$cov[E_\alpha(s), E_\alpha(t)] \overset{t\to\infty}{\to} \frac{s^{2\alpha}}{\Gamma(2\alpha+1)}, \qquad (15)$$

by which the long-range dependence of such a process turns out.

If we denote by $\nu_\alpha(x,t)$ the probability density function (pdf) of $E_\alpha(t)$ and by $\gamma_\alpha(x)$ the pdf of $\sigma_\alpha(1)$, a relationship between them can be highlighted

$$\nu_\alpha(x,t) = \frac{t}{\alpha} x^{-1-\frac{1}{\alpha}} \gamma_\alpha(t x^{-\frac{1}{\alpha}}), \qquad x \geq 0,\ t > 0. \tag{16}$$

Recalling that $E_\alpha(t)$ assumes positive values for any $t > 0$, its density is zero for $x < 0$, with a discontinuity in $x = 0$ (see the Appendix of [N. Leonenko, E.P. (2021)] for further details).

In particular, we keep in mind that E_α is an increasing, continuous process with constant values corresponding to the jumps of σ_α.

Finally, we take note of the Laplace transform of $\nu_\alpha(x,t)$ with respect to t:

$$\mathcal{L}_{t\to\lambda}[\nu_\alpha(x,t)] = \lambda^{\alpha-1}e^{-x\lambda^\alpha}, \tag{17}$$

The time-changed process

The time-changed process is the composition of two processes: the parent process $X(t)$ and the inverse of an α-stable subordinator $E_\alpha(t)$, independent on $X(t)$.

The resulting time-changed process $Y_\alpha(t) = X(E_\alpha(t))$ has continuous sample paths because the parent process is continuous.

Specifically, $Y_\alpha(t)$ is constructed by using a time-non-homogeneous GD process as the parent process (the solution process of (1)), and the inverse of an $\alpha-$stable subordinator processes for the time-change with pdf $\nu_\alpha(s, t)$.

In general, if $f(x,s)$ is the pdf of the parent process, the time-changed process has the following pdf:

$$f_\alpha(x,t) = \int_0^{+\infty} f(x,s)\nu_\alpha(s,t)ds \quad \forall t \in I \subset \mathbb{R}, \tag{18}$$

Furthermore, by means of the change of variable $ts^{-1/\alpha} = w$ and (16) , (18) can alternatively be written as

$$f_\alpha(x,t) = \int_0^{+\infty} f\left(x, \left(\frac{t}{w}\right)^\alpha\right)\gamma_\alpha(w)dw \quad \forall t \in I, \tag{19}$$

In the specific case of the process $X(t)$ solution of (1), we know its pdf $f(x,t)$ is a normal density with mean:

$$m_X(t) = \mathbb{E}[X(t)] = x_0 e^{-t/\theta} + \frac{L}{2}\left(1 - e^{-t/\theta}\right) + e^{-t/\theta}\int_0^t \frac{F(\tau)}{\beta} e^{\tau/\theta} d\tau, \tag{20}$$

and the covariance function

$$c(s,t) = cov[X(s), X(t)] = \frac{\kappa_B T}{\beta}\theta\left(e^{s/\theta} - e^{-s/\theta}\right)e^{-t/\theta} \quad (0 \le s \le t), \tag{21}$$

Due to the Gauss-Markov nature of process $X(t)$, its covariance is the product of two functions

$$\rho(t) = \sqrt{\frac{2\kappa_B T}{\beta}\frac{\theta}{2}\left(e^{t/\theta} - e^{-t/\theta}\right)}, \quad \eta(t) = \sqrt{\frac{2\kappa_B T}{\beta}} e^{-t/\theta}, \tag{22}$$

whose ratio $r(t) = \rho(t)/\eta(t)$ is a monotonically non-decreasing function.

Hence, from (18) or (19), we are able to specify the subordinated pdf of the time-changed process $Y_\alpha(t)$. In particular, we can also determine its mean and covariance functions by recalling that for the GD process $X(t)$, the Doob transform holds, i.e.,

$$X(t) = m_X(t) + \eta(t)W(r(t)), \tag{23}$$

where $\{W(t), t \geq 0\}$ is the standard Brownian motion, $r(t) = \rho(t)/\eta(t)$ with $\eta(t), \rho(t)$ being the functions in (22) (see [Di Nardo et al. (2001)]).

From the Doob transform, the time-changed Y_α process is such that

$$Y_\alpha(t) = X(E_\alpha(t)) = m_X(E_\alpha(t)) + \eta(E_\alpha(t))W(r(E_\alpha(t))), \quad (24)$$

with $\eta(t)$, $m_X(t) \in C^1(I)$, $r(t)$ positive monotone increasing $C^1(I)$–function (with $r(0) = 0$) and

$W(r(E_\alpha(t)))$ is the time-changed Brownian motion.

On the moments of the time-changed process

Note that the time-changed process Y_α is no more Gaussian and no more Markov process.

The expectation

By exploiting the independence of E_α from W, we can calculate the mean of Y_α:

$$\mathbb{E}[Y_\alpha(t)] = \mathbb{E}[m_X(E_\alpha(t))] + \mathbb{E}[\eta(E_\alpha(t))W(r(E_\alpha(t)))] = \mathbb{E}[m_X(E_\alpha(t))], \tag{25}$$

From (20), (12) and (9), we finally have:

$$\mathbb{E}[Y_\alpha(t)] = \mathbb{E}[\mathbb{E}[m_X(u)|E_\alpha(t) = u]]$$
$$= x_0 \mathcal{E}_\alpha(-t^\alpha/\theta) + \frac{L}{2}[1 - \mathcal{E}_\alpha(-t^\alpha/\theta)] + \mathbb{E}[e^{-E_\alpha(t)/\theta} \int_0^{E_\alpha(t)} \frac{F(\tau)}{\beta} e^{\tau/\theta} d\tau].$$

Such a mean function, in case of a constant force $F(t) \equiv F$, immediately becomes:

$$\mathbb{E}[Y_\alpha(t)] = x_0 \mathcal{E}_\alpha(-t^\alpha/\theta) + \frac{L}{2}\left[1 - \mathcal{E}_\alpha(-t^\alpha/\theta)\right] + \frac{F\theta}{\beta}(1 - \mathcal{E}_\alpha(-t^\alpha/\theta)).$$

In case of a decaying exponential force $F(t) = Fe^{-t/c}$ with $t, c > 0$, we have

$$
\begin{aligned}
&\mathbb{E}[Y_\alpha(t)] \\
&= x_0 \mathcal{E}_\alpha(-t^\alpha/\theta) + \frac{L}{2}\left[1 - \mathcal{E}_\alpha(-t^\alpha/\theta)\right] \\
&+ \frac{F\theta c}{\beta(c-\theta)}\left[\mathcal{E}_\alpha(-t^\alpha/c) - \mathcal{E}_\alpha(-t^\alpha/\theta)\right].
\end{aligned}
$$

It appears evident that the mean is written in terms of several Mittag-Leffler functions.

The covariance

Then, by recalling the independence of the Brownian motion W from the inverse subordinator E_a, the covariance of $Y_\alpha(t)$ can be evaluated, for $s < t$, as follows:

$$cov(Y_\alpha(s), Y_\alpha(t)) \tag{26}$$

$$= \mathbb{E}[\eta(E_\alpha(s))\eta(E_\alpha(t))]cov(W(r(E_\alpha(s))), W(r(E_\alpha(t)))). \tag{27}$$

By taking into account that $cov(W(r(E_\alpha(s))), W(r(E_\alpha(t))))=$ $\mathbb{E}(W(r(E_\alpha(s))), W(r(E_\alpha(t)))) = \mathbb{E}[\min\{r(E_\alpha(s)), r(E_\alpha(t))\}]$, one has

$$cov(Y_\alpha(s), Y_\alpha(t)) = E[\eta(E_\alpha(s))\eta(E_\alpha(t))r(E_\alpha(s))] \tag{28}$$

due to the function $r(\cdot)$ and the process E_α both increasing.

The explicit expressions of the functions $\eta(\cdot)$ and $r(\cdot)$ of the parent process $X(t)$ are that of the $\eta(t)$ function as in (22) and

$$r(t) = \frac{\theta}{2}\left(e^{2t/\theta} - 1\right),$$

respectively. Hence, in our specific case, we have

$$\begin{aligned} cov(Y_\alpha(s), Y_\alpha(t)) &= \frac{\kappa_B T\theta}{\beta}\mathbb{E}\left[e^{-E_\alpha(s)/\theta}e^{-E_\alpha(t)/\theta}\left(e^{2E_\alpha(s)/\theta} - 1\right)\right] \\ &= \frac{\kappa_B T\theta}{\beta}\mathbb{E}\left[e^{(E_\alpha(s)-E_\alpha(t))/\theta} - e^{-(E_\alpha(s)+E_\alpha(t))/\theta}\right]. \quad (29) \end{aligned}$$

We apply the self-similarity property (11) of the process E_α, that gives $E_\alpha(t) = E_\alpha(ks) \stackrel{d}{=} k^\alpha E_\alpha(s)$, and finally we obtain

$$cov(Y_\alpha(s), Y_\alpha(t)) = \frac{\kappa_B T\theta}{\beta}\left\{\mathcal{E}_\alpha\left(-\frac{t^\alpha - s^\alpha}{\theta}\right) - \mathcal{E}_\alpha\left(-\frac{t^\alpha + s^\alpha}{\theta}\right)\right\} \quad (30)$$

where we used (9).

