

A Fokker-Planck Approach for Modeling Integrated NanoBio Systems

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ABSTRACT

Evaluation of microfluidic device and sensor designs using continuum modeling is a viable method, but becomes more complex if nanoscale or molecular level physics is to be included in the model. Recently, we have undertaken an effort to incorporate and understand nanoscale effects and how they impact continuum level simulations of microfluidics devices. This research focuses on how nanoscale physics can be incorporated into continuum level simulations using the Fokker-Planck Equation (FPE). The applications currently focus on shear influenced binding and biomolecular motors. The main challenge in these applications is the two way coupling of information generated in nanoscale simulations to the continuum level using a FPE approach.

Keywords: Microfluidics, biomotor, mesoscale dynamics, microcantilever.

1 INTRODUCTION

Physics-based, high-fidelity simulations have emerged as indispensable tools in the design of complex, microfluidic devices (lab-on-chip). However, ab-initio analysis becomes increasingly complicated as the dimensions of the device approach nanoscales and molecular information/interactions must be considered (Integrated Nanobiosystems). The information exchange between the nanoscale and the microscale is difficult for two reasons. First, device/component level simulations are traditionally continuum based while molecular physics is resolved using a variety of methods (e.g. Molecular Dynamics (MD)). Integrating the two schemes to yield a self consistent calculation of biomolecular reactions in a microfluidic device, is a costly and unfeasible task for realistic systems. Secondly, the time scale differences between nanoscale (relaxation phenomena in pico/nano seconds) and microscale (response in milliseconds) poses serious challenges in active coupling between the molecular and continuum aspects of any integrated simulation.

There are essentially two methods one can use to model events at the nanoscale, explicit molecular models and probabilistic models. Molecular modeling (Monte Carlo, Molecular Dynamics) is a very attractive method of modeling the molecular scale since each simulation is analogous to a precise nanoscale laboratory where one is

able to obtain a full molecular level description of the system in motion. The main problems with using explicit molecular modeling are (a) prohibitive computational cost is for realistic systems, (b) time scales limited to less than 10 nanoseconds, and (c) results are sensitive to the atomic interaction potentials used. Probabilistic methods, on the other hand, incorporate the stochastic character of a molecular model into a probability distribution function that can be described by either a Master Equation (ME) or a Fokker-Planck Equation. The advantages of using probabilistic models are (a) ability to incorporate molecular level detail into a simulation, (b) easy to incorporate into an existing continuum code to solve for probability distribution function in real space, (c) computationally cost effective. The main drawback of using probabilistic methods is that in general, a molecular level simulation must be performed in order to parameterize an ME or a FPE.

The Fokker-Planck Equation offers a unique advantage of being based on partial differential equation, which facilitates integration with continuum approach. At CFDRC we have successfully coupled a FPE-based description of biomolecular events with a continuum-based convective-diffusive-reactive treatment of biosystems (CFD-ACE+). The main goal is to be able to simulate nano-resolved, biomolecular reactions (DNA hybridization, Ag-Ab interactions) in spatially inhomogeneous systems with convective (drift)-diffusive transport. FPE formulation and boundary conditions, along with their relationships to Master Equation transition.

Figure 1 represents a widely accepted view of the scales of modeling from quantum level to the scale of engineering unit operations. Our current research efforts focus mainly on the length and time scales known as the mesoscale or middle scale (sometimes referred to as "colloidal scale"). This is the region smaller than the continuum scale, but much larger than the atomic scale. At this level effects from the nanoscale are significant enough to warrant inclusion. Simulation of mesoscale devices generally occurs on the physical timescale much greater than 100 nanoseconds, and usually encompasses a length scale of between 10 nanometers to 10 micrometers [1].

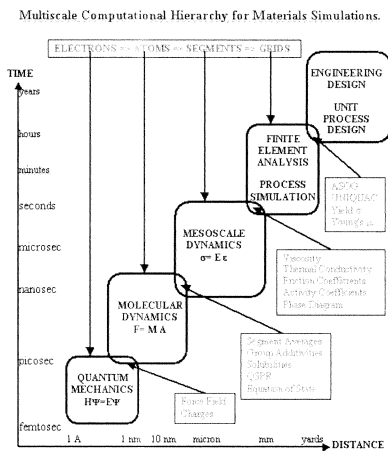


Figure 1: Commonly accepted view of length and time scales of modeling

2 COUPLING BETWEEN NANOSCALE AND CONTINUUM

Communicating information between the nanoscale and continuum scale is challenging due to the nature of the information generated at each scale. At the continuum scale information, such as velocities and pressure, are relatively smooth functions of spatial and temporal variables with no stochastic character (turbulent conditions being the exception). Nanoscale simulations generate information that can only be characterized in terms of a time or ensemble averaging of dynamic variables in order to equate them with a thermodynamic continuum variable such as temperature and pressure. The goal is to develop mathematical models which couple micro/nanoscale phenomena for use in realistic device simulations. The potential impact on the modeling community and the way nanoscale device modeling is performed will be to expand the use of developed nanosystems into secondary application areas.

The hybrid hierarchical approach used at CFDRC is shown in Figure 2. There are two paths one can take once the molecular level simulation/characterization has been performed. The most straight forward method, in principle, is to solve a Master Equation describing the probability distribution function for variables of interest in the system. In general a Master Equation has the form shown in Equation 1.

$$\frac{\partial P(q)}{\partial t} = \sum_{q'} [P(q')W_{q' \rightarrow q} - P(q)W_{q \rightarrow q'}] \quad (1)$$

This equation describes the probability of finding a system in state q at time t . The first term in equation 1 describes the transition of the system into a q state and the second term describes the transition out of a q state summed over all possible transition states q' . The inputs to

the Master Equation are the transition rates, $W_{q' \rightarrow q}$, for each q' state generally obtained from molecular calculations. The outputs from equation 1 are the probability of finding the system in a q state, and the Drift and Diffusion Coefficients for the Fokker-Planck equation. In all but the simplest cases, the Master Equation is difficult to solve analytically and can be solved numerically only by resorting to Monte Carlo techniques. One method of circumventing this problem is to use a Fokker-Planck approach to finding the distribution function.

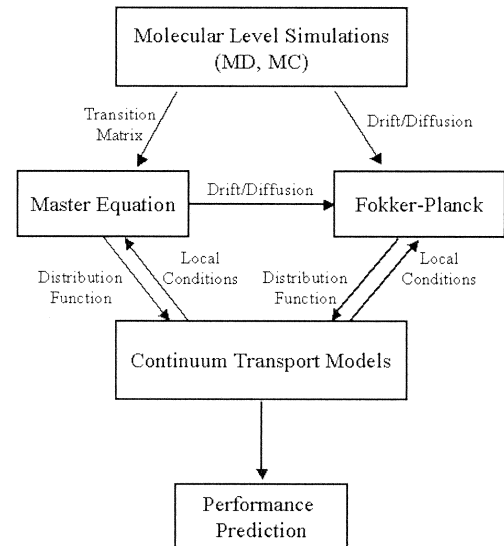


Figure 2: Illustration of coupling between continuum and nanoscale. The two paths illustrate how the Master Equation and Fokker-Planck Equation couple to the continuum models.

In a well characterized limit [2], the Fokker-Planck Equation and Master Equation give the same probability function as output. The FPE is a partial differential equation with a continuous variable, and it replaces the Master Equation which describes probability in discrete states. The general form of FPE is given in Equation 2.

$$\frac{\partial f}{\partial t} + \nabla \cdot [D_1 f - \nabla (D_2 f)] = S \quad (2)$$

