3D Brownian Motion Simulator for High-Sensitivity Nano-Biotechnological Applications

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Abstract

Motivation: A wide variety of nano-biotechnologic applications are being developed for nanoparticle based *in vitro* diagnostic and imaging systems. Some of these systems make possible highly sensitive detection of molecular biomarkers. Frequently, the very low concentration of the biomarkers makes impossible the classical, partial differential equation-based mathematical simulation of the motion of the nanoparticles involved.

Results: We present a three-dimensional Brownian motion simulation tool for the prediction of the movement of nanoparticles in various thermal, viscosity and geometric settings in a rectangular cuvette.

Availability: For non-profit users the server is freely available at the site http://brownian.pitgroup.org.

1 Introduction

As nano-biotechnology is developing, a multitude of diagnostic and visualization applications are being constructed for fast, relaible, on-site molecular recognition. Several of these applications use nanoparticles, that bind to biomarkers, and the nanoparticles make possible the optical recognition of the biomarker molecules [1], [2], [3], [4], [5], [6], [7], [8].

The high-sensitivity applications in molecular recognition need the reliable modelling of the Brownian motion of the nanoparticles in the reaction chamber [9], [10]. The fast distribution of the nanoparticles is generally needed for the completion of the detection, and it is usually the most time-consuming part of the process. Measures, for improving the fast distribution, such as sonication, cannot be used if it breaks the binding of the biomarker-nanoparticle complex, and simple agitation usually does not help much [11].

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In the case of the extremely low concentration of biomarkers, the best choice for the Brownian motion prediction is the stohastic computer simulation, since mathematical models involving concentration-based partial differential equations do not seem to be applicable in the range of several hundred or several thousand biomarker molecules [12].

2 Results: The Dual Time-Step Brownian Server

Our Brownian server simulates the movement of upto 1000 nanoparticles under various, user-selactable circumstances. Each particle is placed randomly and independently with uniform distribution, into the container. Next, random walks are generated for each particle in parallel, and the particles keep walking until they hit the target spot on the bottom of the container; if a particle hit the spot, it will not move further: this phenomenon models a (macro-)molecular binding between the spot and the nanoparticle.

The location of the target spot is selectable either in the center or in the corner of the container.

The simulation returns the docking ratio and the time needed for docking the very first particle in each experiment. The latter is more relevant measure of success than the former if the docked particles are detected by some qualitative, sensitive method. Heat diagrams for the spatial distribution of the docked ratio are also supplied.

The main *technical novelty* of our solution is the dual time-step approach: while the nanoparticle is far from the target spot, we simulate its movement in larger time steps, and when if it is close to the target spot, we turn to a much finer time step. This idea makes possible to create an on-line service for 3D Brownian simulation with user-selactable settings.

Note, that the probability distribution of the movements in the rougher time step will be the same as it were simulated in much finer time steps, since the sum of independent normal distributions is normal distribution.

3 Methods

For generating 100 million pseudorandom numbers of standard normal distribution, we applied the well-known Ziggurat algorithm [13].

Let x, y and z denote independently generated, one-dimensional standard normal distributed pseudorandom variables, resulting from the Ziggurat algorithm [13]. Let $Q = (x, y, z)$ be a three-dimensional vector in normal distribution. Then we generate the simulated Brownian motion of the particle as

$$P_{\texttt{new}} = P_{\texttt{old}} + Q\sqrt{\frac{2}{3}D},$$

where D is the diffusion coefficient, computed from the Einstein-Stokes equation [14]:

$$D = \frac{k_B T}{6\pi\eta r},$$

where k_B is the Boltzmann's constant, η is the viscosity, T is the (absolute) temperature, and r is the radius of the nanoparticle.

In our model, following the model [15], if the particle hits the bottom of the cuvette, it will collide totally elastically with probability 1/2 (i.e., it will continue its 3D movement) and will be sticked to the bottom plane with probability 1/2, to perform a two-dimensional random walk by the rule:

$$P_{\texttt{new}} = P_{\texttt{old}} + Q'\sqrt{D},$$

where $Q' = (x, y)$.