The long-range dependence of the covariance of $Y_\alpha(t)$ can be deduced from the asymptotic behaviors of the above Mittag-Leffler functions involved in its expression. Indeed, it is sufficient to recall from [Mainardi (2014)] that, for $0 < \alpha < 1$, and $z > 0$,

$$\mathcal{E}_\alpha(-z^\alpha) \sim \frac{z^{-\alpha}}{\Gamma(1-\alpha)}, \qquad z \to +\infty.$$

This also means that the long-range dependence property of $E_\alpha(t)$ is inherited in the time-changed process $Y_\alpha(t)$.
From (30), we can also specify the variance:

$$Var(Y_\alpha(t)) = \frac{\kappa_B T\theta}{\beta}\left[1 - \mathcal{E}_\alpha\left(-\frac{2t^\alpha}{\theta}\right)\right]. \tag{31}$$

The dwell-time pdf by subordinated FET of the time-changed process

We give some known results about the FET T_X of $X(t)$ defined in (6) evolving in the strip $[0, L] \in \mathbb{R}$ with $L > 0$, starting from $X(0) = x_0 \in [0, L]$ (in particular, we chose $X_0 = L/2$).

It is such that $T_X = \min\{\mathcal{T}_0, \mathcal{T}_L\}$, where $\mathcal{T}_0$ and $\mathcal{T}_L$ are the FPTs through the lower constant boundary 0 and the upper one L, respectively, i.e.,

$$\mathcal{T}_0 = \inf\{t \geq 0 : X(t) \leq 0 \quad \text{and} \quad X(s) < L, \quad \forall\, 0 \leq s < t\}, \tag{32}$$

$$\mathcal{T}_L = \inf\{t \geq 0 : X(t) \geq L \quad \text{and} \quad X(s) > 0, \quad \forall\, 0 \leq s < t\}, \tag{33}$$

Moreover, $g_{\mathcal{T}_0}(t|x_0,0)$ and $g_{\mathcal{T}_L}(t|x_0,0)$ are the density functions of FPTs $\mathcal{T}_0$ and $\mathcal{T}_L$, respectively.
Hence, the FET pdf of T of $X(t)$ defined in (6) is such that

$$g_X(t|x_0,0) = g_{\mathcal{T}_0}(t|x_0,0) + g_{\mathcal{T}_L}(t|x_0,0), \tag{34}$$

$g_{\mathcal{T}_0}(t|x_0,0)$ and $g_{\mathcal{T}_L}(t|x_0,0)$ are solutions of the two following coupled integral equations:

$$g_{\mathcal{T}_0}(t|x_0,0) = \psi_1(t|x_0,0) - \int_0^t \Big[\psi_1(t|0,\tau)g_{\mathcal{T}_0}(\tau|x_0,0) + \psi_1(t|L,\tau)g_{\mathcal{T}_L}(\tau|x_0,0)\Big]d\tau$$

$$g_{\mathcal{T}_L}(t|x_0,0) = -\psi_2(t|x_0,0) + \int_0^t \Big[\psi_2(t|0,\tau)g_{\mathcal{T}_0}(\tau|x_0,0) + \psi_2(t|L,\tau)g_{\mathcal{T}_L}(\tau|x_0,0)\Big]d\tau \tag{35}$$

where

$$\begin{aligned}\psi_j(t|z,\tau) := -\Big\{ & m'(t) + [S_j - m(t)]\ \frac{\rho'(t)\eta(\tau) - \eta'(t)\rho(\tau)}{\rho(t)\eta(\tau) - \eta(t)\rho(\tau)} \\ & + [z - m(\tau)]\ \frac{\eta'(t)\rho(t) - \rho'(t)\eta(t)}{\rho(t)\eta(\tau) - \eta(t)\rho(\tau)}\Big\}\, f_X[S_j, t|z,\tau] \quad (j = 1, 2)\end{aligned} \tag{33}$$

with $f_X[x,t|z,\tau]$ being the transition pdf of $X(t)$ and with $S_1 = 0$, $S_2 = L$.

Note that the FET pdf (34) of $X(t)$ can be evaluated by applying the standard numerical algorithms for the resolution of this kind of integral equation as (35) or a specific algorithm given in [A. Nobile, E.P. (2006)].

Due to the Gaussian distribution of the $X(t)$ process, only the mean and covariance functions of the process are required to apply the numerical procedure; consequently, the functions $\psi_i(t|z,\tau)$ $(i = 1, 2)$ involved in the integral equations are also completely specified.

