A REVIEW OF MULTISCALE ANALYSIS: EXAMPLES FROM SYSTEMS BIOLOGY, MATERIALS ENGINEERING, AND OTHER FLUID–SURFACE INTERACTING SYSTEMS

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Abstract

Multiscale simulation is an emerging scientific field that spans many disciplines, including physics, chemistry, mathematics, statistics, chemical engineering, mechanical engineering, and materials science. This review paper first defines this new scientific field and outlines its objectives. An overview of deterministic, continuum models and discrete, particle models is then given. Among discrete, particle models, emphasis is placed on Monte Carlo stochastic simulation methods in well-mixed and spatially distributed systems. Next, a classification of multiscale methods is carried out based on separation of length and time scales and the computational and mathematical approach taken. Broadly speaking, hybrid simulation and coarse graining or mesoscopic modeling are identified as two general and complementary approaches of multiscale modeling. The former is further classified into onion- and multigrid-type simulation depending on length scales and the presence or not of gradients. Several approaches, such as the net event, the probability weighted, the Poisson and binomial τ-leap, and the hybrid, are discussed for acceleration of stochastic simulation. In order to demonstrate the unifying principles of multiscale simulation, examples from different areas are discussed, including systems biology, materials growth and other reacting systems, fluids, and statistical mechanics. While the classification is general and examples from other scales and tools are touched upon, in this review emphasis is placed on stochastic models, their coarse graining, and their integration with continuum deterministic models, i.e., on the coupling of mesoscopic and macroscopic scales. The concept of hierarchical multiscale modeling is discussed in some length. Finally, the importance of systems-level tools such as sensitivity analysis, parameter estimation, optimization, control, model reduction, and bifurcation in multiscale analysis is underscored.

I. Introduction

A decadal report recently issued by the National Research Council (NRC), entitled *Beyond the Molecular Frontier: Challenges for Chemistry and Chemical*

Engineering (NRC, 2003a), advances 13 "Grand Challenges" for the field. "Advancing Chemical Theory and Modeling" is viewed as one of the critical, enabling technologies. Quoting from the report: "Chemistry covers an enormous span of time and space from atoms and molecules to industrial-scale processing. Advances in computing and modeling could help us connect phenomena at the electronic and molecular scale to the commercial processing." In the information and communications NRC report and in recent roadmaps, multiscale analysis is repeatedly identified as the emerging computational and mathematical science that could enable design and control of complex engineering systems (Thompson, 1999; NRC, 2003b).

The foundations of transport phenomena, reaction engineering, thermodynamics, and nonlinear analysis, along with significant advances in numerical analysis of differential equations at the continuum level and the increase in computational power, have shaped for the most part the **first engineering process modeling paradigm** of chemical sciences of the 20th century (the BSL paradigm of continuum conservation equations and continuum constitutive relations (Bird *et al.*, 1960)). An outcome of this long-time effort has been the widespread use of computational fluid dynamics (CFD) simulation that nowadays routinely assists the design of many industrial processes.

The rapid growth in computational speed over the past decades has enabled a *molecular-based* approach to product and process engineering. Molecular simulations such as molecular dynamics (MD) and Monte Carlo (MC) algorithms have emerged as preeminent computational tools for science and engineering research. Additional discrete particle simulations, such as Brownian dynamics (BD), lattice Boltzmann (LB), direct simulation Monte Carlo (DSMC), and dissipative particle dynamics (DPD), have attempted to bridge information from the molecular to the mesoscopic scale, but often in a phenomenological manner, as the rules of coarse graining are not fully established. At the other end of the modeling spectrum, quantum mechanical (QM) calculations, such as *ab initio* and density functional theory (DFT), in conjunction with transition state theory (TST), have extended the realm of simulation to smaller scales by providing electronic structure information such as potential energy surfaces (PESs) and activation energies that are used in molecular simulations. The advances in molecular and quantum mechanics theory and simulation have established the **second modeling paradigm** (the molecular and quantum modeling paradigm).

Multiscale simulation is emerging and will unquestionably become the **third modeling paradigm**. The idea of multiscale modeling is straightforward: one computes information at a smaller (finer) scale and passes it to a model at a larger (coarser) scale (see Fig. 1) by leaving out degrees of freedom as one moves from finer to coarser scales. Within this context, the most common goal of multiscale modeling is to predict the macroscopic behavior of an engineering process from first principles (*upscaling or bottom-up approach*). This approach has its roots in the work of Newton, Hooke, Bernoulli, Einstein, Bodenstein,
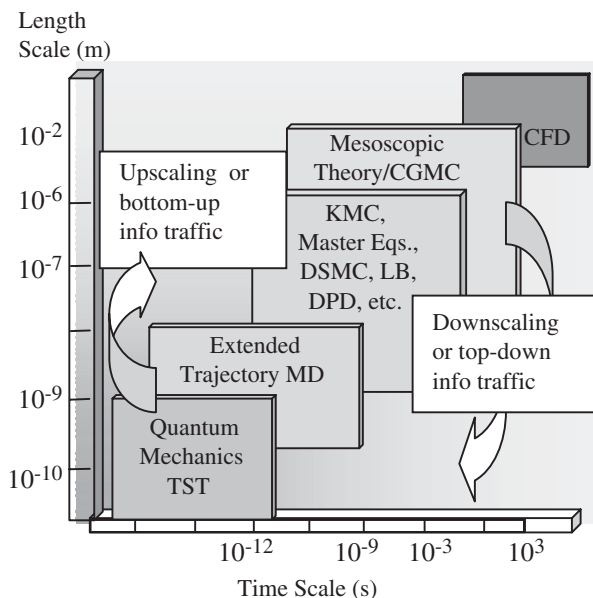
FIG. 1. Schematic representation depicting scales and various simulators. Most multiscale work has focused on the simplest, one-way information passing, usually from the finest to the coarsest scale model. On the other hand, most processes exhibit strong coupling between scales or lack separation of scales.

and others (Phillips, 2002; Raimondeau and Vlachos, 2002a) who left out many degrees of freedom to propose continuum-based constitutive equations and simple models for obtaining answers of interest. In recent times, this goal has been served well, for example, by equilibrium statistical mechanics with QM-based potentials and associated molecular (MD and MC) models. I envision an equally important second goal of multiscale analysis, stemming from the emerging areas of biotechnology, nanotechnology, and device miniaturization. This goal is the ability to predict and control phenomena and devices with resolution approaching nanoscopic scale while manipulating macroscopic (engineering) scale variables such as flow rates, pressures, and temperature (*downscaling or top-down approach*). This manipulation may not happen with active model-based control but instead by properly designing a system, using multiscale model-based information, to function desirably at the molecular level. This issue is further discussed in the section on systems tasks. *Reverse engineering* is yet a third potential goal of top-down information flow: given a desirable property, it is desirable to predict suitable candidate materials (e.g., multicomponent, multifunctional catalysts) and develop rational ways to synthesize them. This last goal addresses product-driven engineering that is believed by many to be the future of chemical sciences (Cussler and Wei, 2003). For the most part, the last two goals have so far remained elusive but are the ones on which

multiscale modeling and simulation would have the most impact in the next decade.

Advances in analytical methods, such as scanning probe and high-resolution transmission electron microscopy, now enable experiments with molecular-level resolution. Furthermore, data from small ensembles of molecules or single entities (e.g., a living cell) become more common. Effectively utilizing these and related emerging tools and data to develop new products and processes will be greatly facilitated by a complementary development in multiscale modeling that can not only model experimentally observed phenomena, but also aid in the *prediction* of new, as of yet, unproven products and processes.

Multiscale simulation is growing so rapidly that it emerges as a new multidisciplinary scientific field. Figure 2 summarizes the number of publications over the past decade using the term ''multiscale'' and ''multi-scale'' in their title only or in all title, abstract, and keywords. While the term multiscale means different things in various fields, the explosion is clear. Two new journals, Multiscale Modeling and Simulation, A SIAM Interdisciplinary Journal, and the International Journal on Multiscale Computational Engineering (Begell House Publishers, NY) started in 2003, point to the rapid evolution of this new field. There have been many activities that speak to the same fact. Examples include the recent issues 8 and 9 of the 59th volume of Chemical Engineering
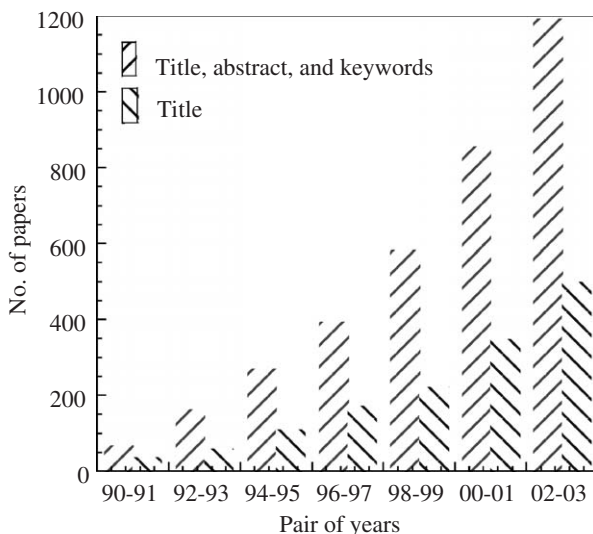
FIG. 2. Sum of the number of publications over periods of two years containing the word ''multiscale'' and ''multi-scale'' in the title only or in the title, abstract, and keywords (found through the Web of Science). An explosion in the number of publications is observed. However, this search is just a measure since many of these papers do not really adhere with the definition of multiscale modeling used here, and others, while truly multiscale, are not accounted for because ''multiscale'' or ''multi-scale'' is not present in their title, abstract, and keywords.

Science in 2004 that have been dedicated to Complex Systems and Multi-scale Methodology, the forth issue of the 29th volume in Computers in Chemical Engineering on Multiscale Simulation published in 2005, the Springer-Verlag IMA edited book on Dispersive Transport Equations and Multiscale Models resulting from a related workshop, numerous workshops, and a topical conference on Multiscale Analysis in the 2005 AIChE meeting, just to mention a few.

Multiscale simulation builds on the foundations developed in the 20th century of continuum, deterministic and discrete, particle-type models. It attempts to seamlessly integrate models at various scales, extend existing tools to larger length and time scales, and develop theoretical connections between tools over multiple scales. It seems then appropriate to first provide a classification and an overview of models at various scales before multiscale simulation is more formally introduced and recent progress is reviewed. Since we have recently given a review on multiscale simulation in catalysis and reaction engineering (Raimondeau and Vlachos, 2002a), here a broader overview of multiscale simulation is given. The multidisciplinary nature of this emerging field makes this a daunting task. For this reason, I have chosen to mainly focus on the areas of systems biology and materials growth because these two fields are enticing an increasing number of chemical engineers. Furthermore, by choosing two areas one can clearly see unifying multiscale concepts that emerge across chemical engineering. Some rather introductory examples from statistical mechanics and reaction systems are also employed to illustrate key points and methods. Finally, I have tried to include references to some key mathematical pieces of work and multiscale references from the physics, materials, and hydrodynamics communities I am aware of with the hope of cross-fertilizing various disciplines without necessarily being exhaustive in coverage (these areas deserve their own review). For example, a recent, very good review from the mathematics community has just appeared after the submission of this manuscript that presents some of the mathematical underpinnings of the algorithms and methods touched upon below (Givon *et al.*, 2004). While the discussed multiscale approach and issues are generic and apply to various models and scales, I have judiciously chosen to mainly focus on the MC method, among other atomistic or mesoscopic models, and the integration of MC with deterministic, continuum models as an example of stochastic/continuum hybrid multiscale models. This naturally provides more coherence to the chapter. Some key references from other types of multiscale models are also given.

II. Deterministic, Continuum Models

Traditionally, modeling in chemical engineering has invoked continuum descriptions of momentum, mass, and energy conservation (Bird *et al.*, 1960)

where substantial mathematical and computational contributions have been made over the past decades. Here, the discussion is limited to a brief classification that introduces the necessary terminology used in the remainder of the chapter.

A. HIERARCHY OF MODELS

Continuum modeling has often been based on algebraic equations (AEs), ordinary differential equations (ODEs), partial differential equations (PDEs), and differential-algebraic equations (DAEs). PDEs provide the most general description at the continuum level. ODEs typically describe transient, well-mixed systems, such as the concentrations and temperature in a batch reactor or in a continuous stirred tank reactor (CSTR), or 1D steady state balances, such as a plug flow reactor (PFR) model or an axial dispersion model. A distinction of ODEs entails initial vs. boundary value problems depending on where the conditions are imposed, namely, only at the entrance or at the entrance and exit, respectively. The hierarchy of deterministic, continuum models is summarized in Fig. 3a. Using concepts of dimensional analysis and symmetry, models toward the bottom of the graph can be thought of as reductions or limits of higher dimensionality models (found toward the top of the graph).
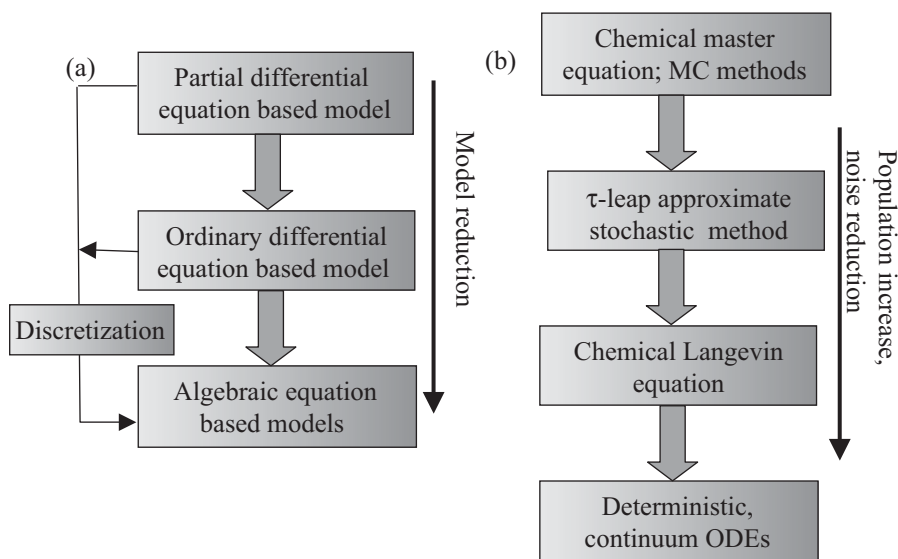

FIG. 3. (a) Hierarchy of deterministic, continuum models. Dimensional analysis and symmetry are powerful concepts in reducing the dimensionality of complex models. (b) Hierarchy of stochastic models for chemically reacting well-mixed systems.

