Engineering Letters, 13:3, EL_13_3_12 (Advance online publication: 4 November 2006)

First passage time density for the disease progression of HIV infected patients

C.F. Lo*
Institute of Theoretical Physics and Department of Physics
The Chinese University of Hong Kong

Abstract

The time-dependent Ornstein-Uhlenbeck process (OU-process) is of immediate relevance to the progression of the CD4-cell counts of HIV infected patients. The first passage time density (FPTD) provides information about the disease level, and the predictions can then be used to optimize medical treatment. Despite the importance and wide applications of the time-dependent OU-process, no explicit analytic solution to such a first passage time problem is known. In this paper we propose a simple and efficient method for computing accurate estimates of the FPTD of the time-dependent OU-process through a constant threshold. This new approach is also able to provide tight upper and lower bounds for the exact FPTD in a systematic manner. Furthermore, this approach can be straightforwardly extended to the more general case of a deterministically modulated boundaries as well.

Keywords: Ornstein-Uhlenbeck; First passage time density; HIV disease

1. Introduction

The study of a progressive chronic disease is often based on the modelling of a prognostic indicator, the values of the indicator providing information about the course of the disease, e.g. HIV infection or organ failure[1,2] The first passage time density (FPTD) is a useful tool to interpret the results, and the predictions can then be used to optimize medical treatment, as indeed the case for the MELD score in end-stage liver disease.[3] When the prognostic indicator is continuous, many researchers model its progression by a time-dependent Ornstein-Uhlenbeck stochastic process (abbreviated as OU-process)[1].[1,2,4] The present work is motivated by recent research on CD4-cell counts modelling for HIV infected patients.[5] The progression of the CD4-cell counts is considered as an efficient indicator of the HIV infection, and numerical values have been inspired by the literature.[1,6] The corresponding FPTD enables us to characterize the disease progression and to compare the progression in groups differentiated according to covariates (sex, treatment, . . .).

The FPTD of the time-dependent OU-process is the solution of a partial differential equation called the backward Chapman-Kolmogorov equation with appropriate boundary conditions. Unfortunately, despite the importance and wide applications of the OU-process, explicit analytic solutions to such a first passage time problem are not known except for a few specific instances. As summarized by Alili *et al.*[7], three representations of analytical nature have been obtained for the FPTD of an OU-process through a constant threshold. The first one is based on an eigenfunction expansion involving zeros of the parabolic cylinder functions, the second one is an integral representation involving some special functions, and the third one is given in terms of a functional of a three-dimensional Bessel bridge. In addition to the numerical methods, *e.g.* the finite-difference approach and the direct Monte-Carlo simulation, these three representations suggest alternative ways to approximate the FPTD. Nevertheless, these three representations are valid for an OU-process with constant model parameters only.

In the present work we derive the closed-form formula for the FPTD of an OU-process with a time-

*The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong (Email: cflo@phy.cuhk.edu.hk)

[1] This is a generalization of the Ornstein-Uhlenbeck process with time-dependent model parameters.

dependent drift to a parametric class of moving boundaries by means of the method of images. We also apply the results to develop a simple, efficient and systematic approximation scheme to compute accurate estimates of the exact FPTD through a fixed threshold. Unlike previous approximate analytical attempts, the proposed method does not involve any sophisticated special functions or numerical inversion of Laplace transforms.

2. First passage time density

We consider the Fokker-Planck equation (FPE) associated with a time-dependent OU-process[8]:

$$\begin{aligned}\frac{\partial P(x,t)}{\partial t} &= \frac{1}{2}\sigma(t)^2 \frac{\partial^2 P(x,t)}{\partial x^2} - \\ & [\mu(t)\ x + \nu(t)] \frac{\partial P(x,t)}{\partial x} - \\ & \mu(t)\ P(x,t) \end{aligned} \qquad (1)$$

where $\sigma(t)$, $\mu(t)$, $\nu(t)$ are arbitrary functions of time t. It is straightforward to show that its solution corresponding to the so-called natural boundary condition is given by