For the FET of the time-changed process $Y_\alpha(t)$, we can proceed similarly to the case of subordinated FPT. Specifically, we define the subordinated FPT pdfs:

$$g_{\mathcal{T}_0,\alpha}(t|x_0,0) = \int_0^\infty g_{\mathcal{T}_0}(\vartheta|x_0,0)\nu_\alpha(\vartheta,t)d\vartheta, \tag{37}$$

$$g_{\mathcal{T}_L,\alpha}(t|x_0,0) = \int_0^\infty g_{\mathcal{T}_L}(\vartheta|x_0,0)\nu_\alpha(\vartheta,t)d\vartheta, \tag{38}$$

in such a way that the FET is:

$$g_{X,\alpha}(t|x_0,0) = g_{\mathcal{T}_0,\alpha}(t|x_0,0) + g_{\mathcal{T}_L,\alpha}(t|x_0,0), \tag{39}$$

Proposition

The subordinated FPT pdf $g_{\mathcal{T}_0,\alpha}(t|x_0,0)$ and $g_{\mathcal{T}_L,\alpha}(t|x_0,0)$ are solutions of the two following coupled equations:

$$g_{\mathcal{T}_0,\alpha}(t|x_0,0) = \psi_{1,\alpha}(t|x_0,0) - \int_0^t \Big[\psi_{1,\alpha}(t|0,\tau)g_{\mathcal{T}_0}(\tau|x_0,0) + \psi_{1,\alpha}(t|L,\tau)g_{\mathcal{T}_L}(\tau|x_0,0)\Big]d\tau \tag{40}$$

$$g_{\mathcal{T}_L,\alpha}(t|x_0,0) = -\psi_{2,\alpha}(t|x_0,0) + \int_0^t \Big[\psi_{2,\alpha}(t|0,\tau)g_{\mathcal{T}_0}(\tau|x_0,0) + \psi_{2,\alpha}(t|L,\tau)g_{\mathcal{T}_L}(\tau|x_0,0)\Big]d\tau$$

and

$$\psi_{j,\alpha}[t|y,\tau] = \int_0^\infty \psi_j[\vartheta|y,\tau]\nu_\alpha(\vartheta,t)d\vartheta. \tag{41}$$

Numerical procedures can be devised in order to solve the coupled equations (40), but note that for each value of t, a quadrature procedure is also required for evaluations of (41) and finally to obtain approximations of the FET density (39).

Additionally, evaluations of FPT pdfs for the parent process $X(t)$ are also required.
Even if it is a practicable method, a particular effort can be done to reduce the computational cost of such procedures. This will be the object of our future work.

An alternative method is provided by simulation algorithms.

Simulation algorithms for fractional stochastic models

We propose some possible simulation algorithms for fractional stochastic models suitably specified for the actin-myosin dynamics. First, we provide the algorithm for the simulation of trajectories of the time-changed process $Y_\alpha(t)$ and the sampling of its first exit times.

Trajectories of the time-changed process can be simulated following the Steps listed below, and then samples of simulated dwell-times can be provided. Consequentially, from simulations, it is possible to give estimations of the pdf of the dwell-time of the actin-myosin interaction for the proposed model.

The Simulation Algorithm

The main Steps of the simulation algorithm are:

- Step1: in INPUT, provide the values of parameters: α, β, θ, L, the force F, the Step size value Δt for the time discretization, N as the maximum number of time Steps, and M the sample size of dwell times to be simulated;
- Step2: generate in correspondence to time instants $0 = t_0 < t_{\Delta t} < t_{2\Delta t} < \cdots < t_{N\Delta t}$ the random variables $E_\alpha(t_{\Delta t}) < E_\alpha(t_{2\Delta t}) < \cdots < E_\alpha(t_{N\Delta t})$ by using ad hoc functions of R programming packages. In short: use the R-package *stabledist* to generate the random time $\sigma_\alpha(s)$ of the α-stable subordinator; then, according to the definition (8), determine the value $E_\alpha(t)$ as the FPT of $\sigma_\alpha(s)$ by t .

• Step3: generate a random path of the time-changed Brownian motion in the random times $r(E_\alpha(t_{\Delta t})) < r(E_\alpha(t_{2\Delta t})) < \cdots < r(E_\alpha(t_{N\Delta t}))$, i.e., $W(r(E_\alpha(t_{\Delta t}))), \dots, W(r(E_\alpha(t_{N\Delta t}))$ as

$$W(r(E_\alpha(t_{i\Delta t})) = W(r(E_\alpha(t_{(i-1)\Delta t}))+\sqrt{r(E_\alpha(t_{i\Delta t})) - r(E_\alpha(t_{(i-1)\Delta t}))}Z_i$$

for $i = 1, \dots, N$, with $W(r(E_\alpha(t_0)) = 0$, with $Z_i \sim \mathcal{N}(0,1)$ as standard normal random variables;

• Step4: evaluate a random path of $Y_\alpha(i\Delta t) = X(E_\alpha(t_{i\Delta t}))$ by means of (24) for $i = 1, \ldots, N$, i.e.,

$$X(E_\alpha(t_{i\Delta t})) = m_X(E_\alpha(t_{i\Delta t})) + \eta(E_\alpha(t_{i\Delta t}))W(r(E_\alpha(t_{i\Delta t}))$$