B. Solving Deterministic, Continuum Differential Equation Models:
   Techniques and Status

Substantial advances in computational power (Moore's law) have had a tremendous impact on the numerical solution of engineering problems. Concomitant with increases in computational power, significant advances in problem solving have resulted through mathematical and/or computational developments. One example is the introduction of stiff ODE solvers by Gear (1969, 1971) that led to the development of adaptive time step, variable-order methods that nowadays are available through the web. LSODA, VODE, and RADAU5 are some commonly employed packages for solving stiff ODEs and DDASSL for DAEs (Brenan *et al.*, 1996; Hairer and Wanner, 1991; Petzold, 1982). As another example, over the last 30 years the solution of systems of linear equations has evolved from sparse Gauss elimination, to Gauss–Seidel, to successive over-relaxation, to conjugate gradient, to multigrid, to parallel multigrid. It was recently reported by Petzold in NRC (2003b) that such algorithm and software development has led to four orders of magnitude speedup.

Methods for solving continuum models have advanced to such a point that they are nowadays considered to be relatively mature. Since several packages are available based on one of these methods, it becomes a matter of choosing an appropriate package. Typical CFD and transport packages include Fluent, FI-DAP, CFX, and Femlab (Femlab is a general purpose finite element (FEM)-based program with specialized modules for chemical engineering applications). Simple 1D problems can be solved with widely used teaching software, such as Matlab and Mathematica. While in the 1980s considerable effort was devoted to the discretization of PDEs and meshing of a complex domain, this is now a relatively routine exercise that uses Gambit and the internal mesh generator of Femlab even for complex geometries. CFD, depicted at the top of the pyramid in Fig. 1, can be used as process simulator in a multiscale simulation of chemical engineering. Memory limitations, especially for 3D simulations, robustness in convergence, speed for complex chemistry in reacting flows, and accuracy are still issues that need further improvements. Finally, interfacing CFD codes with complex homemade chemistry codes or finer scale codes from the multiscale ladder shown in Fig. 1 is also important.

III. Overview of Discrete, Particle Models

Discrete models treat individual atoms, molecules, or particles and can be deterministic or stochastic. Examples of the former include MD simulations. Examples of the latter are various MC methods, BD, DPD, DSMC, and LB simulations. There are different ensembles in which these simulations can be performed, depending on the quantities that one is interested in computing.

Different techniques are suitable for different tasks. For example, BD focuses on molecules and particles in solution where the solvent is implicitly lumped into a friction force. On the other hand, DSMC and LB are typically applied to various fluid-related problems. MD is the only fundamental, first principles tool where the equations of motion are solved using as input an interparticle potential. MC methods map the system description into a stochastic Markov-based framework. MD and MC are often thought of as molecular modeling tools, whereas the rest are mesoscopic tools (lattice MC is also a mesoscopic tool).

Many excellent sources on discrete, particle simulations exist (e.g., Allen and Tildesley, 1989; Binder, 1986; Bird, 1988; Chen and Doolen, 1998; Frenkel and Smit, 1996; Landau and Binder, 2000; Rastogi and Wagner, 1995; Wolf-Gladrow, 2000). Volume 28 of Advances in Chemical Engineering, entitled "Molecular Modeling and Theory in Chemical Engineering," presents an excellent collection of molecular-based papers with applications across chemical engineering. A recent overview of the tasks that can be accomplished via molecular modeling, with special emphasis on MC methods, for irreversible chemical processes is given in Vlachos (2005).

Obviously, the spectrum of mesoscale, particle-based tools is too vast to be covered in a single paper. Therefore, in this and the subsequent sections, I mainly elaborate on MC methods to illustrate various aspects of multiscale modeling and simulation. Below, the modeling hierarchy for stochastic well-mixed chemically reacting systems is first outlined, followed by a brief introduction to MC methods.

A. Hierarchy of Stochastic Models for Well-mixed, Chemically Reacting Systems

A hierarchy of models can often be derived from a more detailed model under certain assumptions. This approach was discussed above in the case of deterministic, continuum models (see Fig. 3a). Such hierarchical models can be valuable in multiscale modeling. Let us just mention two cases. First, one could use different models from a hierarchy of models for different situations or length scales. This approach plays a key role in hybrid multiscale simulation discussed extensively below. Second, one could easily apply systems tasks to a simpler model to obtain an approximate solution that is then refined by employing a more sophisticated, accurate, and expensive model from the hierarchy.

A major difficulty is that such hierarchies of molecular models are not exactly known. Recent work by Gillespie (2000, 2002) has established such a hierarchy for stochastic models of chemical reactions in a well-mixed batch reactor. This hierarchy is depicted in Fig. 3b. In particular, it was shown that the chemical master equation is deduced to a chemical Langevin equation when the population sizes are relatively large. Finally, the deterministic behavior can be

recovered in the limit of an infinite-size system ($N \to \infty$). The concept of hierarchical modeling is revisited in the section on systems tasks.

B. Solving Master Equations Stochastically: Monte Carlo Methods

The introduction of the Metropolis MC algorithm in 1953 (Metropolis *et al.*, 1953) has established a new paradigm in computational statistical mechanics for computing *equilibrium solutions*. Starting from a description of the physical system in terms of a Hamiltonian, MC solves stochastically an underlying master equation using pseudo-random numbers by constructing the probability with which the various states of the system have to be weighted according to a Markov process. The introduction of *simulated annealing* (Kirkpatrick *et al.*, 1983) has substantially expanded the scope of the Metropolis MC method to problems far beyond equilibrium solutions of statistical mechanics. Specifically, MC has been established as a powerful tool in global optimization in process engineering, combinatorial materials library development, and *reverse engineering* of solid state structure determination (Deem, 2001; Vlachos, 2005). However, reverse engineering problems related to structure determination of bulk liquids, solids, nanoparticles, and interfaces, using forward (based on a potential) and reverse (based on experimental data) modes, are outside the scope of this paper.

MC is also successful in far from equilibrium processes encountered in the areas of diffusion and reaction. It is precisely this class of non-equilibrium reaction/diffusion problems that is of interest here. Chemical engineering applications of MC include crystal growth (this is probably one of the first areas where physicists applied MC), catalysis, reaction networks, biology, etc. MC simulations provide the stochastic solution to a time-dependent master equation

$$\frac{\mathrm{d}p_\alpha}{\mathrm{d}t} = \sum_\beta \left[W_{\alpha\beta} p_\beta - W_{\beta\alpha} p_\alpha \right] \tag{1}$$

where $p_{\alpha(\beta)}$ is the probability that the system is in configuration $\alpha(\beta)$ and $W_{\alpha\beta}$ is the transition probability per unit time of the system going from configuration β to α. The master equation is deterministic.

Direct solution of the master equation is impractical because of the huge number of equations needed to describe all possible states (combinations) even of relatively small-size systems. As one example, for a three-step linear pathway among 100 molecules, 10^4 such equations are needed. As another example, in biological simulation for the tumor suppressor p53, 2^{11} states are estimated for the monomer and 2^{44} for the tetramer (Rao *et al.*, 2002). Instead of following all individual states, the MC method is used to follow the evolution of the system. For chemically reacting systems in a well-mixed environment, the foundations of stochastic simulation were laid down by Gillespie (1976, 1977). More

recently, Gillespie's (1992) algorithm was connected with collision theory. His approach is easily extendable to arbitrary complex computational systems when individual events have a prescribed transition probability per unit time. This is often referred to as the *kinetic Monte Carlo (KMC) or dynamic Monte Carlo (DMC)* method, and is the tool used herein. In contrast to the classic Metropolis MC algorithm, KMC provides real-time information.

There are two different exact algorithms for stochastic simulation proposed by Gillespie, namely, the direct simulation method and the first reaction simulation method. The former is computationally much more efficient and has been the method of choice (it requires two random numbers per MC event as compared to N_r random numbers for the latter, where N_r is the number of reactions). The work of Gibson and Bruck (2000) aims at reducing the computational cost of KMC for complex reaction networks by modifying the first reaction simulation method of Gillespie. Their approach uses dependency graphs to minimize the computation time spent on updating the transition probabilities per unit time (propensities in the terminology of Gillespie). This idea resembles the lists of neighbors approach used in spatial distributed molecular models (Allen and Tildesley, 1989; Frenkel and Smit, 1996) and graph theory used in building complex reaction networks (Broadbelt *et al.*, 1994). Furthermore, Gibson and Bruck kept the time increments of unaffected reactions, determining when reactions occur, fixed to their current values. As a result, the number of random numbers needed per MC event is reduced to just one.

The extension of Gillespie's algorithm to spatially distributed systems is straightforward. A lattice is often used to represent binding sites of adsorbates, which correspond to local minima of the PES. The work of Bortz *et al.* (1975) on the *n-fold or continuous time MC (CTMC)* method is a significant achievement in computational speedup of the lattice KMC method, which, however, has been underutilized probably owing to its difficult implementation. In CTMC, probabilities are computed *a priori* and each event is successful, in contrast to null-event algorithms (e.g., Metropolis) whose fraction of unsuccessful (null) events increases considerably at low temperatures and for stiff problems (Reese *et al.*, 2001; Vlachos *et al.*, 1993). While simulations carried out early on reported results in MC events or steps and lacked a connection with real time, calculation of real time by a continuous amount is straightforward, as demonstrated several years ago (e.g., Fichthorn and Weinberg, 1991; Vlachos *et al.*, 1990, 1991). Real time can be implemented in both null event and CTMC methods, and practically the same results are obtained regardless of the algorithm used (Reese *et al.*, 2001). Generalization of the KMC method to treat arbitrarily complex surface kinetics and comparison of null event KMC and CTMC have been presented in Reese *et al.* (2001).

The microscopic processes occurring in a system, along with their corresponding transition probabilities per unit time, are an input to a KMC simulation. This information can be obtained via the multiscale ladder using DFT,

TST, and/or MD simulations (the choice depends mainly on whether the process is activated or not). The creation of a database, a lookup table, or a map of transition probabilities for use in KMC simulation emerges as a powerful modeling approach in computational materials science and reaction arenas (Maroudas, 2001; Raimondeau et al., 2001). This idea parallels tabulation efforts in computationally intensive chemical kinetics simulations (Pope, 1997). In turn, the KMC technique computes system averages, which are usually of interest, as well as the probability density function (pdf) or higher moments, and spatiotemporal information in a spatially distributed simulation.

IV. Classification of Multiscale Simulation Approaches

Multiscale simulation enables coupling of phenomena at various scales from the quantum scale to the molecular, mesoscopic, device, and plant scale (Alkire and Verhoff, 1998; Christofides, 2001; Lerou and Ng, 1996; Maroudas, 2000; Raimondeau and Vlachos, 2002a; Villermaux, 1996; Weinan et al., 2003). For most applications, multiscale modeling has been practiced *sequentially*. The smaller (finer) scale model is typically solved first, and information is passed to the larger (coarser) scale (upscaling), i.e., from the bottom-up. This is a one-way information traffic paradigm (see also Fig. 1), also termed *serial* (Maroudas, 2003), and has been practiced successfully in several applications. One such example includes the development of first principles chemistry via *ab initio* methods, statistical mechanics, and kinetic theory. These finer length scale models parameterize effectively the reaction rate constants that are subsequently employed in reacting process flow simulations. Laminar flames and chemical vapor deposition (CVD) are two reaction-engineering applications where this sequential approach has successfully been used. For gas-phase reacting flows at low to moderate pressures, the density is so low that the probability of trimolecular events is negligible. As a result, the PES of two chemical species describes accurately the reaction coordinate, i.e., the coupling between scales is practically non-existent. Therefore, one-way coupling is adequate. Another example of one-way coupling for crystal growth of GaAs and InP was presented in Rondanini et al. (2004), where FEM-computed fluxes were passed to a 3D KMC code.

In most liquid- and solid-phase systems, the dilute approximation is typically invalid, and, as a result, many body effects play a significant role. Many body effects are manifested through the effect of solvent or catalyst on reactivity and through concentration-dependent reaction rate parameters. Under these conditions, the one-way coupling is inadequate, and fully coupled models across scales are needed, i.e., two-way information traffic exists. This type of modeling is the most common in chemical sciences and will be of primary interest hereafter. In recent papers the terms *multiscale integration hybrid, parallel, dynamic,*

and concurrent simulation have been employed, depending on the algorithm used (Abraham *et al.*, 1998b; Maroudas, 2003; Rudd and Broughton, 2000; Vlachos, 1997).

Figure 4 depicts the most common multiscale simulation approaches. When there is a large separation of length scales between phenomena, then a different model can be used at each scale. This type of multiscale simulation is termed as *hybrid*. At the core QM simulations, farther out molecular models (e.g., MD, KMC), and even farther out continuum mechanics form an *onion* structure or *nested hierarchy of models* (Fig. 5). At the other extreme, in processes whose phenomena do not exhibit separation of scales, one has two options (see Fig. 4). The first one is to extend a suitable tool, such as a MD or KMC method, to large length and time scales to enable comparison with experiments. This is termed *mesoscopic modeling or coarse graining*. The second one is to apply a coarser model over large length and time scales of experimental interest on a coarse grid and estimate small-scale information for the coarser model from a finer scale model on a fine grid (Fig. 6). This last method is hereafter termed *multigrid-type hybrid multiscale simulation*, but the terms heterogeneous hybrid simulation (Weinan *et al.*, 2003) and tooth gap have also been used (Gear *et al.*, 2003) to denote similar ideas.
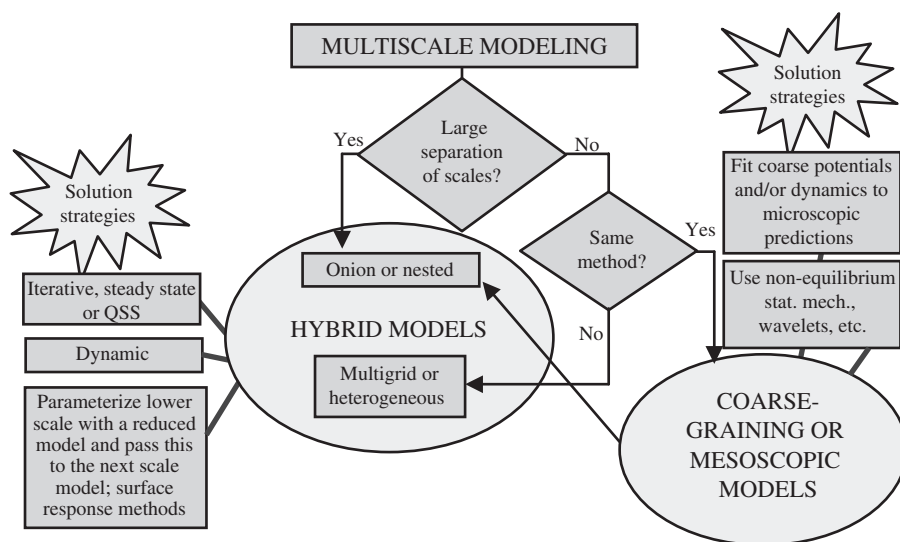
Fig. 4. Types of multiscale modeling and solution strategies. Hybrid models (one model at each scale) apply well when there is separation of scales (onion or nested-type models). When there is lack of separation of scales, mesoscale models need to be developed where the same technique (e.g., MD or MC) is accelerated. Alternatively, multigrid (heterogeneous) hybrid models can be employed where the unresolved degrees of freedom are determined from a finer scale model and passed to a coarser scale model.

Fɪɢ. 5. Schematic of onion-type hybrid multiscale simulation. At each scale a different model is used. Consecutive scale models are simultaneously solved in the overlap region where exchange of information occurs.
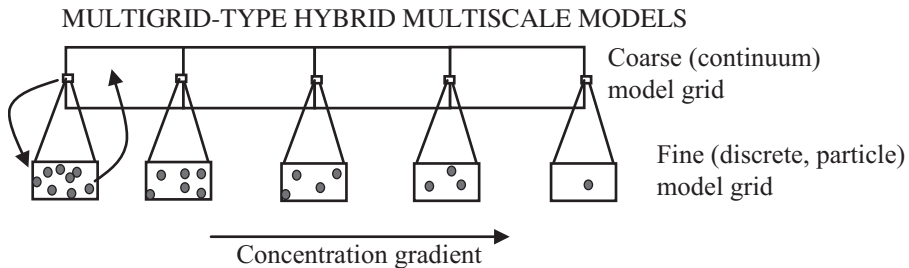
Fɪɢ. 6. Schematic of multigrid-type hybrid simulation with two grids. At the coarse grid a macroscopic model is advanced over large length and time scales. Information is passed to the macroscopic grid/coarse model from a macroscopic simulation executed on a fine grid over short leng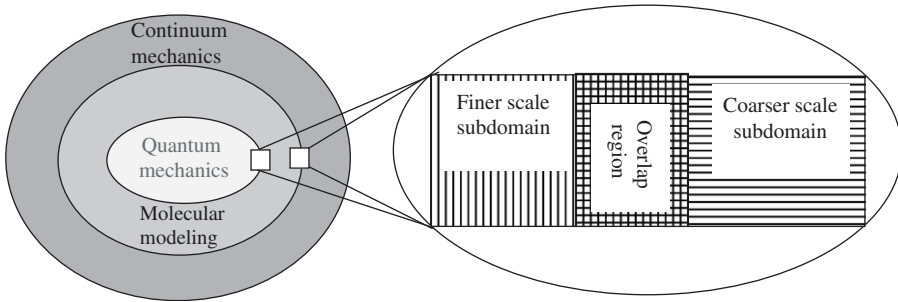th and time scales. The coarse model is advanced over macroscopic length and time scales and provides to the microscopic simulation a field for constraint fine scale simulation.

Below, the various types of multiscale simulation are elaborated and various examples are provided. The presentation on coarse graining is mainly focused on stochastic (KMC) simulations to provide the underlying foundations and ideas in some depth. Coarse graining of other atomistic, e.g., MD, and mesoscopic tools will be covered in a forthcoming communication. Some excellent reviews on coarse graining in soft-matter physics problems are available (e.g., Kremer and Muller-Plathe, 2001; Muller-Plathe, 2002, 2003; Nielsen *et al.*, 2004).

V. Hybrid Multiscale Simulation

Hybrid multiscale simulation is the most developed branch of multiscale simulation and will be covered in this section. The onion-type hybrid simulation

is first covered, followed by a discussion of its application to crystal growth and then to other areas. The multigrid-type hybrid method is also discussed. Finally, some of the challenges in hybrid multiscale simulation are elaborated.

A. Onion-type Hybrid Multiscale Simulations and Algorithms

Consider an example from nucleation and growth of thin films. At least three length scales can be identified, namely, (a) the fluid phase where the continuum approximation is often valid (that may not be the case in micro- and nano-devices), (b) the intermediate scale of the fluid/film interface where a discrete, particle model may be needed, and (c) the atomistic/QM scale of relevance to surface processes. Surface processes may include adsorption, desorption, surface reaction, and surface diffusion. Aside from the disparity of *length* scales, the *time* scales of various processes differ dramatically, ranging from picosecond chemistry to seconds or hours for slow growth processes (Raimondeau and Vlachos, 2002a, b).

The vastly varying time scales and similar variations in length scales prevent simply ''brute force'' molecular simulation of the entire process. No amount of foreseeable advances in computational power will ever enable such a modeling approach. For these processes, application of different models and tools at different scales is essential, resulting in **onion-type hybrid multiscale models** (see Fig. 5). For example, a hybrid model for crystal growth may consist of a CFD model far away from the growing interface, an appropriate molecular or mesoscopic model (e.g., MD, DSMC, or BD) in the boundary layer, and MC or MD, with potentials parameterized using DFT, to simulate microscopic processes on the surface of a growing nanoparticle. Another example of hybrid simulation entails, the ONIOM method of the software Gaussian (Frisch *et al.*, 2002). In particular, one treats quantum mechanically the core where chemical reactivity and high activity is crucial, uses molecular mechanics farther out, and continuum approximation (e.g., via the dielectric constant) for the solvent even farther out.

The overall idea of hybrid simulation lies in the domain being decomposed into subdomains and the application of a different model in each subdomain (see Fig. 5). This approach is called *domain decomposition*. In order to improve the coupling between codes, an *overlapping subdomain or interfacial or handshaking region* is created within which both models are solved and exchange information. The size of the interface can be adjusted to ensure proper coupling between codes (in physics terminology it can be diffuse or sharp, i.e., of zero thickness). In general, the interface width has to be small enough to minimize the cost of the finer scale model but sufficiently large to allow proper relaxation of the macroscopic information in the atomistic domain.

Three algorithms, depicted in Fig. 4, have been proposed to solve onion-type hybrid multiscale models (Vlachos, 1997). The first applies to steady-state

problems. The solution can be obtained iteratively by passing the steady-state information back and forth (in each iteration) between the two models until convergence of the hybrid scheme is achieved (*iterative scheme*). Given the inherent noise of discrete particle simulations, suitable criteria are needed to ensure steady-state convergence of a stochastic model (Vlachos, 1997). Furthermore, owing to nonlinear phenomena, there is no guarantee of convergence (a common observation for realistic systems) (Raimondeau and Vlachos, 2002b).

The second algorithm entails developing an approximate surface (a reduced model) of the finer length scale model as a function of parameters of the coarser scale model. For example, one could compute the isotherm in the case of fluid-surface equilibrium or the reaction rates in the case of a catalytic reaction as a function of surface temperature and partial pressures of the fluid phase. In essence, what one does is to map or parameterize the boundary conditions of the coarser scale model using the finer scale model. This mapping typically entails some ensemble/spatial averaging technique that reduces the degrees of freedom of the finer scale model to provide coarse information needed in the next model up of the multiscale ladder. In mathematical terminology, this step can be thought of as a *restriction or contraction operator* that operates onto the microscopic model to provide coarse information. This reduced model is subsequently coupled with or fed into the coarser scale model. This algorithm is suitable when steady-state or quasi-steady-state (QSS) solutions are desired. In the latter case it is tacitly assumed that the finer scale model relaxes fast enough for QSS to be established. The idea of developing a reduced model (in this case a boundary condition) using the finer scale model works well as long as the mapping is accurate. Accuracy, however, is a non-trivial issue to satisfy (see Ludwig and Vlachos (2004) for an example illustrating the difficulties in DFT/MD coupling).

Obviously, the above algorithms are not suitable when transients of the finer scale model are involved (Raimondeau and Vlachos, 2000), as, for example, during startup, shut down, or at a short time after perturbations in macroscopic variables have occurred. The third coupling algorithm attempts fully *dynamic, simultaneous solution* of the two models where one passes information back and forth at each time step. This method is computationally more intensive, since it involves continuous calls of the microscopic code but eliminates the need for *a priori* development of accurate surfaces. As a result, it does not suffer from the problem of accuracy as this is taken care of on-the-fly. In dynamic simulation, one could take advantage of the fast relaxation of a finer (microscopic) model. What the separation of time scales between finer and coarser scale models implies is that in each (macroscopic) time step of the coarse model, one could solve the fine scale model for short (microscopic) time intervals only and pass the information into the coarse model. These ideas have been discussed for model systems in Gear and Kevrekidis (2003), Vanden-Eijnden (2003), and Weinan *et al.* (2003) but have not been implemented yet in realistic MC simulations. The term *projective method* was introduced for a specific implementation of this approach (Gear and Kevrekidis, 2003).

B. Application of Onion-type Hybrid Multiscale Simulation to Growth of Materials

In the area of nanomaterials and thin films, product "quality" is judged from the sharpness of interfaces, crystallinity, defects, polymorphism, shape, uniformity in particle-size distribution, film texture, etc. Engineering product quality demands linking of phenomena at very different scales and has attracted considerable interest over the last few years (Alkire and Verhoff, 1998; Christofides, 2001; Raimondeau and Vlachos, 2002a). A recent review of multiscale simulation of CVD processes for various materials is given in Dollet (2004).

Several hybrid simulations on crystal growth can be found in recent literature. Examples include dendritic solidification by coupling finite-different discretization of a phase field model to a MC simulation (Plapp and Karma, 2000), coupling a finite difference for the melt with a cellular automata for the solidification (Grujicic et al., 2001), a DSMC model for the fluid phase with a Metropolis-based MC for the surface to address cluster deposition onto substrates (Hongo et al., 2002; Mizuseki et al., 2002), a step model for the surface processes coupled with a CFD simulation of flow (Kwon and Derby, 2001) (two continuum but different feature scale models), an adaptive FEM CVD model coupled with a feature scale model (Merchant et al., 2000), and one-way coupled growth models in plasma systems (Hoekstra et al., 1997). Some specific applications are discussed in more detail below.

1. Polycrystalline Films

Fabrication of polycrystalline films is an inherently multiscale problem of substantial technological importance; as a result, several studies have been conducted recently. For the most part, these have been serial (one-way coupling or even fully disconnected) simulations. Gilmer and co-workers presented decoupled, different scale growth models of sputtering. Specifically, the level-set method was used at the largest scale for film evolution, the level-set method coupled with a diffusion model for dissolution of TiN clusters on a surface, and, finally, a dual lattice KMC model for Al particle growth (see Baumann et al. (2001) and references therein). In a similar spirit, front-tracking techniques were employed by our group to delineate the factors controlling zeolitic film texture fabricated from pre-grown seeds (Bonilla et al., 2001) followed by fundamental transport/colloids or KMC-based models to elucidate single nanoparticle growth mechanisms (Nikolakis et al., 1999, 2000, 2003). The work of Srolovitz et al. on diamond film growth under CVD conditions is yet another example where film texture is important and where decoupled, different type simulations were exploited; see overview in Srolovitz et al. (1997). While these models were applied to different materials and scales (completely decoupled), the insights gained at different scales have been instrumental for materials design in

different applications. It is expected that future work will aim at linking these models and phenomena over multiple scales.

2. *Physical and Chemical Fluid Deposition of Thin Films (Fluid–Surface Coupling)*

In microelectronics fabrication, small-scale features (e.g., trenches) need to be conformally covered, i.e., a spatial uniform deposit is desired. In such small features, the continuum approximation typically breaks down when the mean free path becomes comparable to the feature size, whereas the continuum approximation is often fine in the main body of the reactor. This separation of geometric length scales demands a multiscale approach beyond just mesh adaptation. In CVD, a ballistic growth model was used by Rodgers and Jensen (1998) to compute an effective sticking coefficient of incoming molecules as a function of surface topology in the case of non-continuum transport of molecules in small-scale features (large Knudsen number). This information was passed to the boundary condition of an FEM code of a CVD reactor. Given the disparity of time scales, QSS could be assumed at the reactor scale and iterations could be used where information is passed between the two models to evolve the growing interface of a trench (a moving boundary problem). This coupling algorithm is an example of parameterization of boundary conditions method (surface response approach; see solution strategies at the left of Fig. 4). In order to account for the sticking probability of molecules, semi-empirical potential-based MD have been carried out as a function of incident angle and energy, and this information was incorporated (by suitable integration over necessary degrees of freedom) in a line-of-sight transport model to compute local growth velocities (Hansen *et al.*, 2000). This lower scale model information was then incorporated into a level-set calculation that is ideal for moving boundary problems arising in crystal growth or etching.

Next, coupled hybrid stochastic-continuum models are discussed. The stochastic KMC model is employed to describe surface processes of epitaxy and account for spatial correlation effects, nucleation, and microstructure evolution. The continuum model, on the other hand, describes the fluid mechanics and transport phenomena at the reactor scale. One of the first such hybrid multiscale growth simulations coupled a fluid-phase PDE model with a pseudo-3D KMC model to study the transition between growth modes in epitaxial growth of films (Lam and Vlachos, 2001; Vlachos, 1999). These simulations were performed in stagnation flow geometry, where a similarity transformation reduces the 3D fluid-phase problem into a 1D problem, with isoconcentrations being parallel to the surface (this is an important point, discussed further below in the multigrid methods, because it requires a single KMC-simulation box). Pseudo-3D KMC simulations are based on the solid-on-solid (SOS) approximation and are actually 2D simulations. In particular, each point represents the film height, so the 3D surface can be described by a 2D array of heights; within the SOS
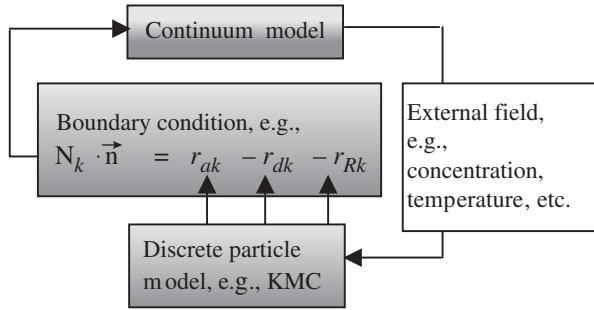
FIG. 7. Schematic illustrating the coupling of a fluid-phase mass transfer model with a discrete, particle model, such as KMC, through the boundary condition. The continuum model passes the external field and the KMC simulation computes spatial and temporal rates that are needed in the boundary condition of the continuum model.

approximation, no vacancies and overhangs can form in a film. While the SOS assumption is not fully realistic, it is commonly employed in KMC simulations of crystal growth.

In these hybrid simulations, coupling happened through the boundary condition. In particular, the fluid phase provided the concentration to the KMC method to update the adsorption transition probability, and the KMC model computed spatially averaged adsorption and desorption rates, which were supplied to the boundary condition of the continuum model, as depicted in Fig. 7. The models were solved fully coupled. Note that since surface processes relax much faster than gas-phase ones, the QSS assumption is typically fulfilled for the microscopic processes: one could solve for the surface evolution using the KMC method alone, i.e., in an uncoupled manner, for a combination of fluid-phase continuum model parameter values to develop a reduced model (see solution strategies on the left of Fig. 4). Note again that the QSS approach does not hold at very short (induction) times where the microscopic model evolves considerably.

These multiscale simulations linked, for the first time, macroscopic variables, such as flow rate, substrate temperature, and composition, with microscopic features, e.g., surface roughness of a growing film. As an example of such a link, Fig. 8a depicts a kinetic phase diagram in the growth rate-inverse temperature plane from simulations where various conditions were varied (Lam and Vlachos, 2001). At relatively high temperatures and slow growth, the atoms have sufficient time to reach steps, and step flow is the observed growth mode. On the other hand, at relatively low temperatures and fast flow, the atoms do not have sufficient time to reach steps, and small nuclei form between steps, contributing to roughening. Typical snapshots of film morphologies from the two modes are also shown in Figs. 8c and d. The solid line in Fig. 8a separates the desirable step propagation growth mode (higher temperatures and lower growth rates) from the 2D nucleation mode (lower temperatures and higher growth rates).
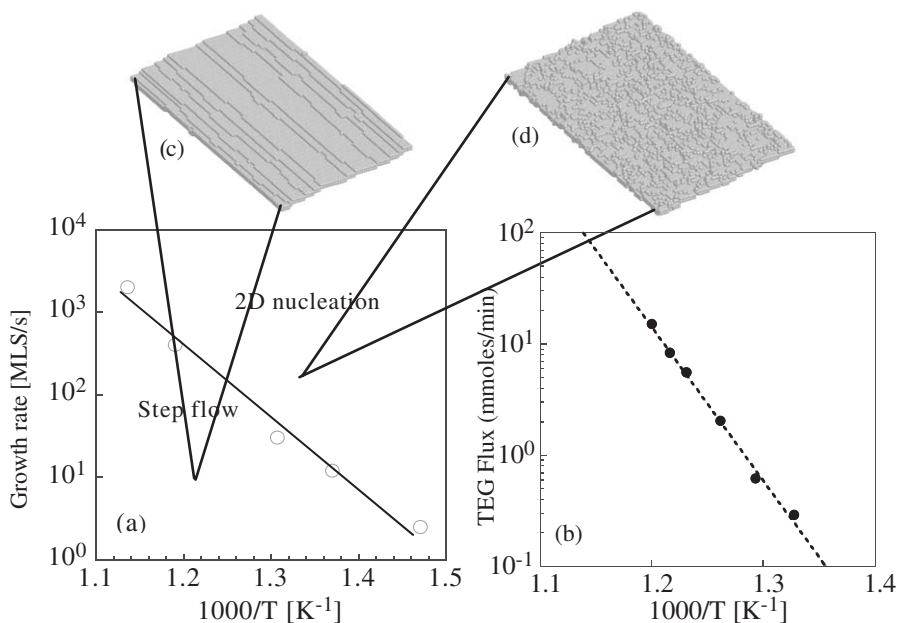
FIG. 8. (a) Kinetic phase diagram from hybrid, onion-type (stagnation, continuum/KMC) simulations of homoepitaxy in an atmospheric pressure reactor depicting the transition from step flow to 2D nucleation as the temperature decreases or the growth increases. Redrawn from Lam and Vlachos (2001). (b) Analogous experimental data of Kisker et al. (1995) for GaAs in terms of tetraethyl–gallium flux. (c) and (d): snapshots depicting different growth modes.

There is a limited number of experiments from coupled systems to enable comparison to experiments, in part because UHV techniques are difficult to apply to higher pressures where coupling of fluid flow and surface processes are important. Nonetheless, Fig. 8b shows a similar kinetic phase diagram for growth of GaAs obtained by X-rays (Kisker et al., 1995). The similarity (e.g., Arrhenius type of behavior) of experimental data with the simulations is striking, but more quantitative comparison with the prototype (simple) model is meaningless. Owing to the linking of micro-features with macroscopic variables, multiscale simulation could be used to enable design or control of films and nanoparticles with certain characteristics, such as a certain surface roughness, i.e., a top-down realization of multiscale simulation depicted in Fig. 1. This issue is further discussed in the systems tasks section.

In a similar spirit, Alkire, Braatz and co-workers developed coupled hybrid continuum-KMC simulations to study the electrodeposition of Cu on flat surfaces and in trenches (Drews et al., 2003b, 2004; Pricer et al., 2002a, b). A 3D KMC simulation accounted for the surface processes as well as diffusion in the boundary layer next to the surface, whereas a 1D or 2D continuum model (with adaptive mesh) was applied to simulate the boundary layer farther away. In

their initial implementation, the continuum model passed fluxes to the KMC and the KMC passed concentrations to the continuum model. Since the length scales simulated by the KMC method are relatively small, each cell of KMC was assumed to extend over a certain non-atomic length scale ($\sim$10–100 nm) to enable comparison with experiments (an *ad hoc* coarse-grained KMC). Comparison of surface roughness to AFM data for Cu deposition was also done. These studies have nicely demonstrated that linking multiscale simulation with experimental results is definitely a reasonable short-term goal. In fact, one could also use such experiments to parameterize transition probabilities of KMC. This issue is revisited in the systems tasks' section.

In coarse graining of KMC on a single monolayer entailing the same microscopic processes as in growth, the transition probabilities of various processes are scaled by different factors (Katsoulakis *et al.*, 2003b; Katsoulakis and Vlachos, 2003); thus, when multiple processes occur (as in the case of growth), appropriate scaling of the various processes is necessary. Future work in coarse graining (see section on spatially coarse-grained KMC) related to crystal growth is essential to further extend the exciting hybrid simulations of Alkire, Braatz and co-workers.

3. *Deposition by Molecular Beam Epitaxy (Uncoupled Fluid–Surface Systems)*

Another problem of hybrid multiscale simulation in crystal growth entails coupling of KMC with a diffusion/reaction, continuum type of model to describe epitaxial growth of a film. Here, the bulk fluid phase is ignored, i.e., the model applies to molecular beam epitaxy (MBE) conditions. Crystal growth may occur on low index crystallographic planes, such as the (1 0 0) surface, or vicinal surfaces, such as an (h10) plane, consisting of terraces separated by steps (see Fig. 8c for step–terrace structure). Planes corresponding to small misorientations with respect to a low index surface ($h \gg 1$) are composed of large terraces separated by steps that are far apart. These surfaces are impossible to simulate with currently available KMC simulations even in the absence of flow. Careful examination of the aforementioned hybrid KMC/flow simulations reveals that they have all been performed for step distances (or more generally features) that are too small so they can be handled by a single KMC simulation box.

So how can one handle situations where the steps are far apart? One answer lies in the pioneering work of Burton *et al.* (1951), also known as the BCF model. The BCF model is a continuum PDE that describes adsorption of atoms to and desorption from terraces along with surface diffusion on terraces [see Eq. (2) below for a simplified version of the BCF model]. When the concentration of adatoms is relatively large, nucleation between distant steps is most likely to occur, because the probability of a diffusing adatom to reach steps before encountering another adatom is low. Under these conditions, the BCF model is inadequate since it does not account for nucleation. Furthermore, the boundary conditions in the BCF model ignore the discrete nature of steps and treat them

as continuum points where either partial equilibrium or Robin boundary conditions are applied. Robin boundary conditions can account for the adatom kinetics of attachment to and detachment from steps. Accumulated recent experimental work from STM and statistical thermodynamic analysis dating back to the original BCF paper have clearly shown that steps consist of kinks and straight ledges, and that thermal fluctuations control the structure of steps and, thus, the velocity by which steps advance on a film. Therefore, a microscopic resolution of the steps could be important under certain conditions.

As a first step toward overcoming the above problems, a hybrid diffusion–adsorption model for the terrace linked with a KMC model near the steps was developed (Schulze, 2004; Schulze et al., 2003). This domain decomposition stems from a natural separation of scales. The continuum terrace model between steps is

$$\frac{\partial c}{\partial t} = D\nabla^2 c + F \tag{2}$$

where D is the surface diffusivity, c the adatom concentration, and F the adsorption flux. A KMC simulation is employed near each step to provide the boundary conditions of Eq. (2).

Note that in this specific model, desorption is neglected, and sites get regenerated upon adsorption, so the classic Langmuir blocking of sites is uncommon for MBE modeling. Furthermore, the diffusion–adsorption model for the terrace is only approximate since interactions between molecules are not accounted for. As a result, this hybrid model cannot handle nucleation between terraces, and applies only to small supersaturations or high temperatures [note that for high temperatures, one needs to include desorption in Eq. (2)] where the adatom concentration on terraces is relatively low.

The rationale of using hybrid simulation here is that a classic diffusion–adsorption type of model, Eq. (2), can efficiently handle large distances between steps by a finite difference coarse discretization in space. As often happens in hybrid simulations, an explicit, forward discretization in time was employed. On the other hand, KMC can properly handle thermal fluctuations at the steps, i.e., provide suitable boundary conditions to the continuum model. Initial simulations were done in $(1 + 1)$ dimensions [a pseudo-2D KMC and a 1D version of Eq. (2)] and subsequently extended to $(2 + 1)$ dimensions [a pseudo-3D KMC and a 2D version of Eq. (2)] (Schulze, 2004; Schulze et al., 2003). Again, the term pseudo is used as above to imply the SOS approximation. Speedup up to a factor of 5 was reported in comparison with KMC (Schulze, 2004), which while important, is not as dramatic, at least for the conditions studied. As pointed out by Schulze, one would expect improved speedup, as the separation between steps increases while the KMC region remains relatively fixed in size. At the same time, implementation is definitely complex because it involves swapping a microscopic KMC cell with continuum model cells as the steps move on the surface of a growing film.

C. Applications of Onion-type Hybrid Multiscale Simulation to Other Areas

There have been many hybrid multiscale simulations published recently in other diverse areas. It appears that the first onion-type hybrid multiscale simulation that dynamically coupled a spatially distributed 2D KMC for a surface reaction with a deterministic, continuum ODE CSTR model for the fluid phase was presented in Vlachos et al. (1990). Extension to 2D KMC coupled with 1D PDE flow model was described in Vlachos (1997) and for complex reaction networks studied using 2D KMC coupled with a CSTR ODEs model in Raimondeau and Vlachos (2002a, b, 2003). Other examples from catalytic applications include Tammaro et al. (1995), Kissel-Osterrieder et al. (1998), Qin et al. (1998), and Monine et al. (2004). For reviews, see Raimondeau and Vlachos (2002a) on surface–fluid interactions and chemical reactions, and Li et al. (2004) for chemical reactors.

In the area of fluids, coupling of MD near a wall with a continuum, deterministic description of the Navier–Stokes unidirectional flow farther away from the wall based on overlapping subdomains of domain decomposition was presented in O'Connell and Thompson (1995). A nice description of ensuring continuity of momentum flux was given and the velocity field was made consistent across the interface by using constraint dynamics in MD. See also Nie et al. (2003) for coupling of MD with a continuum model of flow, and Hadjiconstantinou and Patera (1997), where MD was again coupled with a continuum description of the incompressible Navier–Stokes solved using a spectral element method and the Schwart alternating method with overlapping subdomains. While the work of Hadjiconstantinou and Patera was applied to steady-state problems and invoked an iterative scheme to reach convergence (see solution strategies in Fig. 4), the separation of time scales between microscopic and continuum models was emphasized as a means of reducing the computational burden of hybrid schemes. Another example of MD/CFD for a tethered polymer on a surface in share flow was recently studied (Barsky et al., 2004) and shown to be in very good agreement with MD simulations, with significant reduction in CPU. Coupling of continuum mesoscopic or stochastic models near the Earth's surface with a fluid model has successfully been applied to tropical convection in order to study the effect of fluctuations from unresolved degrees of freedom of fine scales on climatology (Khouider et al., 2003; Majda and Khouider, 2002).

The materials community has made significant advances in predicting mechanical properties of materials and initiation of defects using hybrid multiscale simulation. This is one of the application areas where multiscale simulation has advanced the most. Several nice reviews and perspectives have already been published (Maroudas, 2000, 2003; Miller and Tadmor, 2002; Rudd and Broughton, 2000). Therefore, it suffices to give only a brief account of the evolution of multiscale simulation in this area here. One of the earlier and

successful multiscale approaches in solid mechanics is *the quasi-continuum method* of Tadmor *et al*. (1996), Philips (1998), Shenoy *et al*. (1999), and Miller and Tadmor (2002), where an adaptive finite element mesh that is refined to atomistic dimensions at interfaces is used. The energy of each cell is computed from the underlying Hamiltonian from a single "representative" atom that is embedded in the cell and subject to the deformation field of the cell. Subsequently, the equilibrium configuration at $0\,K$ is determined from an energy minimization of the total energy of all cells to provide the deformation field. It is worth noting that the embedding process of the quasi-continuum method (single atom resolving the energy of a coarse FEM cell) has a stronger parallel to the multigrid-type hybrid simulation discussed in the next section than the onion-type simulation, at least in the overlapping regime.

The quasi-continuum approach has been successful in static problems but limited to equilibrium situations and $0\,K$. Its extension to dynamic problems has not been easy, as revealed by subsequent works (Abraham *et al*., 1998a; Broughton *et al*., 1999; Cai *et al*., 2000; Maroudas, 2000; Weinan and Huang, 2002). The simulations by Abraham *et al*. (1998a) are one of the first to concurrently couple quantum mechanics at the core of a dislocation, MD to capture the atomic motion near the core, and finite elements of continuum elasticity farther out to simulate defect formation and propagation in materials. In a similar spirit, application of onion-type hybrid multiscale simulation to oxidation of Si has also been reported (Nakano *et al*., 2001; Ogata *et al*., 2001). Coupling of atomistic MD and continuum FEM models in the overlapping region can be accomplished by refining the mesh of FEM to atomistic sizes. However, materials simulations have revealed that this approach causes problems in some cases. Coarse graining of MD to large scales (Rudd and Broughton, 1998), or combination of FEM refining and MD coarse graining are other options that may in fact be superior (for a review see Rudd and Broughton (2000)). The issues of proper coupling in the overlapping subdomain, along with additional challenges of hybrid simulations, are discussed in detail in section F.

D. Multigrid-type Hybrid Multiscale Simulations

The above problems exhibit phenomena with well-separated length scales, where the coupling between the continuum and discrete models happens at an interface (the *overlapping or handshaking regime*). In most published work on discrete particle/flow distributed systems, the external field (e.g., the concentration profile) of the continuum model parallel to a surface is either uniform, such as in an ideal, infinite-size stagnation flow, or exhibits nanometer-scale inhomogeneities (smaller than the KMC simulation box size). In this situation, a single discrete particle simulation is adequate to resolve the spatial correlations, and one could couple it with the deterministic, continuum model.

There is another very important class of problems where no well-defined separation of length scales and spatial gradients exist over large length scales. There are numerous examples of such problems. Flow along a long tube is one where gradients in pressure and velocity fields occur. Growth on a large wafer is another where flow, concentration, and temperature non-uniformities across the substrate exist. Nucleation and growth of materials within a thick substrate in the countercurrent diffusion-reaction configuration (Gummalla et al., 2004) and diffusion through realistically thick microporous films used for separation or membrane reactors (Chatterjee et al., 2004a) are two more. These problems exhibit macroscopic gradients (over millimeters to inches), which are beyond the realm of conventional discrete particle models. Furthermore, with a few exceptions, mainly in our group (Lam et al., 2001; Snyder et al., 2003; Vlachos and Katsoulakis, 2000), KMC simulations have been limited to situations where the external field (e.g., pressure) is uniform, and as a result, they were carried out under periodic boundary conditions. On the other hand, non-equilibrium MD simulations under a gradient in chemical potential have already been introduced (Cracknell et al., 1995; Fritzsche et al., 1995; Heffelfinger and van Swol, 1994; MacElroy, 1994; MacElroy and Suh, 1997; Maginn et al., 1993; Sunderrajan et al., 1996; Xu et al., 1998). While microscopic models under gradients are now available, they cannot cope with the large length and time scales of realistic systems.

Recently, there has been strong interest in multigrid-type hybrid multiscale simulation. As depicted in Fig. 6, a coarse mesh is employed to advance the macroscopic, continuum variable over macroscopic length and time scales. At each node of the coarse mesh, a microscopic simulation is performed on a finer mesh in a simulation box that is much smaller than the coarse mesh discretization size. The microscopic simulation information is averaged (model reduction or restriction or contraction) to provide information to the coarser mesh by interpolation. On the other hand, the coarse mesh determines the macroscopic variable evolution that can be imposed as a constraint on microscopic simulations. Passing of information between the two meshes enables dynamic coupling.

The computational advantages of such multigrid methods arise from two key factors. First, microscopic simulations are carried out over microscopic length scales instead of the entire domain. For example, if the size of fine grid is 1% of the coarse grid in each dimension, the computational cost of the hybrid scheme is reduced by 10^{-2d}, compared with a microscopic simulation over the entire domain, where d is the dimensionality of the problem. Second, since relaxation of the microscopic model is very fast, QSS can be applied at the microscopic grid while the entire system evolves over macroscopic time scales. In other words, one needs to perform a microscopic simulation at each macroscopic node for a much shorter time than the macroscopic time increment, as was the case for the onion-type hybrid models as well.

The multigrid branch of multiscale simulation is less developed. To my knowledge, Tammaro and Evans were the first to introduce such multigrid-type

hybrid multiscale simulations for the example of a traveling wave in a catalytic reaction (Tammaro *et al.*, 1995). In their example, species A diffuses very quickly, whereas species B diffuses slowly. To cope with the large length scales and separation of time scales, they advanced over the entire interface of the traveling wave species A, using the continuity equation based on a finite difference coarse grid. At each node of the finite difference grid, they carried out a KMC simulation in which species A was randomly distributed (this approach copes with the huge disparity in time scales between diffusion of species A and B and is another type of hybrid simulation) and species B was treated by KMC. Information was passed back and forth between the two models at the two grids.

Interesting results from coupling MD with continuum equations using the multigrid-type hybrid approach were presented by Weinan *et al.* (2003) for dislocation dynamics and crack propagation. The method was termed *heterogeneous multiscale method* and is conceptually in the same spirit as the work of Tammaro *et al.* (1995). The *tooth-gap method* is a related technique (Gear *et al.*, 2003) to deal with these problems. In a different context of fluid flow simulations, coarse levels were modeled with continuum fluid mechanics and fine levels with discrete particle simulations (the DSMC method) (Garcia *et al.*, 1999). Multigrid ideas to resolve small-scale information and pass it into large-scale models for climate predictions have also been discussed by Majda and coworkers (Majda and Khouider, 2002).

E. AN EXAMPLE OF MULTIGRID-TYPE HYBRID MULTISCALE SIMULATION FOR GROWTH UNDER LARGE LENGTH SCALE GRADIENTS

An example of the aforementioned multigrid-type hybrid multiscale simulation from crystal growth for simulating nucleation and growth in large length scale systems is provided following Gummalla *et al.* (2004). Nucleation and growth are distributed in space and occur often in relatively localized areas, but the time and place where this happens is stochastic, i.e., the multiple grids have to be built as a simulation progresses and remeshing may be necessary as time evolves. The specific system refers to Pd deposition under CO_2 supercritical conditions within an alumina disk $\sim$1 mm thick. Hydrogen and the organometallic precursor are introduced from opposite sides of a countercurrent geometry to react, leaving behind Pd, as depicted in Fig. 9a. Experimentally, a challenge is to confine the chemistry within the substrate in such a way that a thin but continuum Pd film forms, which can be used for hydrogen separation. In this system, gradients in concentrations of species develop over the entire domain owing to diffusion and chemical reactions. On the other hand, nucleation occurs at random locations and times but is limited to the nanometer scale. Nucleation can be thought of as a noisy term within the governing PDEs, whose closed form is unknown, rather than in the boundary condition.
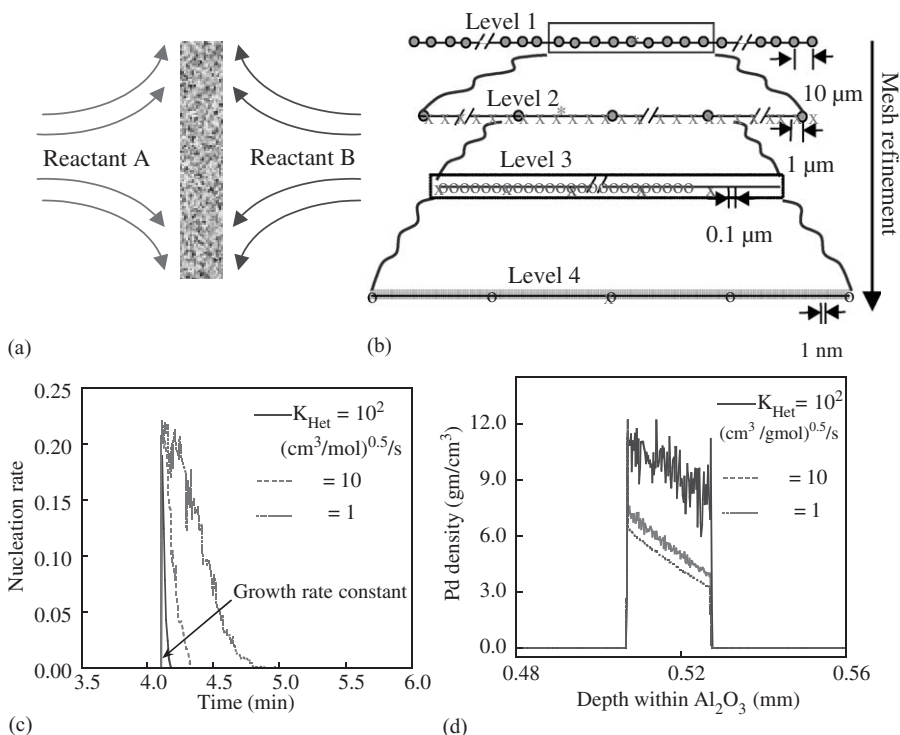
FIG. 9. (a) Schematic of opposed flow geometry. (b) Schematic of four-level refinement starting from coarser (top) and moving toward finer (bottom) meshes. The continuum diffusion–reaction equations are solved at the top three (coarser) grids with a possible consumption (sink) term determined from the fourth level. At the fourth (finest) level stochastic treatment of nucleation and front tracking are used to determine whether and where nucleation occurs and the consumption term of the nucleation precursor fed back to the third level. Effect of growth rate constant on nucleation rate (fraction of sites on finest grid on which nucleation occurs, per unit time) (c) and density of deposit when the alumina pores are plugged (d). Fast growth decreases nucleation and leads to films with less density variation at pore plugging and less Pd used. For these conditions, the Pd film forms in the middle of the Al_2O_3 substrate that is l mm thick. The effect of fluctuations on deposit density is apparent in (d). Data redrawn from Gummalla *et al.* (2004).

This disparity in length scales on the one hand and the stochastic nature of nucleation on the other underscore the multiscale nature of the problem. The governing PDEs describing the concentrations of reagents determine the probability of nucleation and must be solved over large length scales that are far beyond the realm of microscopic KMC. To overcome the disparity of length scales, an adaptive mesh refinement strategy has been used with four levels that enable linking macroscopic scales to the nanometer, as shown schematically in Fig. 9b (note that these multiple grids differ from the schematic of Fig. 6 to better fit the problem at hand). One question is: Where and when does one decide to refine the mesh? This is actually done probabilistically. Since

nucleation has a higher probability of occurrence wherever concentrations are high, the mesh is refined when and where the probability for nucleation is above a certain low threshold. The chosen region for mesh refinement typically involves high concentrations of nucleation precursors. Nuclei can also form in regimes where the probability of nucleation is low, but in our experience, this does not lead to growth but to a few isolated nucleation events. The use of a threshold eliminates spurious mesh refinement in "wrong" regions.

The multigrid, hybrid multiscale approach entails solving the continuum governing (diffusion–reaction) equations in porous media at the three coarser meshes and a stochastic treatment of nucleation at the finest mesh. In the finest mesh, a KMC simulation could be employed and linked to a front tracking technique to follow the evolution of growing clusters. Upon significant growth of clusters (cluster size > mesh size of level 3), growth could be handled from the next coarser mesh. In order to accelerate the hybrid scheme, an exponential distribution was used instead of an actual KMC. KMC simulations in a well-mixed batch reactor have been compared with the hybrid approach, and good agreement was found (Gummalla *et al.*, 2004). Thus, at each location of the finest mesh the probability for nucleation per unit time, P_o, which is proportional to the nucleation rate, is computed. The probability for a nucleation event in a time t_{nuc} after the creation of a previous nucleus is assumed to be

$$P(t_{nuc}) = 1 - \exp[-t_{nuc}P_o] \qquad (3)$$

As time evolves by Δt, the continuum model at the third mesh provides concentrations that affect the nucleation rate of the stochastic model via Eq. (3). At every time step, $P(t_{nuc})$ is computed and compared with a random number between 0 and 1. When the random number is larger than $P(t_{nuc})$, t_{nuc} increases by Δt, whereas when the random number is less than $P(t_{nuc})$, a new nucleus is seeded and t_{nuc} is set to zero. Nucleation and growth, when occurring at the finest mesh, consume nucleation precursors, whose rate of consumption is passed to coarse grids. These hybrid multiscale simulations can provide insights into the roles of nucleation and growth kinetics in microstructure, defects, film continuity, etc. that can be directly compared with experiments. An example is depicted in Figs. 9c and d.

These hybrid approaches have a lot of potential for treating nucleation stochastically while enabling simulations on large domains. Simulations in higher dimensionalities and of self-organization phenomena (e.g., Lebedeva *et al.*, 2004a, b) using multigrid hybrid multiscale models are definitely desirable.

F. Challenges in Hybrid Multiscale Simulations

The major issue in hybrid multiscale simulation is "patching" of models used in different subdomains (Nie *et al.*, 2003; Raimondeau and Vlachos, 2002a). In

brief, coupling may lack convergence (Raimondeau and Vlachos, 2002b) (especially in an iterative scheme) and could result in spurious solutions (Reich, 1999) and violation of conservation laws. One of the best expositions of patching problems can be found in Weinan and Huang (2002) for problems related to dislocations, friction, and crack propagation. Matching conditions were developed between atomistic (MD) and continuum regions to minimize reflection of phonons of MD at the MD/continuum model interface. While the authors were successful, they noted that at higher temperatures and in nonlinear situations, overheating may occur. General solutions to patching in most applications are still needed. These issues are elaborated below, and recent progress made in overcoming them is outlined by focusing on crystal growth problems.

A frequent problem in hybrid multiscale simulations is noise-induced numerical instability (Raimondeau and Vlachos, 2002a, b; Rusli et al., 2004). Such instabilities may occur when the time step of the KMC becomes too large to violate the numerical stability criterion of the continuum model, or when rare events happen that create huge variations in the boundary condition or in the source/sink term of the continuum model. This numerical instability is a result of the small size of the KMC simulation box (a problem stemming from our inability to deal with realistically large length scales). Consequently, the KMC response is considerably noisier than what one would have for realistic length scales. In order to reduce the noise of KMC passed to the continuum model, in Vlachos (1999) and Lam and Vlachos (2001) the KMC simulation was run for a certain number of events before the gas-phase model was solved. This is justifiable, given that the time step of KMC is typically much smaller than that of the gas-phase model, i.e., surface processes have a much shorter relaxation time. Thus, the numerical strategy followed is spatial and temporal averaging in KMC to compute rates with reduced noise (variance reduction) prior to passing them to the continuum model. The number of MC events used in temporal averaging was varied to ensure that the results were unaffected. In cases where the time scales of the KMC and the continuum model are comparable, one could use parallel processing by running multiple images of the KMC to create microscopic-model based rates with reduced noise. Similar problems were also reported by Drews et al. They used a filtering approach to reduce the noise in hybrid simulations for improved code robustness (Drews et al., 2004; Rusli et al., 2004). Note that temporal averaging in a discrete particle model has the advantage of minimizing the number of continuum model calls; as a result, it leads to a speedup of a hybrid scheme. System level tasks, such as filtering, arising from the controls community, was also employed in the work of Lou and Christofides (2003a, b, 2004) (see also corresponding section below).

The exposition in Schulze's (2004) recent paper underscores in an excellent manner some additional difficulties encountered in hybrid multiscale simulation (not just of crystal growth problems) when overlapping subdomains are used. The replacement of KMC on terraces with the continuum model Eq. (2) reduces

the noise of the hybrid scheme compared with the microscopic KMC model, and alters phenomena controlled by noise such as the time scale for bunching of steps (a common instability in crystal growth). It was reported that while bunching of steps occurs under the same conditions as in KMC, the dynamics of the processes was altered. This is obviously an undesirable situation and results from over coarse graining the microscopic processes on a terrace, i.e., from replacing the microscopic KMC method with a continuum model.

The unintentional noise-induced numerical instability in coupled fluid-KMC codes and the reduced noise in the growth on a terrace model underpin just one of the problems of hybrid multiscale simulation that stem from the incorrect (over- or under coarse graining of) noise. We expect that coupling of continuum models with the recently introduced coarse-grained KMC (CG-KMC) simulations, discussed below, will improve or eliminate this noise-induced numerical instability. This improvement is expected because the much larger length scales simulated via CG-KMC will result in (correctly) less noisy signals than those produced by microscopic KMC simulation. On the other hand, use of the adaptive coarse-grained-KMC (ACG-KMC) method, also touched upon below, could completely eliminate the need for hybrid simulation for surface processes, such as the terrace-step model of Schulze, and overcome the reduction in noise that in turn affects nucleation. Further work is needed to exploit these ideas.

There is another subtle but fundamental issue in coupling of hybrid models that has to do with differences in constitutive relations in various subdomains. In particular, models at various scales correspond (upon passing to the continuum limit) to different constitutive relations. For example, in the continuum model on a terrace, Eq. (2), there are no interactions between molecules. Consequently, Fick's first law

$$j = -D\nabla c \tag{4}$$

describes the system adequately. On the other hand, within the KMC subdomain, interactions between molecules result in a different underlying mesoscopic transport equation and constitutive relation, i.e., Fick's first law does not hold. We have found out that the specifics of mesoscopic equations and constitutive relations depend on the microscopic mechanisms of diffusion. For example, when the activation energy depends only on the energy of the departing site, the corresponding continuum model (termed Arrhenius dynamics) for the problem of growth, based on Vlachos and Katsoulakis (2000), is

$$\frac{\partial c}{\partial t} = D\nabla\{e^{-\beta J*c}[\nabla c - \beta c(1 - c)\nabla J * c]\} + F \tag{5}$$

where $D = D_o e^{-\beta U_o}$ is the diffusion coefficient, D_o the diffusion coefficient at high (infinite) temperature, J the intermolecular potential of adatom–adatom

interactions, and $J * c = \int J(|r - r'|)c(r') \, dr'$ a convolution. In this case, the constitutive relation reads

$$j = -D\{e^{-\beta J * c}[\nabla c - \beta c(1 - c)\nabla J * c]\} \tag{6}$$

As another example, when the activation energy for diffusion depends on the energy difference between the initial and final locations (termed Metropolis dynamics), the corresponding continuum model for growth reads

$$\frac{\partial c}{\partial t} = \nabla D_{\text{o}}\{[\nabla c - \beta c(1 - c)\nabla J * c]\} + F \tag{7}$$

and the constitutive relation is

$$j = -D_{\text{o}}\{[\nabla c - \beta c(1 - c)\nabla J * c] \tag{8}$$

Equations (6) and (8) reduce to Eq. (4) only when the intermolecular potential J is zero. These are the proper constitutive relations if the microscopic mechanisms of diffusion are the assumed ones.

What are the implications of different constitutive relations in different regimes? In brief, conservation laws are not that easy to satisfy. For example, in the presence of interactions, matching the concentration profiles in the overlapping regime (a common strategy in domain decomposition) is inadequate since continuity in concentration and its gradient does not ensure the same flux at the interface. Matching of chemical potentials is potentially a more rigorous approach, but different mobility terms do not guarantee continuity in fluxes across the overlapping region. Furthermore, this is a difficult task to accomplish because constitutive equations, such as the ones written above, do not exist for most microscopic models. Matching of fluxes at the interface leads at least to conservation, but further work is needed to fully understand this point.

Another issue in hybrid multiscale simulation pertains to possible mass conservation caused by truncation errors. In particular, mapping discrete molecules into continuum quantities, e.g., updating the concentration, is easy. However, the reverse task of mapping continuum changes of concentrations into an integer number of molecules along with their spatial placement is also important (see Schulze (2004)) for some interesting ideas and a coupling factor that is iteratively determined to match fluxes).

The discussion above focused on onion-type hybrid multiscale simulation. Finally, even though there are a limited number of examples published, I expect that the multigrid-type hybrid simulations share the same problems with onion-type hybrid multiscale models. In addition, appropriate boundary conditions for the microscopic grid model need to be developed to increase the accuracy and robustness of the hybrid scheme. Furthermore, the inverse problem of mapping coarse-grid information into a microscopic grid is ill posed. Thus, it is

not currently clear what the best way of reconstructing the information on the fine grid is. Future work will elucidate these issues.

VI. Coarse Graining of Stochastic Models

Hybrid multiscale simulation is currently by far the main multiscale computational toolkit under development. However, as discussed in the last section, many problems lack separation of scales, and since a molecular model cannot be applied to the entire process, *coarse graining* (upscaling) of molecular models is an appealing approach, leading to *mesoscopic models* that can reach larger length and time scales. These coarse grained or mesoscopic models could be used as stand-alone models (see examples below) or in hybrid multiscale simulators (see Fig. 4), e.g., a coarse grained surface simulator is linked with a fluid-phase model, as in the work of Pricer *et al.* (2002a, b) and Drews *et al.* (2003b, 2004). One advantage of stand-alone coarse-grained models over multigrid-type hybrid simulations is that one does not have to interface multiple models; thus, one avoids the challenges mentioned in the previous section. Another is that it is possible to retain the correct noise and thus overcome either numerical instabilities or the alteration of the physics (see discussion above on challenges in hybrid simulation, and below for the effect of coarse graining on noise).

Next time acceleration is first discussed, followed by space acceleration, and finally by space-time acceleration of KMC methods. Similar developments are under way for MD, but this subject is left for a future communication.

A. Temporal Upscaling of KMC Simulation in Well-mixed Systems

Separation of time scales is the rule rather than the exception in chemical kinetics, irrespective of deterministic or stochastic modeling. The disparity of time scales is easily rationalized by the considerable difference in activation energies and the strong dependence of reaction rates on activation energies via the Boltzmann factor. The stiffness of deterministic ODEs is now easily handled owing to the machinery of implicit, adaptive time step, variable-order solvers. However, extensions to stochastic systems are far behind. Until recently, KMC simulations could not deal with separation in time scales. In a conventional KMC simulation, fast processes with large transition probabilities are frequently sampled, resulting in small simulated times, whereas slow events are rare and are poorly sampled during a simulation.

Recently, several approaches have been proposed to overcome the disparity of time scales for certain classes of problems. In order to overcome the problem of stiffness caused by rapid, partial equilibrated reactions in a living free-radical polymerization system, a hybrid analytical-KMC method was suggested (He

et al., 1997). In particular, the partial equilibrium (PE) was enforced to elim-
inate the fast processes by adjusting deterministically the concentrations of
species involved in PE, whereas the slow reaction events were treated stochas-
tically. A problem with this technique is that when the separation of time scales
is moderate, PE is not as accurate. Furthermore, PE applies only after some
induction time. Finally, PE requires conversion of real numbers into integers,
and while this can be done so that mass is conserved, it is not clear what the
errors are.

Resat *et al.* generalized the above idea and implemented a weighted-prob-
ability KMC method (WP-KMC) to overcome the separation of time scales of
stochastic simulation (Resat *et al.*, 2001). The idea of probability weighting
stems from equilibrium MC umbrella sampling simulations introduced in Torrie
and Valleau (1977). The slow reactions determine the long-term dynamics of
system evolution. In WP-KMC, during each slow reaction event, several events
of fast reactions are simultaneously executed, i.e., one moves a number of mol-
ecules (bundles) rather than moving one molecule per time. The rationale for
this method is that over the time scale of slow reactions (rare events), the
transition probabilities of fast reactions and the concentrations of major reac-
tants (large populations) vary slowly. As a result, one may assume that they do
not change as much, and consequently execute a number of events simultane-
ously. A problem with this approach is that the weighting of probabilities am-
plifies the noise, a physically unrealistic situation (see Fig. 10).

The net-event KMC (NE-KMC) or lumping approach has been introduced
by our group. The essence of the technique is that fast reversible events
are lumped into an event with a rate equal to the net, i.e., the difference
between forward and backward transition probabilities per unit time (Vlachos,
1998). The NE-KMC technique has recently been extended to spatially distrib-
uted systems (Snyder *et al.*, 2005), and it was shown that savings are propor-
tional to the separation of time scales between slow and fast events. The method
is applicable to complex systems, and is robust and easy to implement.
Furthermore, the method is self-adjusted, i.e., it behaves like a conven-
tional KMC when there is no separation of time scales or at short times,
and gradually switches to using the net-event construct, resulting in accelera-
tion, only as PE is approached. A disadvantage of the method is that the noise
is reduced.

A comparison of the WP-KMC, NE-KMC, and conventional KMC is shown
in Fig. 10. These acceleration approaches are successful regarding CPU. How-
ever, since the objective is often to study the role of noise, they do not provide
the correct fluctuations. In a similar vein, use of simple rate expressions, such as
the Michaelis–Menten or Hill kinetics, derived via PE and QSS approximations,
are capable of accelerating KMC simulation since fast processes are eliminated.
However, the noise of the resulting simulation, based on a reduced rate ex-
pression that lumps some of the reaction steps, is usually adversely affected
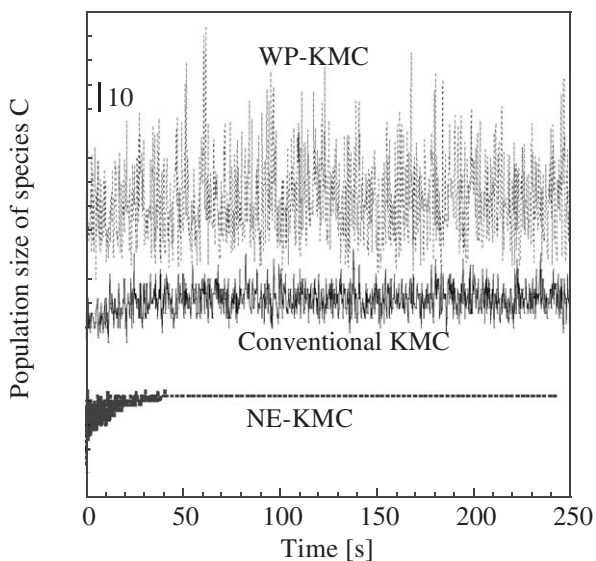(Bundschuh *et al.*, 2003).

FIG. 10. Number of molecules of species C vs. time from two time acceleration algorithms and the microscopic KMC method. The reaction network studied in a constant volume batch reactor is $A + B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C$ and $A + C \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} D$. For the set of conditions picked, a fivefold speedup is obtained using the WP-KMC. However, the amplification in noise is apparent. On the other hand, the NE-KMC gives comparable noise at the beginning and speeds up as equilibrium is approached with the same or better speedup than WP-KMC. The curves have been displaced from each other for better visualization. The rate constants are $k_1 = 10^{-5}$ molecules^{-1} s^{-1}, $k_{-1} = 1$ s^{-1}, $k_2 = 10^{-3}$ molecules^{-1} s^{-1}, and $k_{-2} = 0.1$ and the initial distribution of molecules is $N_A(t = 0) = 10{,}000$, $N_B(t = 0) = 2500$, and $N_C(t = 0) = N_D(t = 0) = 0$.

Recently, Gillespie (2001) introduced an approximate approach, termed the τ-leap method, for solving stochastic models. The main idea is the same as in the WP-KMC method. One selects a time increment τ that is larger than the microscopic KMC time increment, and multiple molecular bundles of fast events occur. However, one now samples how many times each reaction will be executed from a Poisson rather than a uniform random number distribution. Prototype examples indicate that the τ-leap method provides comparable noise with the microscopic KMC when the leap condition is satisfied, i.e., the time increments are such that the populations do not change significantly between time steps.

Gillespie's recent work on the τ-leap method is a significant advance in accelerating KMC simulation with respect to time constraints. However, some issues need to be resolved before the method becomes widely used. First, disparity in time scales caused by reaction rate constants rather than concentrations may not be as easy to handle. Second, negative concentrations result with

probability one, i.e., if one runs long enough, since the Poisson distribution is unbounded and a molecular bundle can be larger than the actual population of a species. This situation becomes common as the size of the molecular bundle, and thus the time step, increases. Additional problems are that large jumps in time can cause incorrect behavior even if the concentrations are non-negative, and that the magnitude of the noise is increased for substantial coarse graining in time increments.

In order to overcome the problem of negative concentrations, two versions of the binomial τ-leap method were recently introduced (Chatterjee *et al.*, 2005d; Tian and Burrage, 2004). While the essence of the techniques is the same, the method of Tian and Burrage (2004) appears to be limited to reaction networks whose species are not shared by multiple chemical reactions. The elimination of negative concentrations enables substantial acceleration of stochastic simulation of complex biological networks (Chatterjee *et al.*, 2005b). It has also been shown analytically and numerically that the binomial τ-leap method gives a better approximation of the noise in comparison with the original Poisson-based τ-leap method of Gillespie (Chatterjee *et al.*, 2005d).

The initial criterion proposed to ensure accuracy and avoid negative concentrations in simulations of typical length required a small change in the propensity functions. While an improved criterion was subsequently proposed (Gillespie and Petzold, 2003), improved and additional criteria should be developed. Finally, calculation of Poisson random numbers required by the method is more expensive. We will illustrate some of these issues below in the context of spatiotemporal CG-KMC. The τ-leap method has further been extended by Petzold, Gillespie, and co-workers (Rathinam *et al.*, 2003) by employing implicit solvers that could potentially further increase the time step increments and overcome the problem of stiffness of stochastic systems. With the implicit τ-leap the evolution is captured more accurately for large jumps in time, even though the noise is now actually reduced. Stability criteria for the various τ-leap methods were recently developed and the variation of noise between various methods was rationalized (Cao *et al.*, 2004). A trapezoidal τ-leap method was found to provide better noise characteristics. The τ-leap method is revisited in the section on spatial CG-KMC methods.

Noteworthy are some alternative approaches that address the issue of separation of time scales by starting with the master equation. Rao and Arkin (2003) have employed the QSS assumption in stochastic simulation, expanding on ''adiabatic elimination'' ideas of fast variables from the master equation discussed in Janssen (1989a, b) and Vlad and Pop (1989). Haseltine and Rawlings portioned events into slow and fast (instead of treating species as done in the work of Rao and Arkin), and treated fast reactions either deterministically or with Langevin equations, and slow reactions as stochastic events (Haseltine and Rawlings, 2002). This hybrid type of modeling builds upon the hierarchy of models depicted in Fig. 3b and is further discussed below in the biological networks section.

It is clear that this is an exploding branch of multiscale simulation. While significant progress has already been made, different methods pose different advantages and disadvantages. The main difficulty with most techniques is their inability to preserve the noise. In this regard, the τ-leap method and its derivatives are promising. I expect more work to be devoted to this rapidly growing branch of multiscale simulation along with many applications from various areas. While simple reaction networks have been treated with some success, I believe that there is a clear need to develop a robust, generic methodology that overcomes the problem of stiffness of *complex reaction networks* while preserving the noise that can be important in some applications.

B. SPATIAL UPSCALING OF DISTRIBUTED (LATTICE) KMC SIMULATION

The problem of coarse graining in space is also very important but has received less attention. The overall idea of coarse graining degrees of freedom to move up in scales comes originally from renormalization group theory. An interesting idea revolves around coarse graining of the Hamiltonian using wavelets. This idea has been applied successfully to study critical behavior of prototype fluids (Ismail *et al.*, 2003a, b) and is being currently extended to complex polymeric systems (Ismail *et al.*, 2005a, b). Coarse graining of the Hamiltonian was also presented by Ishikawa and Ogawa (2002), but it can be shown that the proposed expression does not obey detailed balance.

Recently, the mathematical foundations for spatial CG-KMC have been introduced for grand canonical and canonical ensemble simulations of Ising-type systems in Katsoulakis *et al.* (2003a, b) and Katsoulakis and Vlachos (2003). This work deserves a review of its own. However, in order to put it in context with the other multiscale developments, some exciting developments are briefly summarized. The essence of the method is the creation of a lattice of coarse cells, each consisting of several microscopic cells. Within a coarse cell, the local mean field is assumed (a closure at the stochastic level). In this way, some information (degrees of freedom) is lost during coarse graining. The potential of interactions, the Hamiltonian, and the transition probabilities are all coarse-grained using wavelets for projecting the energetics and by ensuring that the microscopic and macroscopic limits are correctly captured (this is an essential attribute for the success of the method). Simulations have demonstrated that when the intermolecular potential is relatively long, CG-KMC gives results in very close agreement with microscopic KMC in terms of dynamics and equilibrium states, while retaining the noise and reducing the CPU by many orders of magnitude. Thus, CG-KMC is an ideal tool for reaching large length scales.

While CG-KMC can reach large scales at reasonable computational cost, it can lead to substantial errors at boundaries and interfaces where large gradients exist, and the local mean field assumption is not as accurate. Recent

work has extended coarse graining to adaptive meshes (Chatterjee *et al.*, 2005a, 2004b), in a similar spirit to well-established discretization methods of PDEs. This method is termed ACG-KMC, and can considerably improve accuracy with similar or improved computational savings compared with the uniform mesh CG-KMC simulation. Analytical error estimates of information loss during coarse graining from finer to coarser scales can be used to design optimum meshes that ensure high accuracy with minimal computational cost (Chatterjee *et al.*, 2005a, c).

Next, an example of CG-KMC from pattern formation on surfaces is presented. Another application to relatively thick membranes was given in Snyder *et al.* (2004). In the example considered here, atoms adsorb from a fluid reservoir on a flat surface. Subsequently, they may desorb back to the fluid, diffuse on the surface, or be annihilated by a first-order surface reaction, as shown in Fig. 11a. Attractive interactions between atoms trigger a phase transition from a dilute phase (a low coverage) to a dense phase (a high coverage) (Vlachos *et al.*, 1991), analogous to van der Waals loops of fluid–vapor coexistence. Surface reactions limit the extent of phase separation; the competition between microphase separation and reaction leads to nanoscopic patterns by self-organization under certain conditions (Hildebrand *et al.*, 1998).

A major challenge in simulating such problems is that nucleation occurs at the nanometer scale whereas self-organization entails competition between numerous pattern blocks for reagents over microns to millimeters. These problems do not exhibit an obvious separation of length scales. From a different point of view, the stochasticity is built within the PDE as a source or sink term (if one were able to write such a PDE). Furthermore, surface diffusion is faster than the other microscopic processes by many orders of magnitude, but PE cannot be applied since the actual value of diffusion dictates the presence or absence of patterns.
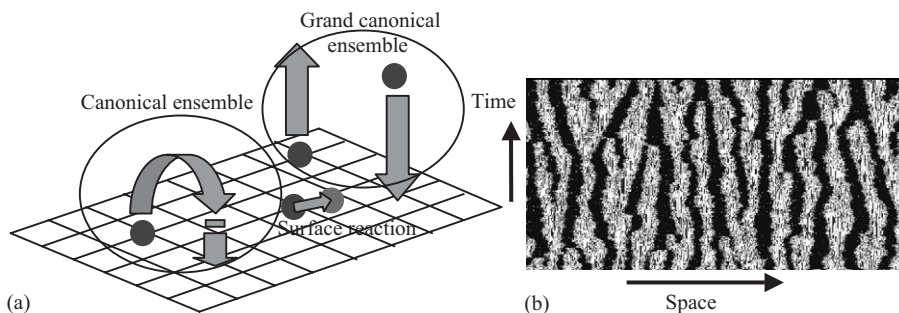

FIG. 11. (a) Schematic of microscopic processes for fluid–surface interacting systems. (b) Spatiotemporal evolution of 1D concentration patterns (coarse graining of two sites into each coarse cell is used). Bifurcation splittings and mergings occur as time evolves. The fast diffusion necessary for pattern formation (five to six orders of magnitude faster than the rest of the processes) renders microscopic KMC unsuitable even for small domains.

Instead of using multigrid-type hybrid multiscale simulation discussed above, the CG-KMC method that retains the noise is employed, and it can thus correctly capture the effect of fluctuations on nucleation and pattern evolution. Figure 11b shows an example of such a 1D simulation [see also Chatterjee *et al.* (2004a)]. Nucleation happens at short times at different locations and times (not shown), and patterns evolve in time owing to thermal fluctuations, giving rise to bifurcation splittings and mergings. This evolution of patterns is driven entirely by thermal fluctuations.

It is expected that simulations like this as well as various other coarse-grained fluid-like simulation tools (e.g., LB) will become key players in nanometer scale design and control in the emerging area of nanotechnology, as well as in intervention for control in biological systems. Examples include pattern formation, self-assembly of nanoparticles, nucleation and growth of materials, and computational cell biology. Given that these models are generic, application to very diverse areas is entirely feasible. For a recent application example to tropical convection, see Khouider *et al.* (2003).

C. Spatiotemporal Acceleration of Distributed (Lattice) KMC Simulation

Integration of spatial and temporal acceleration methods discussed above to create a stochastic simulation toolkit that can reach large length and time scales is entirely possible. The first example of integrating spatial and temporal acceleration methods entails the combination of NE-KMC with ACG-KMC methods to simulate diffusion through relatively thick ($\sim$10 µm) membranes where diffusion becomes rate determining (Snyder *et al.*, 2005). While combination of time-acceleration methods with lattice KMC is possible, most time acceleration methods affect noise adversely. Therefore, it appears that integration of the τ-leap method (or a derivative of it) with a spatially distributed (lattice) KMC simulation is the most promising approach for many applications. It turns out that the τ-leap method developed for well-mixed systems is fully consistent with the local mean field assumption of the CG-KMC method.

Here, the first example of combining the two methods for the grand canonical ensemble (adsorption/desorption) is presented. Figure 12a compares the results of the τ-leap CG-KMC method to the CG-KMC ones for a fixed value of the acceleration parameter ε, (see Gillespie (2001) for a precise definition of ε). In this simulation one starts from an empty lattice and monitors the lattice uptake, i.e., the spatially averaged coverage vs. time, for a fixed value of the fluid chemical potential. Figure 12b shows the corresponding bundle sizes vs. time. It is clear that in each adsorption/desorption event molecular bundles greater than a single molecule occur, leading to acceleration of the simulation. As the acceleration parameter increases, the size of molecular bundles, i.e., the number of molecules or processes participating in each event, increases. However, for larger bundle sizes, the possibility of getting negative concentrations, as happens
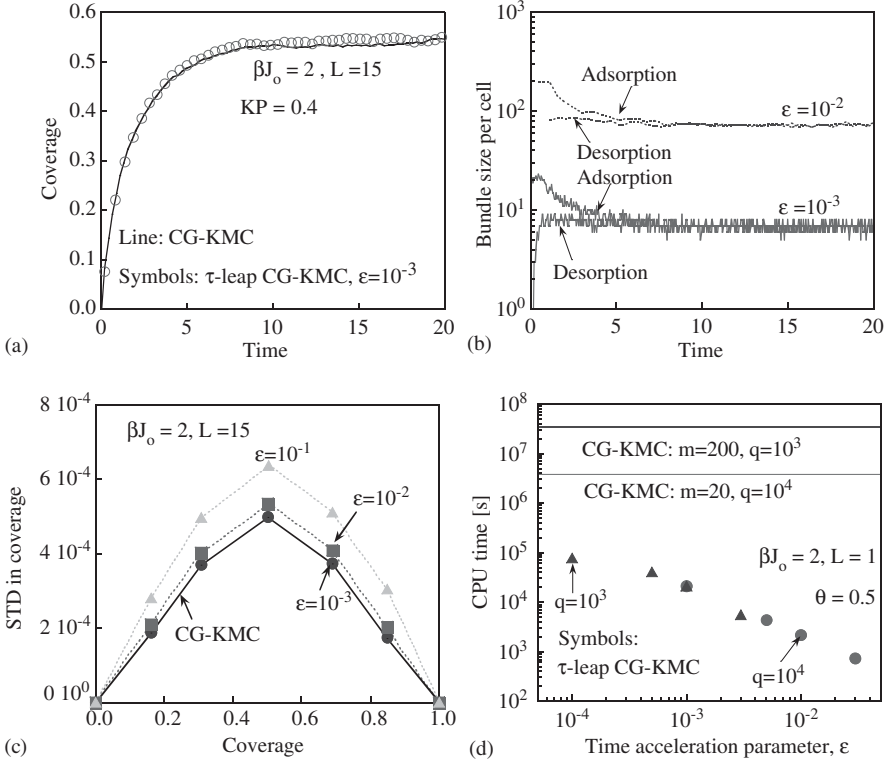
FIG. 12. (a) Coverage on an initially empty lattice vs. time from both the CG-KMC simulation and the Poisson-based τ-leap CG-KMC simulation in the grand canonical ensemble. The agreement is excellent. (b) Corresponding molecular bundles vs. time. (c) Standard deviation (STD) in noise of coverage vs. coverage (corresponding to different values of the fluid chemical potential) for various values of the acceleration parameter ε. For smaller bundles the noise is nearly exact. However, as one coarse-grains considerably the time increments, the noise of the τ-leap method is slightly increased. (d) CPU of CG-KMC and of τ-leap CG-KMC for two meshes (q is the coarse cell size and m is the number of coarse cells) and a fixed lattice size of $N = mq = 2 \times 10^5$ microscopic sites. Application of the Poisson-based τ-leap can accelerate the lattice CG-KMC by orders of magnitude, especially when the meshes are coarse to enable large time increments.

with well-mixed systems, limits the application of the τ-leap CG-KMC method (an expected result; not shown). Use of the binomial τ-leap overcomes this problem (Chatterjee and Vlachos, 2005).

Next, two main issues are discussed. First, Fig. 12c compares the noise of CG-KMC to that obtained from τ-leaping as a function of coverage, obtained by varying the fluid chemical potential, for various values of the acceleration parameter ε. At relatively small bundle sizes compared to the coarse cell size q, the τ-leap CG-KMC method gives very good results in both the expected value

and the standard deviation. However, when larger time increments are attempted, the noise is slightly increased. Finally, Fig. 12d compares the CPU from the standard CG-KMC simulation and the τ-leap CG-KMC simulation for two meshes as the time increments increase. It is clear that substantially higher savings than by CG-KMC simulation can be obtained when large time increments are attempted. This is an exciting result that opens up the possibility of stochastic simulation of large length and time scales.

One may ask, what are some of the important future directions suggested by such findings? Developments so far have been focused on examples of prototype statistical mechanics. There is a need to extend these to realistic, complex systems such as catalytic reactions, crystal growth, polymers, proteins, self-organization, etc. Furthermore, benchmark examples from other areas are needed to further evaluate the success and limitation of various methods. Finally, integration of the τ-leap method with the CG-KMC method, demonstrated here, holds the greatest promise for enabling stochastic simulation of large length and time scales.

VII. Multiscale, Stochastic Modeling of Biological Networks

A. SPATIALLY WELL-MIXED SYSTEMS

The need for multiscale modeling of biological networks in zero-dimensional (well mixed) systems has been emphasized in Rao et al. (2002). The multiscale nature of stochastic simulation for well-mixed systems arises from separation of time scales, either disparity in rate constants or population sizes. In particular, the disparity in species concentrations is commonplace in biological networks. The disparity in population sizes of biological systems was in fact recognized early on by Stephanopoulos and Fredrickson (1981). This disparity in time scales creates slow and fast events. Conventional KMC samples only fast events and cannot reach long times.

Several methods for speeding up Gillespie's original algorithm for well-mixed systems were reviewed above. Among these, the WP-KMC method was recently employed to study the coupled epidermal growth factor receptor (EGFR) trafficking and transduction (Resat et al., 2003). The binomial τ-leap method applied to the complex MAP kinase cascade (94 signaling species among 296 reactions) demonstrated hundred- to thousand-fold savings in CPU with excellent accuracy despite the disparity in species populations (Chatterjee et al., 2005b). An alternative approach to cope with the disparity in population sizes that has received more attention is hybrid multiscale simulation. In particular, one treats deterministically species in excess or reactions that involve species in large populations and stochastically species in low concentration or reactions

invoking species in low population (see hierarchy in Fig. 3b). Other possible pairs of models depicted in Fig. 3b could be employed and are mentioned below.

The first applications of such hybrid approaches have just emerged. An example of coupled deterministic/stochastic ODEs was recently introduced by Zak et al. (2003) for a relatively large regulatory genetic network (118 reactions, 44 species, 97 parameters). In this case, species in large concentrations (proteins and transcription factor dimers) were treated as continuum variables and integrated with the implicit Euler method, whereas species in relatively low concentrations (promoters and transcripts) were treated as discrete variables and their corresponding material balances were solved using the KMC method. The use of an implicit deterministic integrator demands solution of the KMC; therefore, some reactions describing the effect of small species on large ones were omitted (their effect was found negligible when carrying out fully deterministic simulations), leading to one-dimensional coupling of the subsystems, which was found to provide correct solutions.

It is entirely possible that the ensemble average (expected values) of a stochastic system differs from the deterministic model solution. For example, in the simulations of Zak et al. (2003), single stochastic trajectories were found to deviate significantly from the deterministic ones. In particular, the deterministic solution does not show adaptation, whereas some of the stochastic trajectories show adaptation and others do not. One question is whether a system composed of hundreds to thousands of subsystems, i.e., the ensemble average, approaches the deterministic behavior or not. Simulations were performed for the model of Zak et al. (2003) using 2300 different random number initializations, and the simulations were extended to 1000 h (simulated time). To economize simulation time, only genes in the "core" of the network (genes A, B, C, D, E, and F) were simulated. However, the simulation results for the core genes are identical to those that would be obtained if the cascade genes were included in the simulations. The ensemble *mean* of the stochastic simulations converged to approximately the value from the deterministic simulations for only two out of the six genes. However, for the remaining genes, the ensemble *median* or *mode* did generally converge to values that were close to the deterministic value. Figure 13 shows illustrative results from these ensemble-based hybrid multiscale simulations (corresponding to their Fig. 3). Gene F had the most complex distribution of the genes, but the ensemble median did match the deterministic result reasonably well. Despite the large number of simulations, ensemble properties, especially of gene F, exhibit systematic differences from their deterministic prediction.

As another example of hybrid simulation touched upon above, Haseltine and Rawlings (2002) treated fast reactions either deterministically or with Langevin equations and slow reactions as stochastic events. Vasudeva and Bhalla (2004) presented an adaptive, hybrid, deterministic-stochastic simulation scheme of fixed time step. This scheme automatically switches reactions from one type to the other based on population size and magnitude of transition probability.
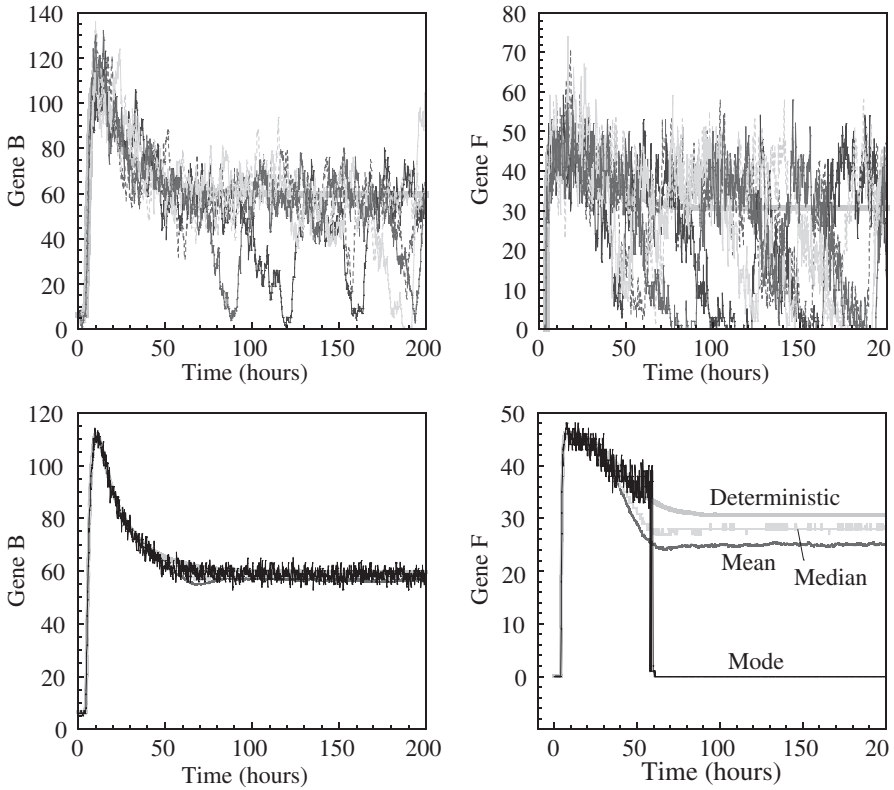
FIG. 13. Deterministic and hybrid stochastic/deterministic simulations for gene B (left) and gene F (right). For all plots: bright green thick line, deterministic simulation. For bottom plots: red line, ensemble mean; magenta line, ensemble median, black line, ensemble mode. Ensemble properties shown in these plots are computed using all 2300 hybrid simulations. Top plots: Deterministic and five representative hybrid simulation results. Note that the fluctuations increase dramatically after ~80 h simulated time, due to the 'transient adaptation' of the genes to the ligand input. Bottom graphs: Deterministic simulation results and ensemble properties versus time. Note that the mode of the distribution (black line) shows some degree of variability but remains centered around the deterministic simulation for gene B and deviates substantially from the deterministic one for gene F. The median and mean of the ensemble follow the deterministic simulation closely, but deviations for gene F are apparent despite the large number of realizations averaged. