How Sample Paths of Leaky Integrate-and-Fire Models Are Influenced by the Presence of a Firing Threshold

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How sample paths of Leaky Integrate and Fire models are influenced by the presence of a firing threshold

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Abstract

Neural membrane potential data is necessarily conditional on observation being prior to a firing time. In a stochastic Leaky Integrate and Fire model this corresponds to conditioning the process on not crossing a boundary. In the literature simulation and estimation has almost always been done using unconditioned processes. In this paper we determine the stochastic differential equations of a diffusion process conditioned to stay below a level S up to a fixed time t_1 and of a diffusion process conditioned to cross the boundary for the first time at t_1. This allows simulation of sample paths and identification of the corresponding mean process. Differences between the mean of free and conditioned processes are illustrated as well as the role of the noise in increasing these differences.

1 Introduction

In simulation or estimation for a Leaky Integrate and Fire model, a fact that is commonly neglected is that neural membrane data comes from a time interval between a resetting and the occurrence of a spike. Hence each piece of recorded data contains further information in addition to its value: a spike has not yet happened on the time interval since the previous resetting, and all the data recorded until that time must be subthreshold. Mathematically this means that data must be modeled as coming from a process conditioned to remain below a firing level. The probabilistic features of the conditioned process are different from those of an unconditioned one. Serious errors may arise from confounding these processes. Analoguous problems with a variety of conditioning constraints arise in different application contexts such as finance (cf. for example Li et al. (2004)).

In this paper we show how to simulate while taking this conditioning into account. We also illustrate the significance of errors which may arise if this point is neglected. A similar situation, regarding the possible confusion between $E(1/T)$ and $1/E(T)$, where T denotes the spiking time, was clarified in Lánský et al. (2004).

Data from the evoked potential of a neural membrane is often regarded as coming from a stochastic Leaky Integrate and Fire model. There exist many neuronal models and their complexity ranges from oversimplified to highly realistic biophysical models (Segev (1992)). The Leaky Integrate and Fire stochastic model is considered a good compromise between tractability and realism. It is derived from an original model of membrane depolarization introduced by Stein (Stein (1965)). In Stein's model the membrane potential evolves due to incoming excitatory and inhibitory inputs, which are assumed to be of constant amplitude and to occur in time according to Poisson processes. Spontaneous decay between inputs is a further feature of this model. A spike is produced by the neuron when a boundary is attained.

The pioneering work of Stein has motivated a large literature studying diffusion limits of his model of membrane potential evolution (cf. Burkitt (2006a), Burkitt (2006b), Sacerdote et al. (2010) and papers cited therein). Diffusion approximations avoid some of the mathematical difficulties of the original discontinuous model. These models take into account the dynamic and stochastic aspects of neuron behaviour. The mem-

brane potential of interest is represented by, and is the solution of, a stochastic differential equation (SDE) and the spike time corresponds to the first crossing of the process through a boundary. Various diffusion processes can be used to model the membrane potential evolution, depending upon the number of specific features one wishes to introduce in the model. The Ornstein-Uhlenbeck process is a common choice (cf. Lánský et al. (1995)).

A fact that has not yet been sufficiently emphasized for Leaky Integrate and Fire models is that all data is from observation prior to neuron firing. The few papers concerning this problem consider the estimation of the parameters of the model. In Bibbona et al. (2009) and Bibbona et al. (2010a) it is shown that if one ignores the fact that the data is produced under the constraint of not crossing a boundary, the resulting estimator of the input will be biased. The estimation problem is also the subject of a recent paper (Bibbona et al. (2010b)), where samples from intracellular recordings, at discrete times, of the membrane potential are used for the estimation problem. The authors propose maximum likehood estimators of the parameters of an Ornstein-Uhlenbeck and of other Leaky Integrate and Fire models, taking into account the presence of the boundary.

In terms of the model, one should describe the membrane potential behaviour before a boundary crossing time. Consequently, any appropriate model for data must be conditioned on not having crossed the boundary. We introduce the term *constrained process* for such a process. Alternatively, depending on the question at hand, one may observe the process until the spike time. In this case the appropriate model must be conditioned on the boundary, S, being first crossed at the end of the observation time. Such a process we call a *constrained bridge to S*, to emphasize the bridge nature of a process ending at S.

In this paper we compute the SDEs of diffusion processes conditioned to stay below a threshold starting from diffusions defined by particular SDEs. Mathematically, the conditioning can be interpreted as an absolutely continuous change of measure. Its effect on the original SDE is to add a term to the drift coefficient and to leave the diffusion coefficient unchanged. We illustrate the differences between the original membrane potential model and its conditioned version with plots of computed sample paths and with computed mean paths.

These conditioned or *constrained* SDEs correspond more closely to real data than

do the unconstrained models currently in use.

Simulated samples are essential for the evaluation of statistical procedures. Knowledge of these constrained SDEs is essential for the simulation of the sample paths determined by Leaky Integrate and Fire models and by their bridges. The typical approach to the simulation of subthreshold sample paths up to a time t_1 makes use of the rejection method: one simulates sample paths on $(0, t_1)$ and rejects paths crossing the boundary at a time $t \in (0, t_1)$. This method is computationally expensive and becomes impossible in the case of the simulation of paths up to the spike time when the SDE for the free bridge process is not known. Furthermore, in this way one gets sample paths from a process which is not normalized. In Section 2 we define this *absorbed* process while we define as *constrained* its normalized version. The availability of SDEs for constrained processes and for the constrained bridge to S facilitates the simulation of these samples, avoiding the computational cost of the rejecton method.

In the next Section we introduce a number of processes related to an initial process of interest. Our mathematical results are stated in Section 3 in terms of only two of these, the *constrained process* and the *constrained bridge to S*. The remaining processes appear in computations. The proof of these results is postponed to the Appendixes. In Section 4 we illustrate, through a set of examples, the consequences of our mathematical results on the Integrate and Fire and on the Leaky Integrate and Fire models.

2   Background and notation

While our primary interest is in processes related to the Ornstein-Uhlenbeck process, it is useful to introduce some ideas and notation in terms of general diffusions that can include other Integrate and Fire and Leaky Integrate and Fire type models.

In order to make the meaning of our notation very clear, in this Section we introduce a number of processes, related to a diffusion process of interest. First, let us describe and motivate these processes informally and mention their names to facilitate the reading of what follows. The first of these is the original membrane potential diffusion process, usually started at 0, altered by excluding those sample paths which cross the positive level S before the observation time t. We call this the *absorbed diffusion*. The total probability mass of this process, at any time $t > 0$, is less than 1, since the

excluded paths take some probability mass away. The next process we introduce is the *constrained process*. This is formed by conditioning on the path not crossing the level S during the fixed time interval $[0, t_1]$. The probability mass of this process up to each time $t < t_1$ is 1. Up to this point we have three types of process. The original membrane potential process may be called *free*, next the *absorbed process*, next the *constrained process*. An example of sample paths of the absorbed process and of the constrained process is shown in Figure 1. Corresponding to each of the previous processes, we introduce a bridge process. The idea of a *bridge process* is that it begins and ends at definite given points. In Figure 2 we illustrate sample paths of the free bridge process and of the constrained bridge process in S where the original free process is the Ornstein-Uhlenbeck process.