Generating tens of millions of elementary movements in three dimensional multi-particle Brownian computer simulation, for thousands of particles is a very time- and resource consuming computational task. In order to build a public web-server for this goal, we applied a dual time-step approach:

While the particle is still far from the target spot, we simulate its motion with 1 s time-steps (rough phase). When the particle gets closer than a predefined limit to the spot, we switch to 0.01 s timesteps (fine phase).

Instead of generating 100 random vectors $Q^{(i)}$, $i = 1, 2, \ldots, 100$ with normal distribution with steps of 0.01 s in the rough phase, we just generate one, this improves the running time of the simulation considerably. Note, that the (coordinate-wise) sum of the 100 random vectors

$$\sum_{i=1}^{100} Q^{(i)}$$

has exactly the same distribution as $10(x, y, z)$, where the independent x, y and z have 1-dimensional standard normal distribution.

The simulation of the nano-particles should be cautious on the border of the rough and the fine phases: it may happen that on the border, because of the time-shift, the particles behave strangely. In order to getting rid of this behaviour, we change from rough simulation to fine simultaion, and vica versa, as follows:

Let R denote the radius of the target spot.

- When we are closer to the central point of the spot, than $1000L + R - \varepsilon$, we change from rough simulation to fine simulation.
- When we move farer from the central point of the spot, than $1000L + R + \varepsilon$, we change from fine simulation to rough simulation.

In the server, $L = 100nm$, $R = 50\mu m$ and $\varepsilon = 20L = 2\mu m$.

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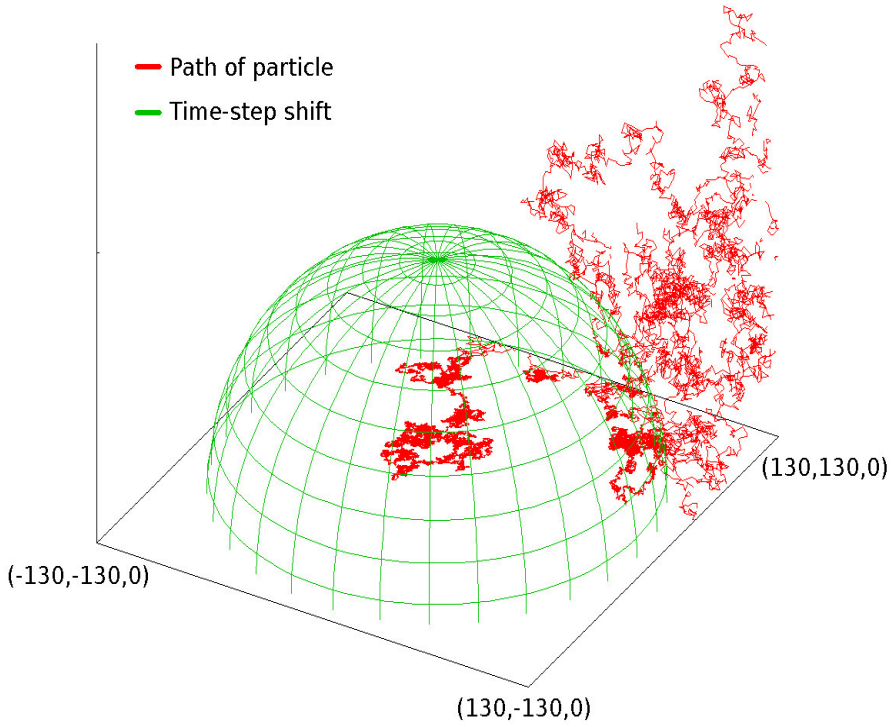

Figure 1: *The simulated movement of a particle at the border of the rough and the fine phases. The coordinates are in* μm.

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