The FPE is used to obtain solutions for the probability distribution function $f(q,t)$ in a continuous sense by describing the rate of change of $f(q,t)$ in terms of a gradient of probability flux and source terms S . The flux term consists of a drift D_1 and diffusion coefficient D_2 . In general the drift and diffusion coefficients are functions of the local conditions in the simulation and must be solved simultaneously with the momentum and mass transport equations. The implementation in the CFD-ACE+ software package breaks the flux of probability into a real space term and an auxiliary variable, making the probability space 4 dimensional given in equation 3.

$$\frac{\partial f}{\partial t} + \nabla_x \cdot [uf - \nabla_x(Df)] + \nabla_\phi \cdot [D_1 f - \nabla_\phi(D_2 f)] = S \quad (3)$$

The inputs to equation 3 are the 3D geometry, process conditions, and Drift/Diffusion coefficients. The output is the flow and transport solution along with the probability distribution function for the auxiliary variable at each real space node in the system.

3 APPLICATIONS

3.1 Biomotors

Many microfluidic devices rely on enhanced transport (micropumps or micromixers) to properly detect or analyze biomolecules. Biomotors are naturally occurring proteins exhibiting modes of motion have been applied to the problem of enhancing transport in microfluidic systems. ATPases are a class of proteins known to exhibit a unique form of rotary motion in response to synthesis or hydrolysis of ATP. The average rate of rotation of the γ -subunit of F1-ATPase has been measured experimentally at 3-4 revolutions per second [3]. The size of the protein, combined with the rate of rotation suggests that it could be used as an agitation mechanism to increase the binding rates in mass transport limited situations.

A model describing the behavior of the F1-ATPase motor has been given in the literature by Oster and Wang [4]. This model predicts the variation in the rotational speed (rad/sec) of the motor as a function of local nutrient concentration and attached Actin propeller length. However, this model is comprised of 64 states and many of the transition rates in the model are estimated. A simpler model capturing the essential physics can be extracted from the more complex 64 state model. The master equation describing the motion of the biomotor is given below in equation 4.

$$\frac{dP_\omega(t)}{dt} = \gamma\omega P_{\omega + \Delta\omega}(t) + K_c[ATP]P_{\omega - \Delta\omega}(t) - [\gamma\omega + K_c[ATP]]P_\omega(t) \quad (4)$$

Where γ is the resistance to rotary motion and $K_c[ATP]$ is the rate of uptake of nutrients (ATP). The balance of nutrient uptake creating rotary motion and the resistance to the motion are the essential pieces of physics captured by the model. Equation 4 can be reduced to a Fokker-Planck equation by calculating the transition rate moments given in equation 5 below.

$$D_n(\omega, t) = K_c[ATP] + (-1)^n \left(\frac{4\pi\eta L^3}{\ln\left(\frac{L}{2r}\right) - 0.447} \right) \omega \quad (5)$$

The first two transition rate moments are the drift and diffusion coefficient of the FPE. Using this information the mean rotational speed can be computed from the distribution function and this can be compared to experimental data. Figure 3 shows that the simplified model proposed above reproduces the measurements in a qualitative way. This model can then be coupled to a continuum solution by allowing the motor to consume ATP at a certain rate producing rotary motion. The rotation of the actin propeller disturbs the local flow solution by a stirring action. Using a more detailed model of the biomotor can aid in the design of a device that contains biomotors.

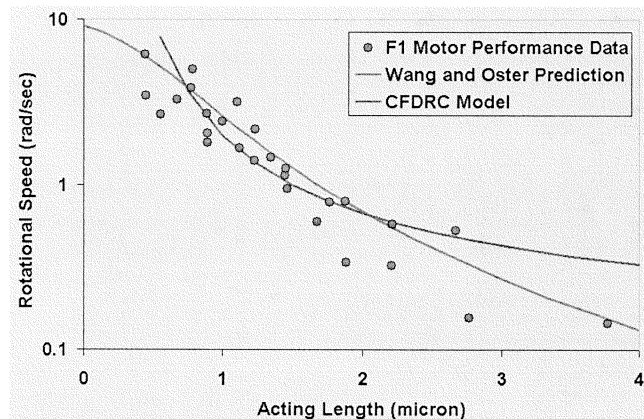
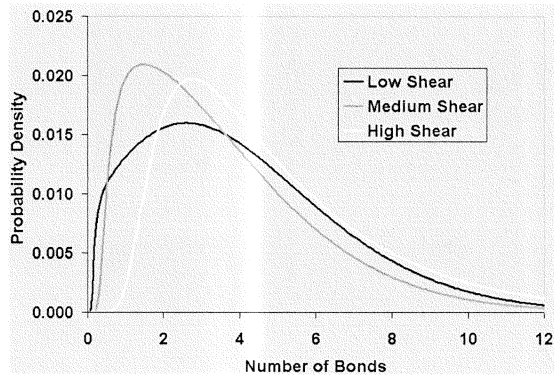