Since our processes all begin at given points, the corresponding bridge process can be defined by additional conditioning on the given end point. A special role will be played by bridge processes which end at the space point which is the firing threshold, S, and at the random firing time, T. We call these *bridges to S*, even though the ending time is the random threshold crossing time T and not a fixed time.

Now we proceed more formally. We consider a time homogeneous diffusion process $X(t) = \{X(t), \ t \geq t_0 \,|\, X(t_0) = x_0\}$ with values in the interval $I = (r_1, r_2), r_1, r_2 \in \mathbb{R}$. In the case of the Ornstein-Uhlenbeck process, $r_1 = -\infty, r_2 = \infty$. The process $X(t)$ is the solution of an SDE

$$
\begin{aligned}
dX(t) &= a\left(X(t)\right) dt + \sigma\left(X(t)\right) dW(t), \\
X(t_0) &= x_0.
\end{aligned}
\tag{1}
$$

The process $X(t)$ is characterized by its drift and diffusion coefficient functions, $a(x)$ and $\sigma(x)$. Each pair of coefficient functions identifies a specific diffusion process. Here $W(t)$ is a standard Wiener process. We assume that the drift and the diffusion coefficients are such that equation (1) admits a unique solution with values in the interval I. For the processes we work with, the transition probability density function

$$
f = f(x, t \,|\, y, s) = \frac{\partial P\left(X(t) \leq x \,|\, X(s) = y\right)}{\partial x}
$$

is the unique solution of the backward Kolmogorov equation

$$
\frac{\partial f}{\partial s} + a(y) \frac{\partial f}{\partial y} + \frac{\sigma^2(y)}{2} \frac{\partial^2 f}{\partial y^2} = 0,
\tag{2}
$$

with the initial condition (cf. Karlin et al. (1981))

$$\lim_{s \to t} f(x, t \,|\, y, s) = \delta(x - y). \tag{3}$$

The firing threshold for a stochastic membrane potential model is represented here by a level $S \in I$, with $x_0 < S$. The firing time corresponds to the first passage time (FPT)

$$T = \inf \{t : X(t) \geq S \,|\, X(t_0) = x_0\}.$$

We denote the probability density function of T by g:

$$g(t \,|\, x_0, t_0) = \frac{\partial P(T \leq t \,|\, X(t_0) = x_0)}{\partial t}.$$

Now we introduce a number of processes associated with a diffusion process limited by a boundary level S. Some of them represent the evolving membrane potential data, while others play supporting roles.

Absorbed process The process obtained by restricting the diffusion defined by (1) not to cross the level S,

$$X^a(t) = \{X^a(t) : X(t), X(s) < S, \forall s < t \,|\, X(t_0) = x_0\},$$

is called the *absorbed process*. Its sample paths are the subset of the sample paths of $X(t)$ characterized by not having crossed the boundary before the time t. The transition probability density of this process, $f^a(x, t \,|\, y, s)$, is, again, the unique solution of (2) but with the further boundary condition, for each $s < t$, $x < S$,

$$\lim_{y \to S} f^a(x, t \,|\, y, s) = 0.$$

Generally, the transition probability density, f^a, is not known in closed form, and a numerical procedure is necessary to get its values from the equation (cf. Siegert (1951))

$$f^a(x, t \,|\, y, s) = f(x, t \,|\, y, s) - \int_s^t g(\tau \,|\, y, s) f(x, t \,|\, S, \tau) \, d\tau. \tag{4}$$

The integral $P^a(S, t \,|\, y, s)$ of $f^a(x, t \,|\, y, s)$, with respect to x, between r_1 and S is not equal to 1 when $t > s$. The densities $f^a(x, t \,|\, y, s)$ and $g(S, t \,|\, y, s)$ are related through the equation:

$$P\left(T>t\,|X\left(s\right)=y\right)\quad:=\quad P^{a}\left(S,t\,|X\left(s\right)=y\right)=\int_{r_{1}}^{S}f^{a}\left(x,t\,|y,s\right)dx$$

$$=\quad 1-\int_{s}^{t}g\left(u\,|y,s\right)du. \tag{5}$$

When we record the evolving membrane potential of spiking neurons we are looking at sample paths of an absorbed process. However, due to (5), their total probability mass is not normalized. It is convenient to introduce the normalized version of the absorbed process, which we call the *constrained* process.

Constrained process   The *constrained process* is of primary importance to our aim of identifying the membrane potential process prior to a firing time. It is defined for $t \in [t_0, t_1]$ as

$$X^{c}\left(t\right)=\left\{X^{c}\left(t\right):X\left(t\right),t_{0}<t<t_{1}\,|X\left(t\right)<S,t_{0}<t<t_{1};X\left(t_{0}\right)=x_{0}\right\}.$$

The *constrained process* is conditioned or constrained to remain under the threshold level S up to the fixed time t_1. We denote by $f_{t_1}^{c}\left(x,t\,|y,s\right)$ its transition probability density, and by $P_{t_1}^{c}\left(X\left(u\right),u\in\left(t_0,t_1\right)|X\left(t_0\right)=x_0\right)$ the measure of the constrained process. In our computations t_0 will be fixed, usually at 0, whereas t_1 will take various values.

Bridge processes (free, absorbed and constrained)   The bridge process that ends when it attains for the first time the threshold of the membrane potential is a central object of our study. Indeed, it represents an intracellular recording from a neuron observed up to the spike time. A step towards its definition is the simple bridge process, which is conditioned to begin at (x_0, t_0) and end at (z, u), $z \in (r_1, r_2), u \in (t_0, \infty)$. The *free bridge process* is denoted by:

$$_{(x_{0},t_{0})}^{(z,u)}X\left(t\right)=\left\{X\left(t\right):X\left(t\right),t_{0}<t<u\,|X\left(u\right)=z;X\left(t_{0}\right)=x_{0}\right\}.$$

The fact that this process, which we describe as obtained by conditioning on a set of measure zero, is indeed defined, is established in Karatzas et al. (1991). Its transition probability density is denoted by $f\left(x,t\,|y,s;z,u\right)$. We call this process "free" since it is not conditioned further. We denote by $_{(x_{0},t_{0})}^{(z,u)}X^{a}\left(t\right)$ and $_{(x_{0},t_{0})}^{(z,u)}X^{c}\left(t\right)$ the

bridges of the absorbed and constrained versions of the process $X(t)$, arising in the presence of the boundary. Their transition probability density functions will be denoted as $f^a(x, t | y, s; z, u)$ and $f^c(x, t | y, s; z, u)$, respectively. Note that for these processes $z < S$.