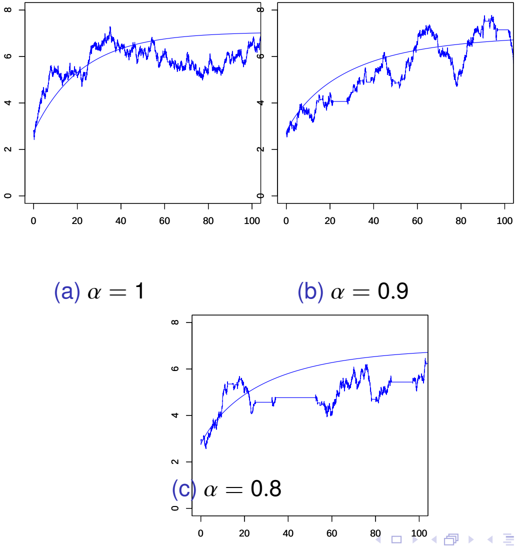
for $i = 1, \ldots, N$, with function $m_X(\cdot)$ being given in (20) and $\eta(\cdot)$ in (22);

• Step5: check if $X(E_\alpha(t_{i\Delta t}))$ is over the level L or under level zero; if so, and if it is the first time this occurs, record the correspondent time instant $E_\alpha(t_{i\Delta t})$ that will be an instance of the dwell time (i.e., the FPT of the time-changed process);

• Step6: go to Step2 and repeat the procedure M times with different seeds for the generation of the sequences of N random instants $E_\alpha(t_{\Delta t}) < E_\alpha(t_{2\Delta t}) < \cdots < E_\alpha(t_{N\Delta t})$ providing the M simulated trajectories of the time-changed process.
• Step7: plot an histogram and/or an approximating density for the sample of the simulated M dwell times.

Note that, for the numerical evaluation of Mittag-Leffler functions in Step4, we use the *MittagLeffleR* R-package.

Means and trajectories with constant tilting force

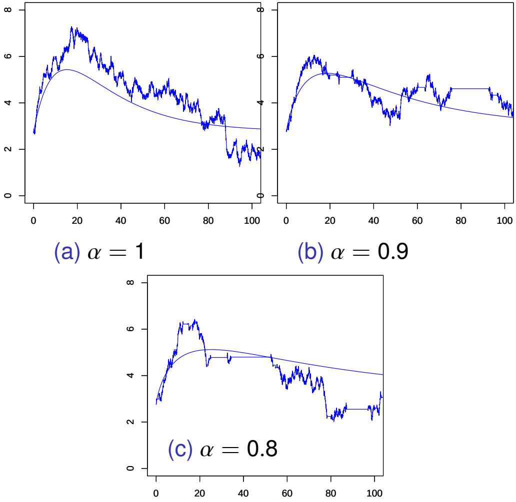


(a) $\alpha = 1$

(b) $\alpha = 0.9$

(c) $\alpha = 0.8$

Means and trajectories with a time-dependent tilting force



(a) $\alpha = 1$ (b) $\alpha = 0.9$

(c) $\alpha = 0.8$

Mean functions of $Y_\alpha(t)$ (solid line) and corresponding simulated trajectories by means of Algorithm 1 with the time discretization Step $\Delta t = 0.01$. (a) the classical (integer case); (b)-(c) mean function (26) and a simulated path of the time-changed process $Y_\alpha(t)$ with a constant tilting force $F/\beta = 0.2$ and specified α values; (d) the classical (integer case); (e)-(f) the same for the mean function (26) with a time-dependent tilting force $\frac{F}{\beta}e^{-t/c}$ with $F/\beta = 0.5, c = \theta/2$ and specified α values.

Mean functions

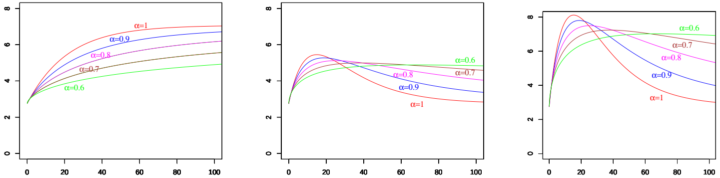


Figure: Left: Mean functions (26) of the time-changed process $Y_\alpha(t)$ with a constant tilting force $F/\beta = 0.2$ for several specified α values. Middle: Mean functions (26) of the time-changed process $Y_\alpha(t)$ with a time-dependent tilting force $\frac{F}{\beta}(e^{-t/c})$ with $F/\beta = 0.2, c = \theta/2$. Right: Mean functions (26) of the time-changed process $Y_\alpha(t)$ with a time-dependent tilting force $\frac{F}{\beta}e^{-t/c}$ with $F/\beta = 1$.

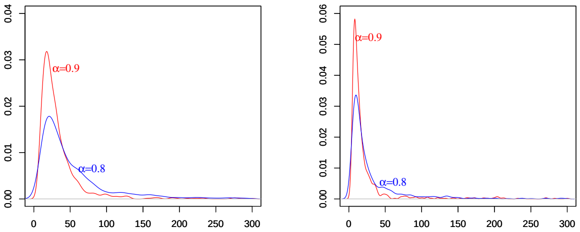


Figure: Dwell time (FET) density estimations by 10^3 simulated paths of the time-changed process $Y_\alpha(t)$ with the time discretization Step $\Delta t = 0.01$, with a constant tilting force $F/\beta = 0.2$ (LEFT), and with a time-dependent tilting force $\frac{F}{\beta}(e^{-t/c})$ with $F/\beta = 0.2, c = \theta/2$ (RIGHT).

