

Coupling between Nanoscale and Microscale Modeling for MicroFluidic Devices

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ABSTRACT

Evaluation of microfluidic device and sensor designs using continuum modeling is a valuable method, but becomes more complex if nanoscale or molecular level physics must 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 developing nanoscale simulation methods, and how nanoscale physics can be incorporated into continuum level simulations. The applications currently focus on microcantilevers and biomolecular motors. The main challenge in these applications is the coupling of information generated in nanoscale simulations to the continuum level

Keywords: Microfluidics, biomotor, mesoscale dynamics, microcantilever.

1 INTRODUCTION

The design of microfluidic devices becomes increasingly complicated as the dimensions of the device approach sizes where nanoscale or molecular level information must be considered. An optimal design of a microfluidic device requires a combined knowledge of statistical physics, continuum transport, engineering, molecular biology and biochemistry. Even at small length scales, continuum modeling is a powerful tool in the evaluation of device designs, however information from the nanoscale must be incorporated in the simulation in order to account for important nanoscale physics (for example, intermolecular forces play a critical role in biomolecular binding). We have undertaken a research effort to incorporate and understand nanoscale effects and how they impact continuum level simulations of microfluidics devices. The main focus of this line of research is to understand how the nanoscale physics can influence the design of microfluidic devices. The applications currently focus on microcantilevers and biomolecular motors. The main challenge in these applications lies in coupling the results generated in the nanoscale simulations to the continuum finite element code.

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. Mesoscale modeling 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].

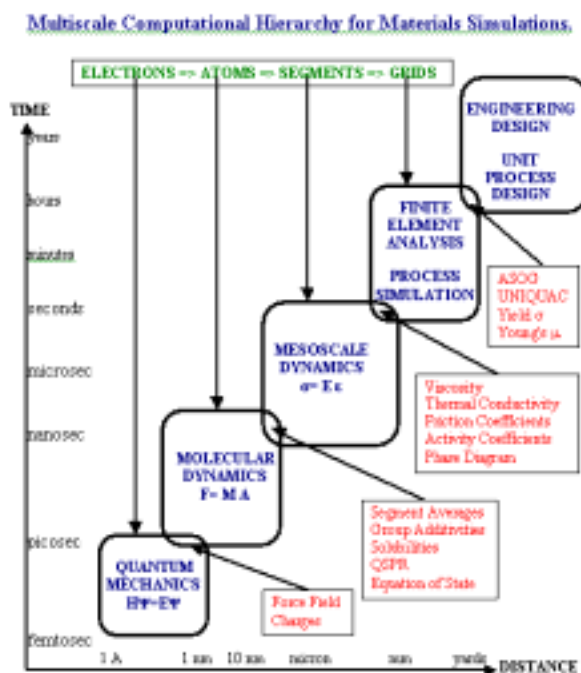


Figure 1: Commonly accepted view of length and time scales of modeling

Many methods are available to predict the behavior of large macromolecular structures, including regular Monte Carlo, Direct Simulation Monte Carlo, Molecular Dynamics, Langevin/Brownian Dynamics, Lattice Boltzmann, Cellular Automata, and Dissipative Particle Dynamics (DPD) [2]. All of the above methods were evaluated using the criteria of providing information at the microscale. The leading candidate is currently DPD because of the length and time scales this method is able to access.

DPD is a fairly young technique, appearing originally in 1993 [3] (by comparison molecular dynamics and Monte Carlo techniques have been around for more than 50 years), however there have been many theoretical studies

performed on DPD and it has been applied to many complex physical systems [4-6]. The main strengths of DPD are that the solvent is explicitly included and the length and time scales can be greatly increased over molecular dynamics. The time increase comes from the clustering of molecules into dissipative particles, thereby decreasing the number of degrees of freedom to be considered (Figure 2). The explicit inclusion of solvent allows for the application of a shear field to explore the local dynamics of a system in a shear field. Many simulations in the microsecond and micrometer range have been reported in the literature requiring only 10^5 integration steps and taking only 20 hours of CPU time [7]. Mesoscale simulations help to fill the gap between continuum and molecular simulations.