The transition probability densities of the process $X(t)$ and that of its bridge ${}^{(z,u)}_{(x_0,t_0)}X(t)$ are related through (cf. Giraudo et al. (1999)):

$$f(x, t | y, s; z, u) = \frac{f(x, t | y, s) f(z, u | x, t)}{f(z, u | y, s)}.$$

Similar relationships hold for the transition probability densities of the absorbed and the constrained processes.

Bridges to S (three additional processes: free, absorbed, and constrained) Finally we come to the case of most importance in connection with the sample paths of membrane potential processes up to the moment of firing, the case when $z = S$. In particular we define the bridge process:

$$ {}^{(S,u)}_{(x_0,t_0)}X(t) = \{X(t) : X(t), t_0 < t < u \,|\, X(u) = S; X(s) < S, \forall s < u; X_0 = x_0\}, $$

with transition probability density $f(x, t | y, s; S, u)$.

To define its absorbed and constrained versions we set $z = S$ in the absorbed and constrained bridges with endpoint z at time u, and we denote them as ${}^{(S,u)}_{(x_0,t_0)}X^a(t)$ and ${}^{(S,u)}_{(x_0,t_0)}X^c(t)$, respectively. The corresponding transition probability densities will be denoted $f^a(x, t | y, s; S, u)$ and $f^c(x, t | y, s; S, u)$. We give the name *constrained bridge to S* to the process conditioned by the event that the crossing of S is at the first passage time T. This is the same as the free process stopped at T, conditioned on T.

Wiener and Ornstein-Uhlenbeck processes Although different diffusion processes may be used to describe the membrane potential time evolution, the Ornstein-Uhlenbeck process is surely the best known. A simplification of the Ornstein-Uhlenbeck model can be obtained by disregarding the spontaneous decay of membrane potential toward the resting potential, in the absence of incoming input. The model corresponding to this case is the Wiener process. This model, also known as the Integrate and Fire model, was first proposed by Gerstein and Mandelbrot who gave experimental motivations for it (cf. Gerstein et al. (1964)). Later it was discarded as too simple but it is

still considered helpful for intuition about the more complex dynamics of the Ornstein-Uhlenbeck model. This last model is generally referred to as the Leaky Integrate and Fire model. In Sections 3.1, 3.2 we discuss our results for the Integrate and Fire model, characterized by:

$$
\begin{aligned}
a\left(y\right) &= \mu, \\
\sigma\left(y\right) &= \sigma,
\end{aligned}
$$

where $\mu \in \mathbb{R}, \sigma > 0$, and for the Leaky Integrate and Fire model, characterized by:

$$
\begin{aligned}
a\left(y\right) &= -\frac{y}{\theta} + \mu, \\
\sigma\left(y\right) &= \sigma,
\end{aligned}
$$

where $\mu \in \mathbb{R}, \theta > 0$ and $\sigma > 0$. The constant drift, μ, common to the two models, specifies the deterministic input to the membrane potential. The diffusion coefficient specifies the variability of the noise term. The constant θ quantifies the spontaneous decay of the membrane potential toward its resting value in the absence of external input. The processes are generally assumed to originate at $x_0 = 0$ because a simple shift can always translate the biological initial value to zero. A large literature exists on the role of these models in neural transmission (cf. for example Bulsara et al. (1994), Longtin et al. (1991), Shimokawa et al. (1999)). In both models the spiking time is taken to be the first passage time of the process through a threshold $S > 0$. In Appendix 1 we list well known results about these processes that will be used.

3   Results

In Section 2 we defined and estabilished notation for several stochastic processes associated with the general Leaky Integrate and Fire model. One of the most central to this paper is the *constrained process*, $X^c(t)$, which is conditioned to remain under a threshold level S up to a fixed time t_1. In this Section we identify the drift and diffusion coefficients of the *constrained process* as well as those of the *constrained bridge process* and the *constrained bridge to the threshold S* and evaluate these for the Integrate

and Fire and for the Leaky Integrate and Fire models. We use the fact that the drift and diffusion coefficients appearing in the SDE (1) are the same as the functions $a(\cdot)$ and $\sigma(\cdot)$ appearing in the Kolmogorov backward equation (2).

Consider the joint probability of the process $X(t)$ with the indicator of the event $\{T > t\}$. The distribution of $X^c(t)$ is obtained from this by dividing by $P(T > t_1)$, where $X(t)$ starts at (y, s) and $t_1 > t$. The joint distribution can be factored using the Markov property of $X(t)$ into the joint distribution of $X(t)$ with the indicator of $\{T > t\}$ and the probability that $T > t_1$, starting from (x, t). Hence the transition probability density function $f_{t_1}^c(x, t \,|y, s)$ of the process $X^c(t)$, $t \in [t_0, t_1]$, is related with the transition probability density function $f^a(x, t \,|y, s)$ of the process $X^a(t)$ through the following equation:

$$f_{t_1}^c(x, t \,|y, s) = \frac{f^a(x, t \,|y, s)\, P(T > t_1 \,|X(t) = x)}{P(T > t_1 \,|X(s) = y)}. \tag{6}$$

A more formal derivation of (6) is in Appendix 2.

For many purposes it is desirable to simulate paths of constrained processes. The method which has been used up to now produces sample paths of the absorbed process by generating a large number of samples from equation (1) and throwing away any path which crosses S before time t. This is a computationally expensive approach. We propose the following method for simulating the constrained process. First, we derive the coefficients appearing in the Kolmogorov equation satisfied by the transition probability density function $f_{t_1}^c(x, t \,|y, s)$ of the process $X^c(t)$ on the time interval $[t_0, t_1]$, which reads (see Appendix 2)

$$\frac{\partial f_{t_1}^c}{\partial s} + \left[a(y) + \sigma^2(y) \frac{\partial}{\partial y} \ln P^a(S, t_1 \,|y, s) \right] \frac{\partial f_{t_1}^c}{\partial y} + \frac{\sigma^2(y)}{2} \frac{\partial^2 f_{t_1}^c}{\partial y^2} = 0$$

with the initial condition

$$\lim_{s \to t} f_{t_1}^c(x, t \,|y, s) = \delta(x - y)$$

and boundary conditions

$$\lim_{y \to S} f_{t_1}^c(x, t \,|y, s) = 0$$
$$\int_{r_1}^{S} f_{t_1}^c(x, t \,|y, s)\, dx = 1. \tag{7}$$

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Then the SDE for the constrained process $X^c(t)$ can be read from (3),

$$
\begin{aligned}
dX^c(t) &= \left[a\left(X^c(t)\right) + \frac{\sigma^2\left(X^c(t)\right)}{P^a\left(S, t_1 \,|x, t\right)} \left.\frac{\partial P^a\left(S, t_1 \,|x, t\right)}{\partial x}\right|_{x=X^c(t)} \right] dt \\
&+ \sigma\left(X^c(t)\right) dW(t).
\end{aligned}
\tag{8}
$$

Finally, classical numerical methods (cf. Kloeden et al. (1992)) can be used to simulate $X^c(t)$ from (8). Usually we have no closed form expression for the second term in square brackets. A numerical scheme would involve (4) and (5). The first passage time density is involved, and usually must be obtained numerically.

We observe that the drift process for $X^c(t)$, which we denote by $A^c(x,t), t \in [0, t_1]$, is obtained by adding the second term in square brackets in (8) to the drift coefficient for $X(t)$, and that the diffusion coefficient for X^c is the same as that for $X(t)$.

The expressions for the drift and the diffusion coefficient of a diffusion process constrained to remain in a bounded region of $\mathbb{R}^n, n \geq 1$ were determined in Pinsky (1985) and coincide with (8) when $n = 1$ and the boundary is a constant. The Proof in Pinsky (1985) is more sophisticated than ours due to the more general frame of that Theorem.

Next we consider the constrained bridge process $^{(z,u)}_{(x_0,0)}X^c(t), t \in (0, u), u < t_1$, associated with the diffusion process $X(t)$. Its drift coefficient is

$$
^{(z,u)}_{(x_0,0)}A^c(x,t) = a(x) + \frac{\sigma^2(x)}{f^a(z, u \,|x, t)} \frac{\partial f^a(z, u \,|x, t)}{\partial x}
\tag{9}
$$

with $x \in (r_1, S)$, while the diffusion coefficient is unchanged. The computation is in Appendix 2.

As in the case of the constrained process $X^c(t)$, the knowledge of the drift expression (9) allows the simulation of the process $^{(z,u)}_{(x_0,0)}X^c(t)$. However, this task requires a major computational effort to determine the function $f^a(z, u \,|x, t)$ using relation (4).

Notice that the drift and the diffusion coefficients (9) of the constrained bridge do not depend upon the endpoint, t_1, of the interval of constraint.

Finally, we compute the SDE of the bridge to S process $^{(S,u)}_{(x_0,0)}X^c(t)$. This is the particular case of the constrained bridge process where $u \equiv t_1$ is the first passage time, T, of the bridge through S. We find that for $t \in (0, u)$ and $x < S$, its drift coefficient is

related to the drift coefficient of the process $X(t)$ via:

$$\begin{matrix} (S,t_1) \\ (x_0,0) \end{matrix} A^c(x,t) = a(x) + \frac{\sigma^2(x)}{g(t_1|x,t)} \frac{\partial g(t_1|x,t)}{\partial x}. \tag{10}$$

The diffusion coefficient is unchanged. The computation is in Appendix 2.

The knowledge of the infinitesimal moment (10) allows the simulation of $\begin{smallmatrix}(S,u)\\(x_0,0)\end{smallmatrix}X^c(t)$ by means of its SDE with the classical discretization schemes (cf. Kloeden et al. (1992)).

3.1 Integrate and Fire model

Here we use our results to illustrate the problems arising when one misunderstands the membrane potential data and disregards the effect of the conditioning determined by the presence of the boundary in Integrate and Fire and in Leaky Integrate and Fire models.

In the case of the Integrate and Fire model we can write down the analytical expression for the drift of its constrained version. This makes it easy to simulate sample paths of this version, but we do not present here any examples.

In order to illustrate the effect of conditioning with biologically compatible parameter values, we set S=10 mV, $\theta = 10$ ms^{-1}, μ ranging from 0.5 mVms^{-1} to 1.5 mVms^{-1} and σ^2 ranging from 0.5 mV^{2}ms^{-1} to 9 mV^{2}ms^{-1}.

Let $W(t)$ be a Wiener process started at 0, with drift $a(x) = \mu > 0$ and diffusion coefficient σ. The drift of the process $W^c(t)$ constrained to remain below the boundary S up to time t_1 is:

$$A^c(x,t) = \mu + \frac{\sigma^2}{P^a(S,t_1|x,t)} \frac{\partial P^a(S,t_1|x,t)}{\partial x} \tag{11}$$

where

$$\frac{\partial P^a\left(S,t_1\,|x,t\right)}{\partial x} = \frac{d}{dx}(1 - \frac{1}{2}Erfc\left[\frac{S - x - \mu\left(t_1 - t\right)}{\sigma\sqrt{2\left(t_1 - t\right)}}\right]$$

$$- \frac{1}{2}\exp\left[\frac{2\mu\left(S - x\right)}{\sigma^2}\right]Erfc\left[\frac{S - x + \mu\left(t_1 - t\right)}{\sigma\sqrt{2\left(t_1 - t\right)}}\right])$$

$$= -\frac{1}{\sigma\sqrt{2\pi\left(t_1 - t\right)}}e^{\left[-\left(\frac{S-x-\mu(t_1-t)}{\sigma\sqrt{2(t_1-t)}}\right)^2\right]}$$

$$+ \frac{\mu}{\sigma^2}\exp\left[\frac{2\mu\left(S - x\right)}{\sigma^2}\right]Erfc\left[\frac{S - x + \mu\left(t_1 - t\right)}{\sigma\sqrt{2\left(t_1 - t\right)}}\right]$$

$$- \frac{1}{\sigma\sqrt{2\pi\left(t_1 - t\right)}}e^{\left[\frac{2\mu(S-x)}{\sigma^2}\right]}e^{\left[-\left(\frac{S-x+\mu(t_1-t)}{\sigma\sqrt{2(t_1-t)}}\right)^2\right]} \qquad (12)$$

where Erfc denotes the complementary Error function (cf. Abramowitz et al. (1970)).

In Figure 3 we plot the second term of (11), i.e. the difference between the drift of the constrained process and the drift μ of the free one, to illustrate the importance of this correction as t varies when $\mu = 1$ mVms^{-1}. Different curves in this figure correspond to different values of σ^2. Note that the importance of the correction, determined by the effect of the boundary on the drift, increases when σ^2 increases while it decreases as the time grows up. One could simulate the sample paths of the process $W^c(t)$ by means of the discretization procedures in Kloeden et al. (1992) and observe their different behaviors (Figure not shown).

We compute the mean membrane potential, i.e. the mean value $E[W^c(t)]$, of the constrained process $W^c(t)$, by numerical integration of the formula

$$E[W^c(t)] = \int_{-\infty}^{S} x f_{t_1}^c\left(x, t\,|0, 0\right)dx$$

$$= \frac{1}{P^a\left(S, t_1\,|0, 0\right)}\int_{-\infty}^{S} x f^a\left(x, t\,|0, 0\right)P^a\left(S, t_1\,|x, t\right)dx,$$

which is a simple consequence of (6). Figure 4 illustrates $E\left[W(t)\right]$ and $E\left[W^c(t)\right]$ for two different choices of t_1, $t_1 = 6$ ms and $t_1 = 40$ ms. The importance of the correction increases in the case of absence of spikes for a longer interval.

When one observes the membrane potential up to the spike time, the correct model is the constrained bridge process with coefficient given by (10). It is interesting to

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look at the behavior of sample paths of the process $_{(0,0)}^{(S,t_1)}W^c(t)$. In this case the drift coefficient, for $\mu = 0$, is given by

$$_{(0,0)}^{(S,t_1)}A^c(x,t) = -\frac{\sigma^2}{S-x} + \frac{S-x}{t_1-t}.$$

Note that the drift of a bridge to S, in the absence of absorption, is

$$_{(0,0)}^{(S,t_1)}A(x,t) = \frac{S-x}{t_1-t}.$$

In this case we do not need a figure to illustrate the effect of the constraint, which is more important as σ^2 increases.

3.2 Leaky Integrate and Fire model

Let $X(t)$ be an Ornstein-Uhlenbeck process started at x_0 at time t_0, solution of

$$dX(t) = (\mu - \frac{X(t)}{\theta})dt + \sigma^2 dW(t).$$

No closed form expression exists for its first passage time distribution across a constant boundary. Hence to simulate the sample paths of the constrained processes (8) and (10), one should numerically evaluate their drift terms at each point of the time discretization scheme. Numerical techniques (cf. Buonocore et al. (1987)) can be employed to evaluate the crossing probability density $g(t|x_0,t_0)$. The numerical integration of this density gives the crossing probability evaluations in (8) while their numerical differentiation gives the necessary quantities in (10).

The mean value of the unconstrained process, $X(t)$, is the solution of the differential equation

$$\frac{dE[X(t)]}{dt} = \mu - \frac{E[X(t)]}{\theta}$$

and is given by $E[X(t)] = \mu\theta(1 - e^{-\frac{t}{\theta}})$ in the case where $x_0 = 0$.

For the bridge process $_{(x_0,0)}^{(S,u)}X^c(t)$, sample paths can be obtained only by means of combined numerical and simulation techniques, in the same way as for the constrained process $X^c(t)$.

Many qualitative studies of neuronal dynamics described through the Ornstein-Uhlenbeck process distinguish two types of behaviors: supra and subthreshold dynamics, characterized by the asymptotic mean $E[X(\infty)] = \mu\theta \geq S$ or $< S$ respectively, where X_t is the "free" process (cf. Sacerdote et al. (2010)). The mean value of the process $X^c(t)$, obtained as an arithmetic mean of a set of samples of the process, is illustated in Figure 5. Note that all the examples shown from here on are done setting $x_0 = 0$ mV. In the two panels of Figure 5 different choices for the parameters of the process are made. Panel A illustrates an example of subthreshold behavior while in Panel B there is an example of suprathreshold behavior. The effect of the constraint increases in both cases with the time but it is more remarkable in the suprathreshold regime.

The mean value of the constrained bridge to S is represented in Figure 6 together with the mean value of the free bridge process taking the value S at the same time as the previous process. The parameters are chosen in the subthreshold regime, but the same behavior arises also in the suprathreshold regime.

In Figure 7 we compare the simulated mean values of the constrained process $X^c(t)$ with $E[X(t)]$ for different values of σ^2 to show the effect of the noise on the mean of the constrained process. The difference between the free and the constrained processes is stronger in the suprathreshold regime and the noise increases this difference.

As we have pointed out, an important part of the analysis of neuronal recordings is to establish whether the observed dynamics arises in the subthreshold or in the suprathreshold regime. In the subthreshold dynamics crossings of the boundary may happen only in the presence of noise. If one disregards the constraint of the boundary in modelling the data and uses a biased estimator to decide whether the neuron is in the suprathreshold regime, an error arises and the conclusion can be wrong, i.e. one can classify as subthreshold a case that is suprathreshold. This is illustrated with an example in Figure 8, where suprathreshold behavior results can be confused with a subthreshold dynamics if one does not recognize the constrained nature of the observed data.

Conclusions

If we ignore the fact that membrane potential data is conditional on firing not yet having occurred, serious errors in model interpretation can result, particularly when the noise

is strong. The problem is corrected when we use the conditioned processes computed in this paper to model the membrane potential behavior.

The SDE of the constrained process (8) should be used for a correct simulation of the sample paths to compare with data recorded up to a fixed time prior to firing. If data is recorded up to a firing time, simulation of comparable synthetic data should be done using the drift coefficient (10) instead of that in the SDE (8).

Our examples of simulations in the case of the constrained Wiener and Ornstein-Uhlenbeck processes, and these processes bridged to the firing boundary S, illustrate the striking difference conditioning makes to the nature of simulated paths and hence the important misunderstanding that can arise confounding these processes for modelling purposes. A typical risk concerns the distinction between the subthreshold and suprathreshold regimes for the Ornstein-Uhlenbeck model. This point becomes more important in the presence of stronger noise intensity.

The results obtained allow to suggest the right choice of the SDE to employ if one wants to simulate sample paths analoguous to real experimental data obtained from registration of neuronal activity. The SDE for the bridge to S process should be used if one wants to simulate registrations up to the first spike, while the SDE for the constrained process is suitable to simulate sample paths up to any time instant before the spike occurs.

Appendix 1

For both the Wiener and the Ornstein-Uhlenbeck processes the diffusion interval coincides with the real line and their transition probability density is the only solution of the corresponding Kolmogorov equation (2) with the initial condition (3). The transition probability density function of the Wiener process is (cf. Karlin et al. (1981)):

$$f_W\left(x, t \mid y, s\right) = \frac{1}{\sqrt{2\pi\sigma^2\left(t - s\right)}} \exp\left\{-\frac{\left[x - y - \mu\left(t - s\right)\right]^2}{2\sigma^2\left(t - s\right)}\right\}$$

while that of the Ornstein-Uhlenbeck process is:

$$
f_{OU}\left(x,t\,|y,s\right) \;=\; \frac{1}{\sqrt{\pi\sigma^2\left(1-e^{-2(t-s)}\right)}}
$$

$$
\times\quad \exp\left\{-\frac{\left[x-ye^{-(t-s)/\theta}-\mu\left(1-e^{-(t-s)/\theta}\right)\right]^2}{\sigma^2\left(1-e^{-2(t-s)}\right)}\right\}.
$$

In the case of the Wiener process the first passage time probability density for $S > x_0$ is:

$$
g\left(t\,|x_0,t_0\right)=\frac{S-x_0}{\sqrt{2\pi\sigma^2\left(t-t_0\right)^3}}\exp\left\{-\frac{\left[S-x_0-\mu\left(t-t_0\right)\right]^2}{2\sigma^2\left(t-t_0\right)}\right\}.
$$

The analogous expression for the Ornstein-Uhlenbeck process is not known in closed form but it can be obtained numerically solving an integral equation proposed in Buonocore et al. (1987).

