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Analysis of single particle diffusion with transient binding using particle filtering

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HIGHLIGHTS

- Diffusion with transient binding is a pervasive phenomena in biology, as small proteins, organelles, etc. undergo Brownian transport interspersed with periods of stationarity at binding sites.
- High-speed microscopy has given researchers a vast amount of high quality data on these phenomena of transient binding.
- Using an EM algorithm along with particle filters, the model can be fit in a computationally efficient way.

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ABSTRACT

Diffusion with transient binding occurs in a variety of biophysical processes, including movement of transmembrane proteins, T cell adhesion, and caging in colloidal fluids. We model diffusion with transient binding as a Brownian particle undergoing Markovian switching between free diffusion when unbound and diffusion in a quadratic potential centered around a binding site when bound. Assuming the binding site is the last position of the particle in the unbound state and Gaussian observational error obscures the true position of the particle, we use particle filtering to predict when the particle is bound and to locate the binding sites. Maximum likelihood estimators of diffusion coefficients, state transition probabilities, and the spring constant in the bound state are computed with a stochastic Expectation–Maximization (EM) algorithm.

1. Introduction

Single particle tracking experiments provide high-resolution time traces of proteins, lipids, viruses, and synthetic probes in biofluids (Saxton and Jacobson, 1997; Joo et al., 2008). Statistical analysis plays an increasingly important role in our understanding of the dynamical processes observed in these experiments (Qian and Kou, 2014). In particular, a significant amount of statistical methodology has been developed and applied to the analysis of particles switching between multiple diffusive states, henceforth called regimes (Bosch et al., 2014). This paper focuses on switching processes that can be described as diffusion interspersed with transient periods of binding and on the related problems of predicting the unobserved regime of the particle, locating the binding sites, and estimating model parameters.

A large body of research relates to cell membrane proteins transiently binding to the cortical cytoskeleton or cytoskeletal-associated elements. Since binding reduces the mobility of a diffusing protein, transient binding may explain why diffusing transmembrane proteins have lower diffusion coefficients in cell membranes than in artificial membranes (Jacobson et al., 1987; Gennis, 1989). This behavior was qualitatively described in the "transient interaction" model of Zhang et al. (1991, 1993), in which cell membrane glycoproteins become transiently bound to transmembrane anchor proteins attached to and immobilized by the cytoskeleton. The "conveyor-belt" model of Saxton (1994) formalizes and generalizes the transient interaction model by allowing for directed flow of cytoskeletal elements. Transient binding by cytoskeletal attachment may have a functional role as well; for example, Cairo et al. (2006) suggest that transient binding of the lymphocyte function-associated antigen 1 (LFA-1) has a regulatory effect on T cell adhesion.

Akin to transient binding is the temporary confinement of diffusing particles in cage-like structures. This process is called confined or corralled diffusion when membrane proteins or phospholipids become trapped in membrane skeletal corrals (Saxton and Jacobson, 1997). Corrals in the "picket-fence" model

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are created from transmembrane anchor protein "pickets" connected by actin-filament "fences" (Fujiwara et al., 2002; Kusumi et al., 2005). In microrheology experiments, transient confinement is often called caging and has been observed in colloidal fluids near the glass transition (Weeks and Weitz, 2002) and suggested as the cause for the anomalous diffusion of particles in granular materials and in a suspension of rod-like viruses (Marty and Dauchot, 2005; Lettinga and Grelet, 2007). Transient binding may also lead to anomalous diffusion in a variety of non-biological systems and biofluids (Metzler and Klafter, 2000; Saxton, 2007), although the relationship is not considered in this paper.

We model diffusion with transient binding as Markovian switching between regimes of free Brownian diffusion and Brownian diffusion in a quadratic potential centered around a binding site, where the binding site is assumed to be the last position of the particle in the unbound regime. The model is placed in a state space framework under the assumption of Gaussian observational error, though other distributional assumptions can be accommodated, allowing the use of particle filtering to predict the unobserved regime, true position, and locations of the binding sites. A stochastic Expectation–Maximization (EM) algorithm is used to compute maximum likelihood estimates of model parameters, including diffusion coefficients, regime transition probabilities, and the spring constant. The particle filter and the EM algorithm are relatively simple to code, computationally inexpensive, and numerically stable. Furthermore, they may be applicable to other switching models of interest in single particle tracking.

The remainder of the paper is structured as follows. Section 2 presents our mathematical model for diffusion with transient binding. In Section 3, we review the literature on models and inferential methods for switching processes in single particle tracking, show how the unobserved regimes of a particle are predicted and the binding sites located using particle filtering, and explain how this prediction enables parameter estimation using a stochastic EM algorithm. Simulation results in Section 4 validate the method, demonstrate robustness to the assumptions of a Markovian regime switching process and quadratic potential, and provide a setting to discuss model diagnostics.

2. Mathematical model

This section presents a physically motivated, continuous-time mathematical model for a particle undergoing diffusion with transient binding and explicitly connects it to a discrete-time statistical model. The regime of the particle is assumed to follow a continuous-time Markov chain $\{J(t)|t \geq 0, J(t) \in \{1, 2\}\}$, where 1 represents the bound regime and 2 the unbound regime. Associated with each regime is a transition rate λ_i parameterizing the exponentially distributed time regime i is occupied before the other regime is entered. For each time $t \geq 0$, the switching time $\tau(t)$ gives the most recent time the particle switched into the current regime $J(t)$, where we define $\tau(0) = 0$.