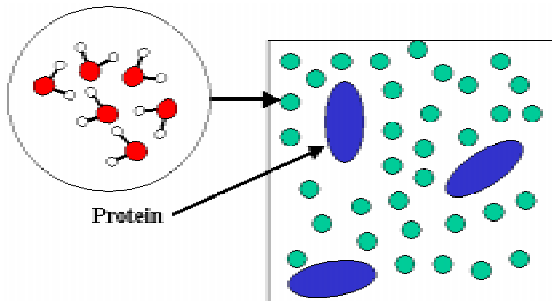


Figure 2: Dissipative Particle Dynamics clusters solvent molecules (6 water molecules shown) into coarse grained particles. Proteins are represented as larger particles.

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 little or 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.

Currently we are applying both sequential and coupled methods as an integrated coupling framework to solving problems with microfluidic devices. Figure 3 is a general representation of the methods of coupling. The lower loop in Figure 3 shows the sequential coupling whereby the nanoscale simulation is performed with some preset boundary conditions in order to extract information or a reduced model. The continuum scale variables are then extracted using time averaging and statistical techniques to produce a modified boundary condition for use in the continuum simulations. When the coupled coupling method is used there is a continuous feedback of

information from the continuum solver to the nanoscale in the form of a variable boundary condition.

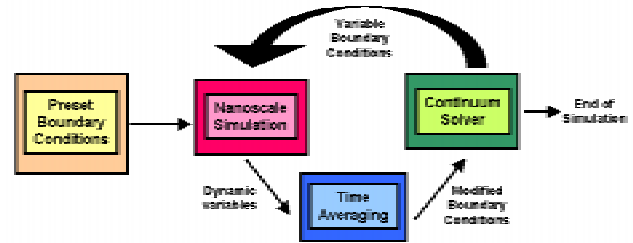


Figure 3: Illustration of coupling between continuum and nanoscale. The lower loop illustrates the sequential coupling. The upper feedback loop illustrates the coupled method of coupling.

3 PRELIMINARY APPLICATIONS

In this section we discuss two representative applications where the coupled nanoscale/continuum approach is implemented.

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 [8]. 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. Explicitly modeling the effect of a large number of F1-ATPase proteins on the binding of a probe molecule to a receptor is not feasible due to the computational requirements. The coupling between the nanoscale and continuum levels is critical in this example since the rate of rotation of the biomotor is related to the local nutrient concentrations. In the example simulation we have used a sequential approach and assumed a constant rate of rotation.

Simulations of biomotors have been performed using CFD-ACE+ to determine the influence a series of biomotors would have on the rate and total amount of protein bound to a surface. These simulations use a sequential coupling of nanoscale information to the continuum level illustrated in Figure 3. The velocity field produced by a series of biomotors was incorporated into the continuum simulation via a specialized boundary condition. The nanoscale information came from the literature [8], however in the future this information will come from nanoscale DPD simulations.

A simulation was performed using a standard microwell (3.3 mm diameter, 11.3 mm height) as the base geometry.

The microwell is assumed to be initially filled with IL-2 at a uniform concentration of 100 nM. The IL-2 in the microwell is assumed to bind with IL-2 receptor ($K_a=8E+6$ ($M s$)⁻¹ and $K_d=0.24 s$ ⁻¹) placed at the bottom of the well at a surface concentration of $5E-6$ moles/ m^2 . A series of 100 F_1 -ATPase micromotors are placed in the middle of the bottom of the microwell. The micromotors are assumed to rotate at 3Hz [8] with a radius of 5 microns. Figure 4 shows that the presence of a collection of biomotors at the bottom of a microwell enhances the local mixing and increases the total amount of IL-2 bound by 10%. Figure 5 shows the results of two simulations, with and without the biomotors as an agitation device. This figure illustrates how the action of the biomotors influences the local concentration gradients.