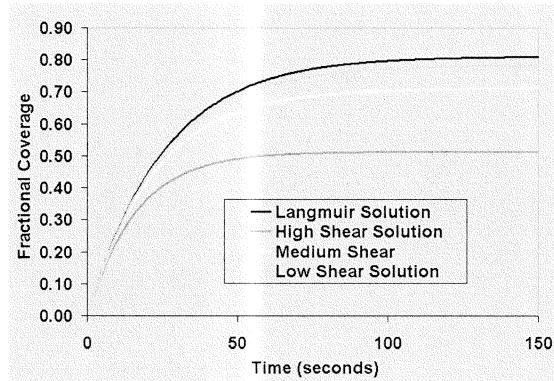
Figure 3: Graph shows the actual performance data taken from the paper of Oster and Wang [4] along with the prediction from the paper and the CFDR model prediction

3.2 Shear Influenced Binding

Consider the effect of a force (for e.g. fluid shear) on the binding of certain ligand/receptor pairs (with obvious implications for DNA hybridization). A Fokker-Planck Equation can be derived from the Master Equation model of Long [5]. Experiments have shown that when a force (hydrodynamic shear) is applied to a system where the ligand and receptor require multiple bonds to bind, the mean number of bonds decreases with increasing shear force. Figure 4(a) below shows the distribution of the number of bonds as a function of hydrodynamic shear. Increasing shear can lead to suppression of surface complexation (compared to standard continuum treatments) as seen in Figure 4(b)



(a)



(b)

Figure 4: Top graph (a) shows the probability distribution of the number of bonds varying with shear rate (nanoscale phenomena). The lower graph (b) shows the influence of hydrodynamic shear on the observed binding curves (macroscale phenomena).

The master equation describing the shear binding is given below in equation 6 taken from the work of Long, et al. [4]

$$\frac{dP_n}{dt} = A_c C_r C_l k_f P_{n-1} + (n+1)k_r^{n+1} P_{n+1} - [A_c C_r C_l k_f + nk_r^n] P_n \quad (6)$$

This can be transformed into a Fokker-Planck equation and the drift and diffusion coefficients are given in equation 7 below.

$$D_1(n, t) = A_c C_r C_l k_f - nk_r^0 \exp\left[\frac{aF(t)}{nkT}\right] \quad (7)$$

$$D_2(n, t) = A_c C_r C_l k_f + nk_r^0 \exp\left[\frac{aF(t)}{nkT}\right]$$

Where $A_c C_r C_l k_f$ is the forward binding rate, n represents the number of bonds, k_r^0 is reverse rate constant, a is a characteristic length in nanometers, $F(t)$ is the shear force in picoNewtons, and kT is the thermal energy. Three different shear conditions were analyzed and the results show that coupling the effects of shear into a system could

have an impact on the solution properties as a whole. As shown below in the comparison of three calculations using a low, medium, and high shear force on the surface. The figure shows that the higher the shear, the less coverage since more is being swept off of the surface. The limit of low shear is the regular Langmuir solution kinetics with an on rate and an off rate.

In this paper we have shown that molecular level effects can be coupled into continuum simulations using a Fokker-Planck Equation approach, which has been obtained from the Master Equation describing the system.

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