$$P(x,t) = \int_{-\infty}^{\infty} K(x,t;x',0)\, P(x',0)\, dx' \qquad (2)$$

where

$$\begin{aligned}& K(x,t;x',0) \\ =& \frac{1}{\sqrt{4\pi\eta(t)}} \exp\left\{-\frac{\left[xe^{\alpha(t)} + \gamma(t) - x'\right]^2}{4\eta(t)}\right\} \times \\ & \exp\{\alpha(t)\} \end{aligned} \qquad (3)$$

with

$$\begin{aligned}\alpha(t) &= -\int_0^t \mu(t')\ dt' \\ \gamma(t) &= -\int_0^t \nu(t')\, e^{\alpha(t')}\ dt' \\ \eta(t) &= \int_0^t \frac{1}{2}\sigma(t')^2\, e^{2\alpha(t')}\ dt' \quad . \end{aligned} \qquad (4)$$

By the *method of images* we are able to derive the solution

$$\begin{aligned}P(x,t) &= \int_1^{\infty} \{K(x-1,t;x'-1,0) - \\ & K(x-1,t;-x'+1,0)\, e^{-2\beta(x'-1)}\} \times \\ & P(x',0)\, dx' \quad , \end{aligned} \qquad (5)$$

which vanishes at $x = 1 - [\gamma(t) + 2\beta\eta(t)]\, e^{-\alpha(t)} \equiv x^*(t)$ at any time $t \geqslant 0$. Here β is a real adjustable parameter. The solution is valid for the interval $x^*(t) \leqslant x < \infty$. Hence, we have obtained a parametric class of closed-form solutions of Eq.(1) with a moving absorbing boundary whose movement is controlled by the parameter β.

Accordingly, the corresponding FPTD conditional to $P(x,0) = \delta(x - x_0)$ can be analytically obtained in closed form as follows:

$$\begin{aligned}P_{\mathrm{fp}}(x_0,t) &= 1 - \int_{x^*(t)}^{\infty} \{K(x-1,t;x_0-1,0) - \\ & K(x-1,t;-x_0+1,0)\, e^{-2\beta(x_0-1)}\} \, dx \\ &= N\left(-\frac{2\beta\eta(t) + x_0 - 1}{\sqrt{2\eta(t)}}\right) + \\ & N\left(\frac{2\beta\eta(t) - x_0 + 1}{\sqrt{2\eta(t)}}\right) \times \\ & e^{-2\beta(x_0-1)} \end{aligned} \qquad (6)$$

where $N(\cdot)$ is the cumulative normal distribution function. In order to approximate the FPTD through a **fixed boundary** at $x = 1$, we would choose an optimal value of the adjustable parameter β in such a way that the integral

$$\int_0^{\tau} [x^*(t) - 1]^2\ dt$$

is minimum. In other words, we try to minimize the deviation of the moving boundary from the fixed boundary by varying the parameter β. Here τ denotes the time at which the solution of the FPE is evaluated. Simple algebraic manipulations then yield the optimal value of β as follows:

$$\beta_{\mathrm{opt}} = -\frac{\int_0^{\tau} \gamma(t)\, \eta(t)\, e^{-2\alpha(t)}\, dt}{2\int_0^{\tau} \eta^2(t)\, e^{-2\alpha(t)}\, dt} \quad . \qquad (7)$$

Making use of the maximum principle for parabolic partial differential equations[9], we can also determine the upper and lower bounds for the exact solution associated with the fixed boundary. It is not difficult to show[2] that the lower bound can be provided by the solution of the FPE associated with a moving boundary whose $x^*(t)$ is *always larger than or equal to unity* for the duration of interest. Similarly, the

[2]The proof is based upon the maximum principle for parabolic partial differential equations (see the appendix of Lo *et al.* (2003) for the relevant proof).

solution of the FPE associated with a moving boundary whose $x^*(t)$ is *always smaller than or equal to unity* for the duration of interest can serve as the upper bound. Furthermore, the upper and lower bounds can be optimized by adjusting the corresponding values of the parameter β.[3] The FPTD corresponding to the "upper-bound" solution is *smaller* than the exact FPTD, whilst the one derived from the "lower-bound" solution is *larger* than the exact value.

3. Multi-stage approximation

Now, we propose a systematic multi-stage scheme to approximate the exact solution of the FPE with a fixed absorbing boundary at $x = 1$. This approximation scheme has been successfully applied to compute tight upper and lower bounds of barrier option prices with time-dependent parameters very efficiently, where the underlying asset prices follow the lognormal process and the constant elasticity of variance process[10,11]. For demonstration, we consider the evaluation of the approximate FPTD in two stages.

Stage 1: the time interval $[0, \tau/2]$

We choose an appropriate value of the parameter β, denoted by β_1, such that $x^*(t=0) = x^*(t=\tau/2) = 1$. This determines the movement of the boundary within the time interval $[0, \tau/2]$. The corresponding solution is given by

$$\begin{aligned} & P(x, 0 \leqslant t \leqslant \tau/2) \\ = & \int_1^\infty G(x, t; x', 0; \beta_1) P(x', 0)\, dx' \quad , \end{aligned} \tag{8}$$

where

$$\begin{aligned} & G(x, t; x', 0; \beta_1) \\ = & K(x-1, t; x'-1, 0) - \\ & K(x-1, t; -x'+1, 0)\, e^{-2\beta_1 (x'-1)} \quad . \end{aligned} \tag{9}$$

Stage 2: the time interval $[\tau/2, \tau]$

We repeat the procedure in stage 1 such that $x^*(t=\tau/2) = x^*(t=\tau) = 1$. This will give us another value of β, denoted by β_2, and determine the moving boundary's trajectory for the time interval $[\tau/2, \tau]$. Then, the corresponding solution is evaluated as follows:

$$\begin{aligned} & P(x, \tau/2 \leqslant t \leqslant \tau) \\ = & \int_1^\infty \bar{G}(x, t; x', \tau/2; \beta_2) P(x', \tau/2)\, dx' \end{aligned} \tag{10}$$

where

$$\begin{aligned} & \bar{G}(x, t; x', \tau/2; \beta_2) \\ = & \bar{K}(x-1, t; x'-1, \tau/2) - \\ & \bar{K}(x-1, t; -x'+1, \tau/2)\, e^{-2\beta_2 (x'-1)} \end{aligned} \tag{11}$$

with

$$\begin{aligned} & K(x, t; x', 0) \\ = & \frac{1}{\sqrt{4\pi\eta'(t)}} \exp\left\{ -\frac{\left[x e^{\alpha'(t)} + \gamma'(t) - x' \right]^2}{4\eta'(t)} \right\} \times \\ & \exp\{\alpha(t)\} \end{aligned} \tag{12}$$

and

$$\alpha'(t) = -\int_{\tau/2}^{t} \mu(t')\, dt' \tag{13}$$

$$\gamma'(t) = -\int_{\tau/2}^{t} \nu(t')\, e^{\alpha'(t')}\, dt' \tag{14}$$

$$\eta'(t) = \int_{\tau/2}^{t} \frac{1}{2}\sigma(t')^2 e^{2\alpha'(t')}\, dt' \quad . \tag{15}$$

As a result, the associated FPTD is found to be

$$\begin{aligned} & P_{\text{fp}}(x_0, 0 \leqslant t \leqslant \tau/2) \\ = & 1 - \int_{1-[\gamma(t)+2\beta_1\eta(t)]e^{-\alpha(t)}}^{\infty} G(x, t; x_0, 0; \beta_1)\, dx \\ = & N\left(-\frac{2\beta_1\eta(t) + x_0 - 1}{\sqrt{2\eta(t)}} \right) + \\ & N\left(\frac{2\beta_1\eta(t) - x_0 + 1}{\sqrt{2\eta(t)}} \right) e^{-2\beta_1 (x_0-1)} \end{aligned} \tag{16}$$