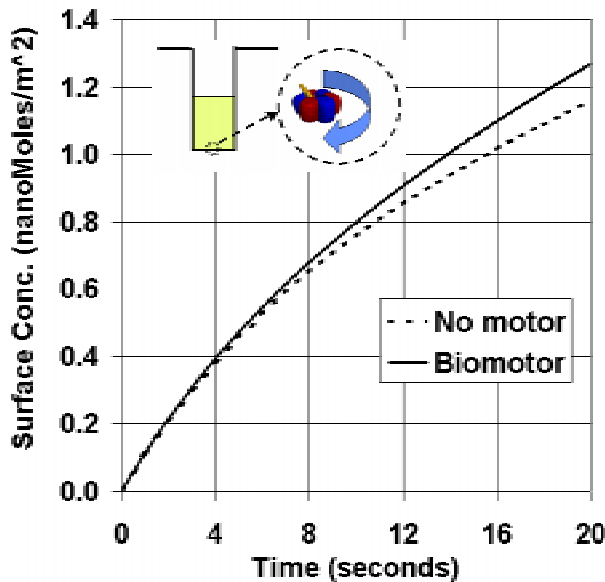


Figure 4: (left) Plot of the surface concentration of IL-2 as a function of time with and without the biomotor. The inset figure shows the location and action of the biomotor.



Figure 5: Bulk IL-2 concentration profiles at the end of the simulation. The upper figure is with the biomotors as an agitation device, the lower figure is without the biomotors.

3.2 Microcantilevers

The detection of specific signals from a microfluidic sensor is challenging, especially if there are several biomolecules to detect simultaneously. Quantitative detection of multiple biomolecules, such as DNA and proteins, in a high-throughput manner is becoming

increasingly important for diagnostics of complex diseases such as cancers as well as for drug discovery and fundamental scientific knowledge of signaling pathways. However, common methods for biomolecular analysis such as gel electrophoresis and mass spectrometry (MS) are slow, inefficient, and costly. Mechanical DNA and protein sensors that rely on changes in surface free energy induced by surface reactions are likely to have major impact in the future [9-11]. In particular, biological reactions on one surface of a microcantilever beam changes the surface stresses due to intermolecular energetic and entropic interactions. The surface stress generates sufficient torque to bend the cantilever beam (Figure 6).

Feedback between the nanoscale and continuum is critical in this case since the continuum level deflection of the microcantilever is determined by the nanoscale binding events and intermolecular forces. The individual binding events are resolved by the nanoscale solver, and this information is communicated to the continuum solver in the form of an adsorbed surface concentration and an induced cantilever deflection. The continuum solution will take this information and proceed to the next iteration or time step. The coupled simulations are currently being developed jointly with UC Berkeley.

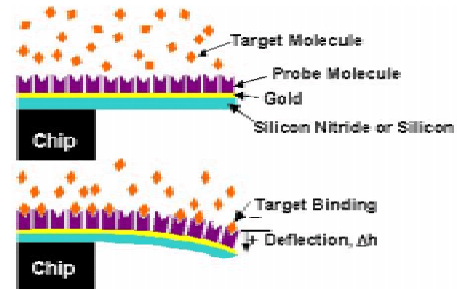


Figure 6: Specific biomolecular interactions between target and probe molecules produce surface stresses, causing the cantilever to deflect. (Figure courtesy of Arun Majumdar of UC Berkeley)