Fractionally integrated processes to model the actin-myosin dynamics

Another way to model memory effects in the dynamics of the actin-myosin is to reconsider equation (1) and substitute the classical derivative with the fractional Caputo derivative, in such a way that the following fractional SDE can be assumed for the model:

$$D^{\alpha}\mathcal{X} = -\left[\frac{1}{\theta}\left(\mathcal{X} - \frac{L}{2}\right) - \frac{F(t)}{\beta}\right]dt + \sqrt{\frac{2\kappa_B T}{\beta}}dW, \qquad \mathcal{X}(0) = x_0 \in (0, L), \tag{42}$$

Here, by following the approach adopted in [E.P. (2024)], we first recall the theoretical results of [P. T. Anh et al. (2019)] and specialize them for this kind of equations. Note that the stochastic fractional differential equation (42) will be understood in a sense of equation (5) of [P. T. Anh et al. (2019)] (to avoid collision with the theory developed in [M. G. Hahn, K. Kobayashi, S. Umarov (2011)] and [K. Kobayashi (2011)]). Indeed, by comparing with Eq. (2) of [P. T. Anh et al. (2019)], this fractional SDE can also be written as follows

$$\frac{1}{\Gamma(1-\alpha)}\int_0^t D\mathcal{X}(\tau)(t-\tau)^{-\alpha}d\tau \tag{43}$$

$$= -\left[\frac{1}{\theta}\left(\mathcal{X}(t)-\frac{L}{2}\right)-\frac{F(t)}{\beta}\right]+\sqrt{\frac{2\kappa_B T}{\beta}}\frac{dW}{dt}, \qquad \mathcal{X}(0)=x_0\in(0,L),$$

with $D=\frac{d}{dt}$ the usual derivative.

Proposition

The solution process of (42) *is*

$$\begin{aligned}\mathcal{X}(t) = \mathcal{E}_\alpha(-t^\alpha/\theta)x_0 &+ \frac{L}{2\theta}\int_0^t (t-s)^{\alpha-1}\mathcal{E}_{\alpha,\alpha}\left(-(t-s)^\alpha/\theta\right) ds \\ &+ \frac{1}{\beta}\int_0^t (t-s)^{\alpha-1}\mathcal{E}_{\alpha,\alpha}\left(-(t-s)^\alpha/\theta\right) F(s) ds \\ &+ \sqrt{\frac{2\kappa_B T}{\beta}}\int_0^t (t-s)^{\alpha-1}\mathcal{E}_{\alpha,\alpha}\left(-(t-s)^\alpha/\theta\right) dW_s.\end{aligned} \tag{44}$$

Moments of $\mathcal{X}(t)$

The solution process (44) is a Gaussian process (see, for instance, [G.Ascione, E.P. (2021)]:Theorem 4) with the following mean:

$$\begin{aligned}\mathbb{E}[\mathcal{X}(t)] = \mathcal{E}_\alpha(-t^\alpha/\theta)x_0 \quad &+ \quad \frac{L}{2\theta}\int_0^t (t-s)^{\alpha-1}\mathcal{E}_{\alpha,\alpha}\left(-(t-s)^\alpha/\theta\right) ds \\ &+ \quad \frac{1}{\beta}\int_0^t (t-s)^{\alpha-1}\mathcal{E}_{\alpha,\alpha}\left(-(t-s)^\alpha/\theta\right) F(s)ds.\end{aligned}$$

The calculus of its covariance leads to:

$$Cov(\mathcal{X}(u), \mathcal{X}(t)) = \mathbb{E}[(\mathcal{X}(u) - \mathbb{E}[\mathcal{X}(u)]) \cdot (\mathcal{X}(t) - \mathbb{E}[\mathcal{X}(t)])]$$

$$= \frac{2\kappa_B T}{\beta} \mathbb{E}\left[\int_0^u (u-s)^{\alpha-1} \mathcal{E}_{\alpha,\alpha}\left(-(u-s)^\alpha/\theta\right) dW_s \int_0^t (t-s)^{\alpha-1} \mathcal{E}_{\alpha,\alpha}\left(-(t-s)^\alpha/\theta\right) dW_s \right]$$

$$= \frac{2\kappa_B T}{\beta} \mathbb{E}\left[\mathfrak{I}^\alpha \left(\mathcal{E}_{\alpha,\alpha}\left(-(u-s)^\alpha/\theta\right) dW_u \right) \mathfrak{I}^\alpha \left(\mathcal{E}_{\alpha,\alpha}\left(-(t-s)^\alpha/\theta\right) dW_t \right) \right] \quad (45)$$

where $\mathfrak{I}^\beta$ is the stochastic fractional integral is that defined in [E.P. (2024)].