A closed form expression for the transition probability density in the presence of an absorbing boundary at S is known for the Wiener process with drift (cf. Ricciardi et al. (1989)):

$$
\begin{aligned}
f^a\left(x,t\,|y,s\right) \;=&\; \frac{1}{\sqrt{2\pi\sigma^2\left(t-s\right)}}\left\{\exp\left[-\frac{\left(x-y-\mu\left(t-s\right)\right)^2}{2\sigma^2\left(t-s\right)}\right]\right.\\
&\;\left.-\exp\left[-\frac{\left(x+y-2S-\mu\left(t-s\right)\right)^2}{2\sigma^2\left(t-s\right)}+\frac{2\mu\left(S-y\right)}{\sigma^2}\right]\right\}
\end{aligned}
$$

for $y < S$. Hence for the Wiener process, when $y < S$, one has:

$$
\begin{aligned}
P^a\left(S,t\,|y,s\right) \;=&\; \int_{-\infty}^{S} f^a\left(x,t\,|y,s\right)dx\\
=&\; 1-\frac{1}{2}\left\{Erfc\left[\frac{S-y-\mu\left(t-s\right)}{\sigma\sqrt{2\left(t-s\right)}}\right]\right.\\
&\;\left.+\exp\left[\frac{2\mu\left(S-y\right)}{\sigma^2}\right]Erfc\left[\frac{S-y+\mu\left(t-s\right)}{\sigma\sqrt{2\left(t-s\right)}}\right]\right\}.
\end{aligned}
$$

Analoguous closed form expressions are not available for the Ornstein-Uhlenbeck process.

Appendix 2

Proof of (6).

The transition probability density $f_{t_1}^c(x, t | y, s)$ may be rewritten according to the following chain of equations:

$$f^c(x, t | y, s) dx = P\left(X^c(t) \in (x, x + dx) | X^c(s) = y\right)$$

$$= P\left(X(t) \in (x, x + dx) | X(u) < S, u \in [s, t_1]; X(s) = y\right)$$

$$= \frac{P\left(X(t) \in (x, x + dx); X(u) < S, u \in [s, t_1] | X(s) = y\right)}{P\left(X(u) < S, u \in [s, t_1] | X(s) = y\right)}$$

$$= \frac{P\left(X(t) \in (x, x + dx); X(u) < S, u \in [s, t]; X(u) < S, u \in [t, t_1] | X(s) = y\right)}{P\left(T > t_1 | X(s) = y\right)}$$

$$= \frac{P\left(X(t) \in (x, x + dx); X(u) < S, u \in [s, t] | X(s) = y\right)}{P\left(T > t_1 | X(s) = y\right)}$$

$$\times \quad P\left(X(u) < S, u \in [t, t_1] | X(t) = x\right)$$

$$= \frac{f^a(x, t | y, s) P\left(T > t_1 | X(t) = x\right)}{P\left(T > t_1 | X(s) = y\right)} dx$$

Proof of (3), (7) and (8).

Since $X^c(t)$ is a diffusion process, its transition probability density satisfies the Kolmogorov equation

$$\frac{\partial f_{t_1}^c}{\partial s} + A^c(y, s) \frac{\partial f_{t_1}^c}{\partial y} + B^c(y, s) \frac{\partial^2 f_{t_1}^c}{\partial y^2} = 0. \tag{13}$$

Making use of (6) we can relate the drift and the diffusion coefficient of equation (13) with the drift $a(y)$ and the diffusion coefficient $\sigma(y)$ of the process $X(t)$. To this purpose we write the derivatives with respect to s and to y of $f_{t_1}^c(x, t | y, s)$:

$$\frac{\partial f_{t_1}^c}{\partial s} = \frac{\frac{\partial f^a}{\partial s} P^a(S, t_1 | y, s) - f^a(x, t | y, s) \frac{\partial P^a(S, t_1 | y, s)}{\partial s}}{[P^a(S, t_1 | y, s)]^2} P^a(S, t_1 | x, t) \tag{14}$$

$$\frac{\partial f_{t_1}^c}{\partial y} = \frac{P^a(S, t_1 | x, t)}{[P^a(S, t_1 | y, s)]^2}$$

$$\times \left\{ \frac{\partial f^a}{\partial y} P^a(S, t_1 | y, s) - f^a(x, t | y, s) \frac{\partial P^a(S, t_1 | y, s)}{\partial y} \right\}$$

$$\frac{\partial^2 f_{t_1}^c}{\partial y^2} = \left\{ -f^a(x, t | y, s) \frac{\partial^2 P^a(S, t | y, s)}{\partial y^2} \frac{1}{[P^a(S, t_1 | y, s)]^2} \right.$$

$$+ \frac{\partial^2 f^a}{\partial y^2} \frac{1}{P^a(S, t_1 | y, s)} - 2 \frac{\partial f^a}{\partial y} \frac{\partial P^a(S, t_1 | y, s)}{\partial y} \frac{1}{[P^a(S, t_1 | y, s)]^2}$$

$$+ \left. f^a(x, t | y, s) \left[\frac{\partial P^a(S, t_1 | y, s)}{\partial y} \right]^2 \frac{2}{[P^a(S, t_1 | y, s)]^3} \right\}.$$

Let us now substitute (14) into (2); making use of equation (2) for $f^a(x, t | y, s)$ we get:

$$
\begin{aligned}
0 = {} & \frac{\partial^2 f^a}{\partial y^2} \left[B^c(y, s) - \frac{\sigma^2(y)}{2} \right] + \frac{\partial f^a}{\partial y} [A^c(y, s) - a(y) \\
& - \frac{\partial P^a(S, t_1 | y, s)}{\partial y} \frac{2 B^c(y, s)}{P^a(S, t_1 | y, s)}] \\
& + \frac{f^a(x, t | y, s)}{P^a(S, t_1 | y, s)} [a(y) \frac{\partial P^a(S, t_1 | y, s)}{\partial y} + \frac{\sigma^2(y)}{2} \frac{\partial^2 P^a(S, t_1 | y, s)}{\partial y^2} \\
& - A^c(y, s) \frac{\partial P^a(S, t_1 | y, s)}{\partial y} \\
& - B^c(y, s) \frac{\partial^2 P^a(S, t_1 | y, s)}{\partial y^2} + 2 \left(\frac{\partial P^a(S, t_1 | y, s)}{\partial y} \right)^2 \frac{B^c(y, s)}{P^a(S, t_1 | y, s)}].
\end{aligned}
$$

Hence by the homogeneity principle we have

$$
A^c(y, s) = a(y) + \frac{\sigma^2(y)}{P^a(S, t_1 | y, s)} \frac{\partial P^a(S, t_1 | y, s)}{\partial y} \tag{15}
$$

while the diffusion coefficient is unchanged. This gives (3) since the second term of (15) can be written as the derivative of the log. The second boundary condition in (7) arises from (6), since $f_{t_1}^c(x, t | y, s) dx$ is normalized to integrate to 1. Finally the SDE (8) for the constrained process immediately follows from the drift (15).

Computation of (9).