Simulations of DNA hybridization kinetics on microcantilevers have been performed using CFD-ACE+. The surface biochemistry module was used to simulate a cantilever system. The geometry of the flow cell used in these simulations is shown in Figure 8. The cantilever has a length of $600 \mu m$ and a height of $0.50 \mu m$. The buffer solution was assigned some representative fluid properties with a density of $1014 kg/m^3$ and a kinematic viscosity ($\nu=\mu/\rho$) of $7.6 \times 10^{-7} m^2/s$. Surface binding calculations were performed on a DNA hybridization system. Adsorption ($K_a = 2.2 \times 10^5 (M s)^{-1}$) and desorption ($K_d = 1.7 \times 10^{-5} 1/s$) constants were taken from binding data for 20 bp oligomers generated using BIACORE by David Myzyska of the University of Utah. The flow rate was set at $100 \mu L/min$ with a $300 nM$ inlet concentration of DNA. The surface receptor concentration was set at $7.2 \times 10^{-10} moles/m^2$ and the diffusion coefficient of DNA was taken to be $1E-10 m^2/s$. Binding was assumed to take place along

the entire length of the cantilever. After an initial period of 30 seconds the inlet concentration of DNA was turned off and pure buffer solution was flowed in as a wash step for 50 seconds for a total simulation time of 80 seconds. A time step of 1 second was used for these calculations. Figure 7(a) shows that there is more binding occurring on the cantilever shaft with less binding on the optical pad. This is desirable since the pad is only for the optical detection and should be as flat as possible for the best signal. Figure 7(b) shows a typical binding/debinding curve for the DNA system. The inlet flow of DNA is shut off after 30 seconds, and a buffer solution is flowed in for 50 seconds. The curve shows that the debinding stage is much slower than the binding.

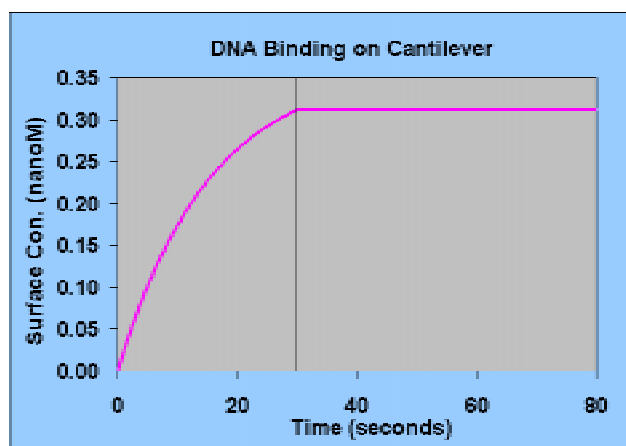
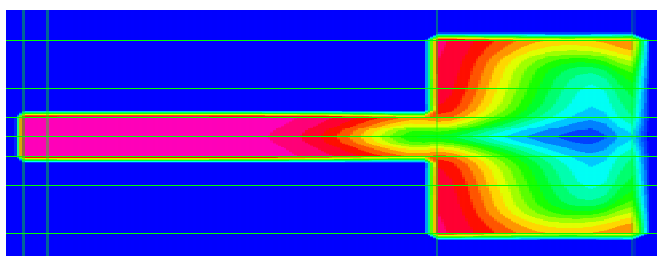


Figure 7: (a) Surface binding on the cantilever with the red areas being of higher concentration and blue being of low concentration. (b) Plot of the increase in average surface concentration with time.

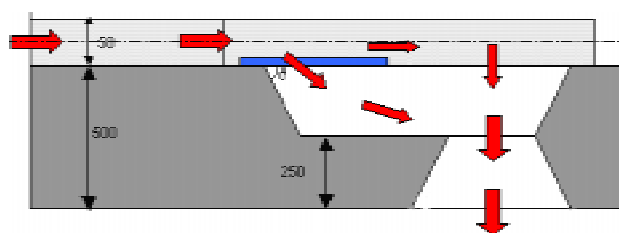


Figure 8: The red arrows indicate the direction of flow. The cantilever is shown in blue. The dimensions are given in micrometers. The angle shown is 57°.

4 SUMMARY

Coupling between the nanoscale and continuum level can be critical in accurate evaluation of microfluidic device design. We propose to use a coupled approach to link the nanoscale physics to the continuum scale, and have given two example cases where the use of the coupled approach is critical for an accurate simulation. The methods described in this paper could also be applied to the problem of ab initio prediction of protein binding kinetics and the formation of multiple protein layers.

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