Finally, by solving Eq.(45) as in [E.P. (2024)], we obtain, for $u < t$,

$$Cov(\mathcal{X}(u), \mathcal{X}(t)) = \frac{2\kappa_B T}{\beta} \int_0^u (u-s)^{\alpha-1} \mathcal{E}_{\alpha,\alpha}\left(-(u-s)^{\alpha}/\theta\right) (t-s)^{\alpha-1} \mathcal{E}_{\alpha,\alpha}\left(-(t-s)^{\alpha}/\theta\right) ds.$$

From the covariance we can also derive the variance as follows:

$$Var(\mathcal{X}(t)) = \frac{2\kappa_B T}{\beta} \int_0^t (t-s)^{2\alpha-2} \left(\mathcal{E}_{\alpha,\alpha}\left(-(t-s)^{\alpha}/\theta\right)\right)^2 ds. \quad (47)$$

We remark that the provided expressions of the mean (45) and of the covariance (45) of the process $\mathcal{X}(t)$ are extremely useful to obtain simulations of these processes.

A strategy for simulations of sample paths of $\mathcal{X}(t)$ is that adopted in Section 3 of [E.P. (2018)], substantially based on the following discretization formula of the Caputo derivative, for $t = N\Delta t$:

$$D^\alpha \mathcal{X}(t) \approx \frac{(\Delta t)^{-\alpha}}{\Gamma(2-\alpha)} \sum_{k=0}^{N-1} [\mathcal{X}((k+1)\Delta t) - \mathcal{X}(k\Delta t)][(N-k)^{1-\alpha} - (N-k-1)^{1-\alpha}], \tag{48}$$

From (48), an iterative discretization scheme of the fractional SDE (42) can be derived and, specifically, the simulation of sample paths is obtained as follows:

SIMULATION Algorithm

Step1: in INPUT, provide the values of parameters: α, β, θ, L, the force F, the Step size value Δt for the time discretization, N the maximum number of time Steps, and M the sample size of dwell times to be simulated;

Step2: in correspondence to time instants $0 = t_0 < t_{\Delta t} < t_{2\Delta t} < \cdots < t_{N\Delta t}$ construct the path of $\mathcal{X}(t)$ process adopting the following iterative scheme:

$$\mathcal{X}(n\Delta t) = \mathcal{X}((n-1)\Delta t) - \sum_{k=0}^{n-2}[\mathcal{X}((k+1)\Delta t) - \mathcal{X}(k\Delta t)][(n-k)^{1-\alpha} - (n-k-1)^{1-\alpha}]$$
$$+(\Delta t)^{\alpha}\Gamma(2-\alpha)\left(-\frac{1}{\theta}\mathcal{X}((n-1)\Delta t) + \frac{L}{2\theta} + \frac{F((n-1)\Delta t)}{\beta} + \sqrt{\frac{2\kappa_B T}{\beta}}\frac{Z_n}{\Delta t}\right), \ n=2,\ldots,N, \tag{49}$$

with $Z_n \sim \mathcal{N}(0, \Delta t)$ normal random variables, $\mathcal{X}(0) = x_0$ and

$$\mathcal{X}(\Delta t) = \mathcal{X}(0) + \frac{(\Delta t)^{\alpha}\Gamma(2-\alpha)}{2}\left(-\frac{1}{\theta}\mathcal{X}(0) + \frac{L}{2\theta} + \frac{F(0)}{\beta} + \sqrt{\frac{2\kappa_B T}{\beta}}\frac{Z_1}{\Delta t}\right)$$

Step3: check if $\mathcal{X}(n\Delta t)$ is over the L value or under zero; if so, and if it is the first time this occurs, record the correspondent time instant $n\Delta t$ that will be an instance of the dwell time;

Step4: go to Step2 and repeat the procedure M times with different seeds for the generation of the sequences of N independent random pseudo-Gaussian numbers $Z_n \sim \mathcal{N}(0, \Delta t)$, $n = 1, \ldots, N$, providing the M simulated trajectories of the process $\mathcal{X}(t)$.

Step5: plot an histogram or/and an approximating density for the sample of the simulated M dwell times.

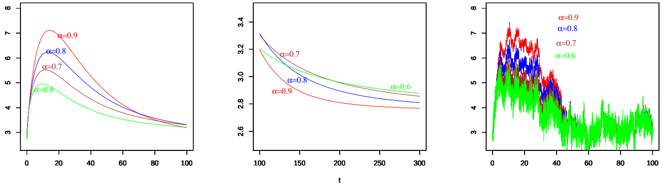


Figure: Left: Mean functions from Eq. (45) of the fractionally integrated process $\mathcal{X}(t)$ with the time-dependent tilting force $\frac{F}{\beta}e^{-t/c}$ with $F/\beta = 1$, $c = \theta/2$. Middle: Tails of the same mean functions on left. Right: Simulated trajectories by means of Algorithm 2 of the same process $\mathcal{X}(t)$ with the same tilting force as on the left, and $\Delta t = 0.01$.