Consider the constrained process on $[0, t_1]$; according to (8) its drift is given by

$$
A^c(y, s) = a(x) + \frac{\sigma^2(x)}{P^a(S, t_1 | x, t)} \frac{\partial P^a(S, t_1 | x, t)}{\partial x},
$$

while its diffusion coefficient coincides with that of the free process. It is known that the drift of a bridge process is related with that of the corresponding free process $X(t)$ through the relationship (cf. Giraudo et al. (2001)):

$$
{}_{(x_0, t_0)}^{(z, u)} A(x, t) = a(x) + \frac{\sigma^2(x)}{f(z, u | x, t)} \frac{\partial f(z, u | x, t)}{\partial x} \tag{16}
$$

and the diffusion coefficient does not change. We substitute a constrained process for the free one in (16), and hence $f_{t_1}^c(z, u | x, t)$ as given by (6) for $f(z, u | x, t)$ and $A^c(x, t)$ as given by (15) to $a(x)$, to obtain

$$
\begin{aligned}
{}_{(x_0, t_0)}^{(z, u)} A^c(x, t) = {} & a(x) + \frac{\sigma^2(x)}{P^a(S, t_1 | x, t)} \frac{\partial P^a(S, t_1 | x, t)}{\partial x} \\
& + \frac{\sigma^2(x)}{f_{t_1}^c(z, u | x, t)} \frac{\partial f_{t_1}^c(z, u | x, t)}{\partial x}, \quad u \leq t_1
\end{aligned}
$$

Recalling (6), after some algebra, one gets

$$\frac{\sigma^2\left(x\right)}{f_{t_1}^c\left(z,u\,|x,t\right)}\frac{\partial f_{t_1}^c\left(z,u\,|x,t\right)}{\partial x} = \frac{\sigma^2\left(x\right)}{f^a\left(z,u\,|x,t\right)}\frac{\partial f^a\left(z,u\,|x,t\right)}{\partial x}$$
$$- \frac{\sigma^2\left(x\right)}{P^a\left(S,t_1\,|x,t\right)}\frac{\partial P^a\left(S,t_1\,|x,t\right)}{\partial x}$$

and (9) follows.

Remark. Note that to prove (9) we first consider a constrained process up to time t_1 and then its bridge to z at time $u \leq t_1$. One could also introduce another process by first considering a bridge to z at time u, with $z \leq S$, and then its constrained version up to the time $t_1 < u$. In the limit when $u \to t_1$ (or $t_1 \to u$) these two processes coincide.

Proof of (10).

Let us take the limit of equation (9) when $z \to S$. We use l'Hopital's rule to compute this drift coefficient for the constrained bridge to S:

$$\lim_{z \to S}\left\{a\left(x\right) + \frac{\sigma^2(x)}{f^a\left(z,u\,|x,t\right)}\frac{\partial f^a\left(z,u\,|x,t\right)}{\partial x}\right\}$$

$$= \lim_{z \to S}\left\{a\left(x\right) + \sigma^2(x)\frac{\frac{\partial}{\partial z}\left[\frac{\partial f^a(z,u|x,t)}{\partial x}\right]}{\frac{\partial f^a(z,u|x,t)}{\partial z}}\right\}$$

$$= a\left(x\right) + \sigma^2(x)\frac{\frac{\partial}{\partial x}\left[\frac{\partial f^a(z,u|x,t)}{\partial z}\bigg|_{z=S}\right]}{\frac{\partial f^a(z,u|x,t)}{\partial z}\bigg|_{z=S}} \tag{17}$$

Taking the derivative of (5) with respect to t and using the forward Kolmogorov equation, gives us

$$\frac{\partial f^a\left(y,u\,|x,t\right)}{\partial y}\bigg|_{y=S} = g\left(u\,|x,t\right). \tag{18}$$

We substitute then (18) in the right hand side of (17) to obtain the result.

Figure Captions

Figure 1 Sample paths of the absorbed process (dashed lines) and of the corresponding constrained process with $t_1 = 30$ ms (continuous lines). The paths of the absorbed process are killed at the time where they first reach $S = 10$ mV.

Figure 2 Sample paths of the free bridge process in $S = 10$ mV with $u = 15$ ms, $u = 20$ ms (continuous lines) and two sample paths of the corresponding constrained bridge processes in S (dashed lines).

Figure 3 Additional term in the drift of the constrained Wiener process with $\mu = 1$ mVms^{-1}, $S = 10$ mV, $t_1 = 40$ ms, as a function of t, for $\sigma^2 = 1, 4, 6, 9$ mV^{2}ms^{-1} (continuous, dashed, dotted, dashed-dotted lines respectively).

Figure 4 Mean of the constrained (continuous line) and of the free (dashed line) Wiener process, $E[W(t)] = \mu t$, with $\mu = 0.5$ mVms^{-1}, $\sigma^2 = 1$ mV^{2}ms^{-1}, $S = 10$ mV, $t_1 = 6$ ms (inset) and $t_1 = 40$ ms. Here $P(T \leq 6) \cong 5*10^{-5}$ while $P(T \leq 40) \cong 0.12$.

Figure 5 Mean of the constrained (continuous line) and of the free (dashed line) Ornstein-Uhlenbeck process with $\sigma^2 = 2$ mV^{2}ms^{-1}, $\theta = 10$ ms^{-1}, $S = 10$ mV. Panel A: sub-threshold regime with $\mu = 0.5$ mVms^{-1}, $t_1 = 6$ ms (inset) and $t_1 = 20$ ms. Here $P(T \leq 6) \cong 5*10^{-3}$ while $P(T \leq 20) \cong 0.16$. Panel B: supra-threshold regime with $\mu = 1.5$ mVms^{-1}, $t_1 = 5$ ms (inset) and $t_1 = 20$ ms. Here $P(T \leq 5) \cong 0.09$ while $P(T \leq 20) \cong 0.96$.

Figure 6 Mean of the free (dashed line) and of the constrained (continuous line) Ornstein-Uhlenbeck bridge process to S with $\theta = 10$ ms^{-1}, $S = 10$ mV, $\mu = 0.5$ mVms^{-1}, $\sigma^2 = 2$ mV^{2}ms^{-1}. Here $u \equiv T = 9.3$ ms.

Figure 7 Mean of the free (dashed line) and of the constrained (continuous lines) Ornstein-Uhlenbeck process with $\theta = 10$ ms^{-1}, $S = 10$ mV. Panel A: sub-threshold regime with $\mu = 0.5$ mVms^{-1}, $t_1 = 20$ ms, $\sigma^2 = 0.5, 2, 6$ mV^{2}ms^{-1} (from top to bottom). Panel B: supra-threshold regime with $\mu = 1.5$ mVms^{-1}, $t_1 = 20$ ms, $\sigma^2 = 1, 2, 6$ mV^{2}ms^{-1} (from top to bottom).

Figure 8 Continuous line: mean of a constrained Ornstein-Uhlenbeck process with $\mu = 1.2$ mVms^{-1}, $\sigma^2 = 1$ mV^{2}ms^{-1}, $\theta = 10$ ms^{-1}, $S = 10$ mV, i.e. possible recorded data (suprathreshold); dashed-dotted line: mean of a corresponding free process; dashed line: mean of a corresponding free Ornstein-Uhlenbeck process with $\mu = 0.8$ mVms^{-1}, which is estimated from the continuous curve as originated from a free process.