[3] Each of the moving barriers associated with the upper and lower bounds could be determined by requiring that either the moving barrier returns to its initial position and merges with the fixed barrier at time $t = \tau$, *i.e.* $x^*(t=\tau) = x^*(t=0)$, or the instantaneous rate of change of $x^*(t)$ must be zero at time $t = 0$. Both of the criteria are to ensure the deviation from the fixed barrier to be minimum.

and

$$\begin{aligned}
& P_{\mathrm{fp}}\left(x_0, \tau/2 \leqslant t \leqslant \tau\right) \\
= \;& 1 - \int_{1-\left[\gamma'(t)+2\beta_2\eta'(t)\right]e^{-\alpha'(t)}}^{\infty} \times \\
& \int_1^{\infty} \bar{G}\left(x, t; x', \tau/2; \beta_2\right) \times \\
& G\left(x', \tau/2; x_0, 0; \beta_1\right)\; dx'\; dx \\
= \;& 1 - \int_1^{\infty} \left\{ N\left(\frac{2\beta_2\eta'(t) + x' - 1}{\sqrt{2\eta'(t)}}\right) - \right. \\
& \left. N\left(-\frac{2\beta_2\eta'(t) - x' + 1}{\sqrt{2\eta'(t)}}\right) e^{-2\beta_2\left(x'-1\right)} \right\} \times \\
& G\left(x', \tau/2; x_0, 0; \beta_1\right) dx' \qquad . \qquad (17)
\end{aligned}$$

The integration can be performed analytically and the result can be expressed in closed form in terms of the cumulative bivariate normal distribution function $N_2(\cdot)$. However, in practice it is also very efficient to calculate the integral numerically, *e.g.* using the Gauss quadrature method. Apparently, one can further improve the estimate by splitting the evaluation process into four stages instead, namely $[0, \tau/4]$, $[\tau/4, \tau/2]$, $[\tau/2, 3\tau/4]$ and $[3\tau/4, \tau]$. Then, what one needs to do is to determine the corresponding values of β for these four different stages and perform successive integrations similar to the one in the two-stage approximation. The final expression of the associated FPTD can be expressed in closed form in terms of the $N(\cdot)$, $N_2(\cdot)$, $N_3(\cdot)$ and $N_4(\cdot)$ functions.

In summary, the essence of this multi-stage approximation scheme is to replace the smooth barrier track by a continuous and piecewise smooth trajectory in order that the deviation from the fixed barrier is minimized in a systematic manner. We then need to perform some simple one-dimensional numerical integrations (*e.g.* using the Gauss quadrature method)[4] at the connecting points of the piecewise smooth barrier in order to evaluate the approximate value of the FPTD. By construction, it is expected that the multi-stage approximation becomes better and better as the number N of stages increases; in fact, the error is asymptotically reduced to zero. In practice, even a rather low-order approximation can yield very accurate estimates of the FPTD. Furthermore, similar multi-stage approximation procedures can be applied to obtain very tight upper and lower bounds of the exact FPTD.

For illustration, we apply the approximation method to the example of a linear time-varying drift term, namely $\mu(t)\, x + \nu(t) = -\Gamma x + a(1 + \Gamma t) + \Gamma b$, with the other input parameter σ being constant. This process mimics the progression of the CD4-cell counts which is considered an efficient marker of the evolution of HIV infection from the origin date of the disease.[1,2] The numerical values of the input parameters used have been inpired by the literature.[1,6] In our calculations we have normalized the parameters ($\Gamma = 0.1$, $a = -5.47723 \times 10^{-3}$, $b = 1.13622$, $\sigma = 0.02236$, $\tau = 50$ and $x_0 = 1.02669$) such that the absorbing fixed boundary is located at $x = 1$. The moving boundaries used in the multistage approximation are shown in Figure 1. Numerical results of the FPTD up to the two-stage approximation are exhibited in Figure 2.[5] Obviously, the FPTD improves dramatically as we go from the single-stage approximation to the two-stage approximation. It is expected that, as the number of stages involved increases, the multi-stage approximation for the exact FPTD would keep improving significantly.