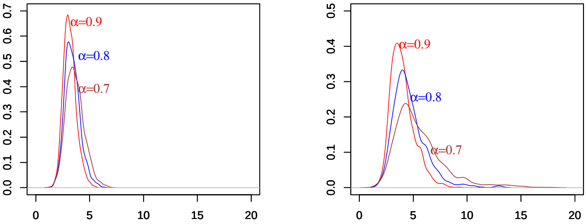


Figure: Dwell time (FET) density estimations by 10^3 simulated paths by means of Algorithm 2 of the fractionally integrated process $\mathcal{X}(t)$. Left: Constant tilting force $F/\beta = 1$. Right: Time-dependent tilting force $F/\beta e^{-t/c}$ with $F/\beta = 1$, $c = \theta/2$.

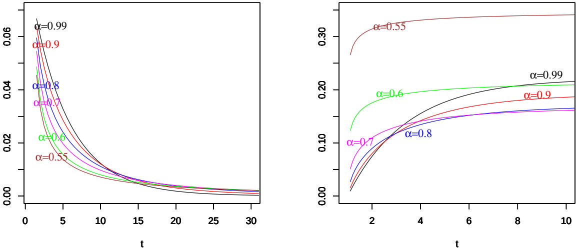


Figure: Left: Covariance $cov(\mathcal{X}(s), \mathcal{X}(t))$ as in Eq. (46) with $s = 1$, for $t > s$, time Step size $\Delta t = 0.5$. Right: Variance of $\mathcal{X}(t)$ as in Eq. (47) with time Step size $\Delta t = 0.1$

Coming Back to the time-changed process $Y(t)$

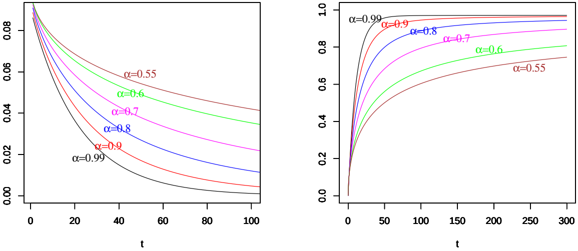


Figure: Left: Covariance $cov(Y_\alpha(s), Y_\alpha(t))$ as in Eq. (30) with $s = 1$, for $t > s$, time Step size $\Delta t = 1$. Right: Variance as in Eq. (31)

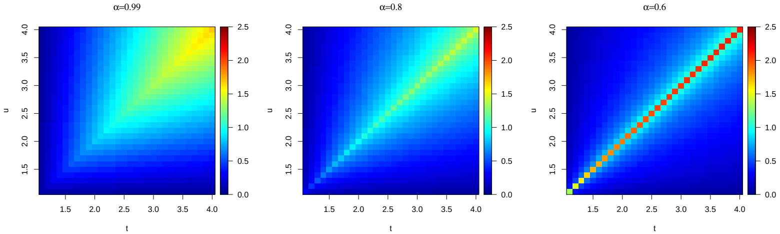


Figure: Color map of covariance of $X(t)$ as in (46)

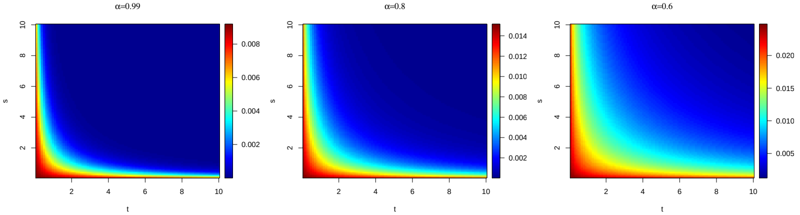
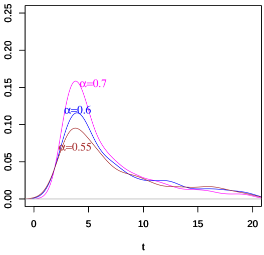


Figure: Color maps for the covariance $cov(Y_\alpha(s), Y_\alpha(t))$ as in Eq. (30): $s = 0.1$, time Step size $\Delta t = 0.1$.



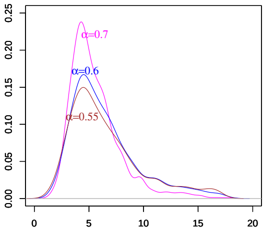


Figure: Comparisons of simulated dwell times. LEFT: FET density estimations by 10^3 simulated paths by Algorithm 1 of the time-changed process $Y_\alpha(t)$ with a time-dependent tilting force $Fe^{-t/c}/\beta$ with $F/\beta = 1, c = \theta/2$. RIGHT: FET density estimations by means of Algorithm 2 of the fractionally integrated process $\mathcal{X}(t)$ with the same time-dependent tilting force. (In both cases : 10^3 simulated paths with the time discretization Step $\Delta t = 0.01$).

THANK YOU for YOUR KIND ATTENTION!!