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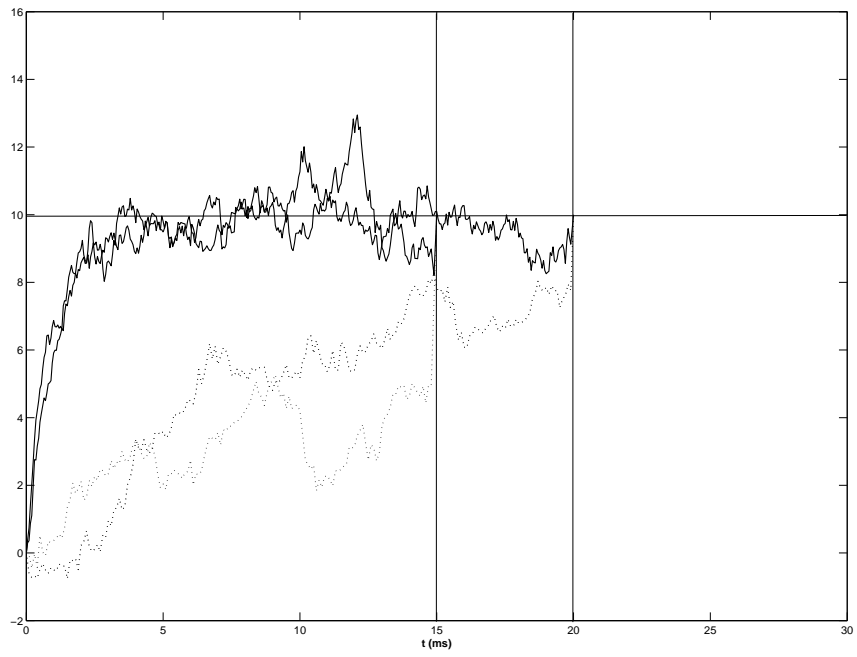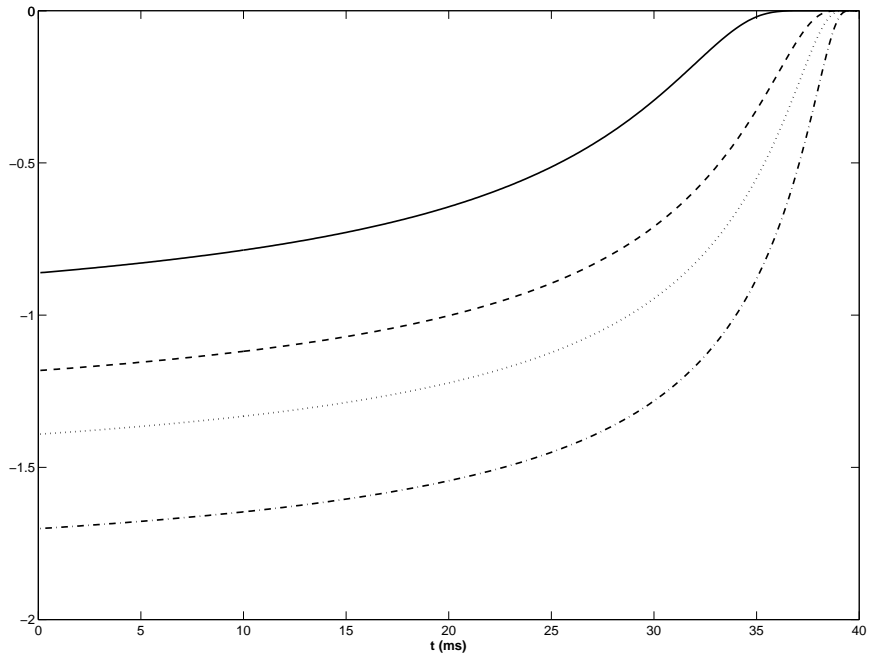
Figure 1

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Figure 2

Figure 3

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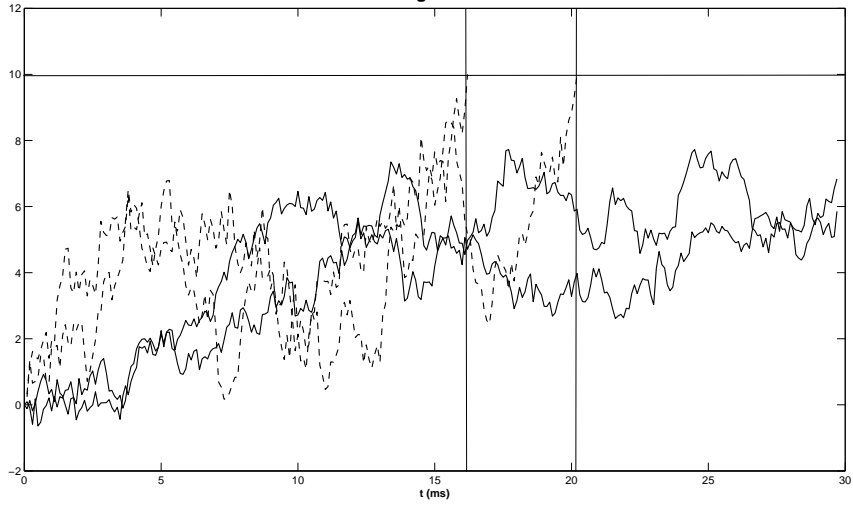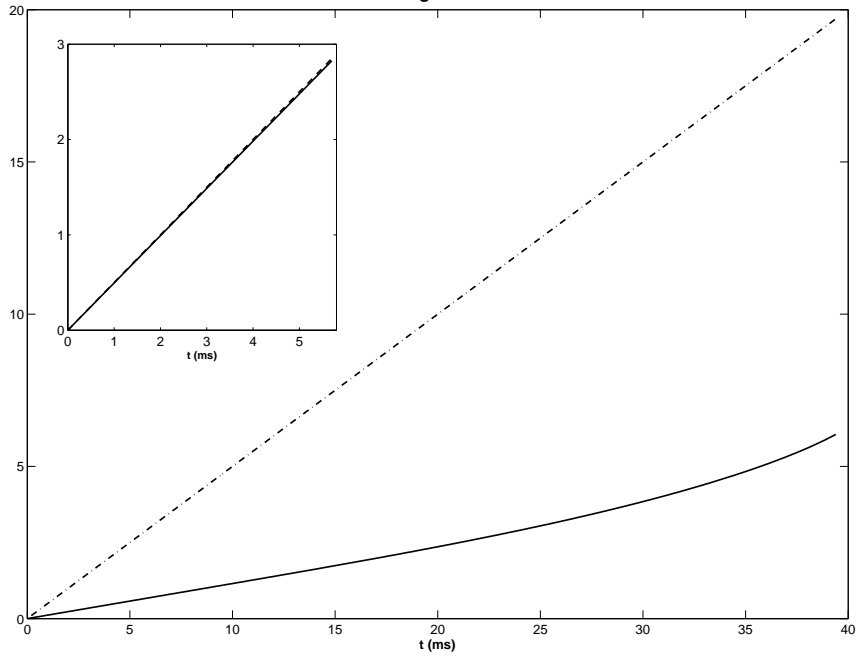
Figure 4

Figure 5

Figure 6

Figure 7

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Figure 8