4. Conclusion

In this paper we have proposed a simple and efficient method for computing accurate estimates (in closed form) of the FPTD of the time-dependent Ornstein-Uhlenbeck model through a fixed boundary, representing the disease level of the HIV infection. This new approach can also provide very tight upper and lower bounds (in closed form) for the exact FPTD in a systematic manner. Unlike previous approximate analytical attempts, our novel approximation scheme not only goes beyond the linear response and weak noise limit, but it can also be systematically improved to yield the exact results. Furthermore, it is straightforward to extend our approach to study the more general case of a deterministically modulated boundary.

References

1. J.M.G. Taylor, W.G. Cumberland and J.P. Sy, *JASA* **89**(427), p.727 (1994).

[4] The integration can be performed analytically and the result can be expressed in closed form in terms of the multivariate normal distribution functions. However, in practice the numerical integrations are indeed very efficient.

[5] It should also be noted that the numerical results presented in Figure 2 provide the upper bounds of the exact FPTD.

2. H. Jacqmin-Gadda, R. Thibaud, G.Chne, D. Commenges, *Biostatistics* **1**(4), 355 (2000).

3. P.S. Kamath *et al.*, *Hepatology* **33**, 464 (2001); R.H. Wiesner *et al.*, Liver Transpl. 7, 567 (2001).

4. T. Nagylaki, *J. Math. Biol.* **51**, 268 (2005).

5. P.W. Hunt, S.G. Deeks, B. Rodriguez, H. Valdez, S.B. Shade, D.I. Abrams, M.M. Kitahata, M. Krone, T.B. Neilands, R.J. Brand, M.M. Lederman and J.N. Martin, *AID* **17**, 1907 (2003).

6. A.J. MacNeil and S.M. Gore, Stat. Med. 15(1), 75 (1996).

7. L. Alili, P. Patie and J.L. Petersen, *Stoch. Models* **21**(4), 967 (2005).

8. C.W. Gardiner, *Handbook of Stochastic Methods for Physics, Chemistry and the Natural Sciences*, 3rd ed. (Springer-Verlag, Berlin, 2003).

9. A. Friedmann, *Partial Differential Equations of Parabolic Type* (Prentice Hall, New Jersey, 1964).

10. C.F. Lo, H.C. Lee and C.H. Hui, Quant. Finance **3**, 98 (2003).

11. C.F. Lo, H.M. Tang, K.C. Ku and C.H. Hui, *Proceedings of the 2nd IASTED International Conference on Financial Engineering and Applications, 8-10 November 2004, Cambridge, MA, USA*, 34 (2004).

Figure 1: Moving boundaries within the multistage approximation

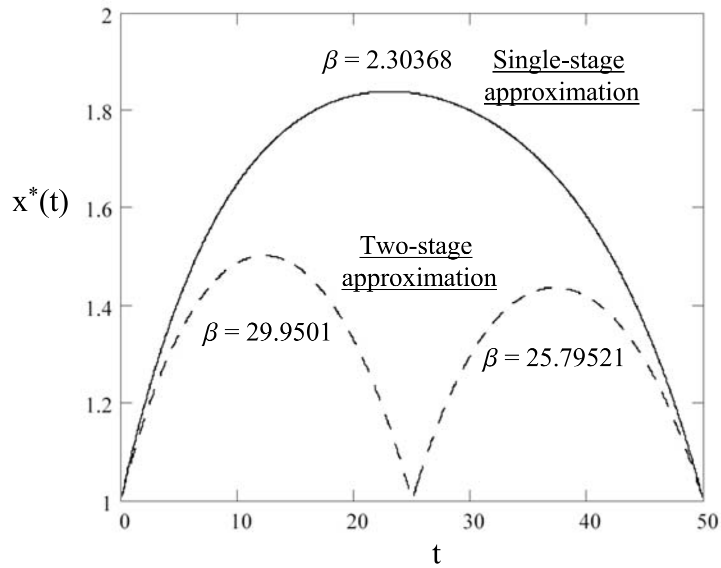

Figure 2: First passage time density vs. time within the multistage approximation