The position of the particle is denoted $Z(t) = (Z^1(t), Z^2(t))'$. In the bound regime, the particle dynamics are described as diffusion in a quadratic potential centered around the binding site $Z(\tau(t)) = (Z^1(\tau(t)), Z^2(\tau(t)))'$, so that

$$Z(t) = Z(\tau(t)) - \kappa \int_{\tau(t)}^{t} \left[Z(u) - Z(\tau(t)) \right] du + \sqrt{2D_1} \int_{\tau(t)}^{t} dW(u),$$

where $W(t) = (W^1(t), W^2(t))'$ are independent, standard Brownian motions and D_i denotes the diffusion coefficient in regime i. The constant $\kappa > 0$ is interpreted as a linear-spring constant, where larger κ correspond to stiffer springs or tighter binding. In the unbound regime, the particle undergoes free or possibly directed diffusion,

$$Z(t) = Z(\tau(t)) + \int_{\tau(t)}^{t} \mu \, du + \sqrt{2D_2} \int_{\tau(t)}^{t} dW(u),$$

where the drift term $\mu = (\mu_1, \mu_2)'$ is zero for undirected, free diffusion. Combining the bound and unbound models for the position of the particle yields the continuous-time, physical model for diffusion with transient binding,

$$\begin{aligned} Z(t) = Z(\tau(t)) &+ \left[-\kappa \int_{\tau(t)}^{t} \left[Z(u) - Z(\tau(t)) \right] du + \sqrt{2D_1} \int_{\tau(t)}^{t} dW(u) \right] I_{\{J(t)=1\}} \\ &+ \left[\int_{\tau(t)}^{t} \mu \, du + \sqrt{2D_2} \int_{\tau(t)}^{t} dW(u) \right] I_{\{J(t)=2\}}, \end{aligned} \tag{1}$$

where $I_{\{\cdot\}}$ is the indicator function defined as 1 if the expression in the brackets is true and 0 otherwise. A realization of this model appears in Fig. 1.

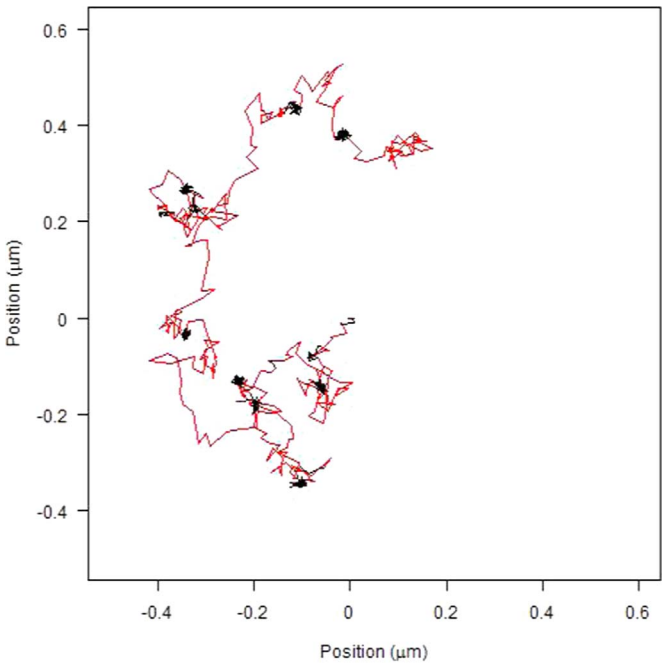

Fig. 1. Simulated trajectory from the proposed continuous-time, physical model (1) with changes in position when bound and unbound marked in black and red, respectively. Parameters are $\mu = (0, 0)'$ μm/s, $\kappa = 916.3\ s^{-1}$ $D_1 = 0.03\ \mu m^2/s$, $D_2 = 0.21\ \mu m^2/s$, $\lambda_1 = 20.8\ s^{-1}$, and $\lambda_2 = 62.5\ s^{-1}$. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)

Additive, Gaussian observational error is assumed to obscure the true position of the particle. Hence, the observed position of the particle, denoted $Y_k = (Y_k^1, Y_k^2)'$, is

$$Y_k = Z_k + \eta e_k, \quad k = 1, 2, 3, \ldots, \tag{2}$$

where Δ denotes the time between observations, $Z_k = Z(k\Delta)$, and $e_k = (e_k^1, e_k^2)'$ are independent sequences of independent Gaussian random variables with mean zero and variance one. Without loss of generality, the initial observed position is assumed to be $Y_0 = (0, 0)'$.

Following Das et al. (2009), the assumption that regime changes occur only at times of observation is made to facilitate inference for the proposed continuous-time model. This assumption enables the construction of an approximate discretization of (1) which, as we show in Section 3.3, permits maximum likelihood-based inference. To construct the discretization, let $\tau_k \in \{0, \Delta, 2\Delta, \ldots, (k-1)\Delta\}$ be the most recent observation time at which the particle was in the unbound regime. Then, the assumption implies that the discrete-time position process Z_k,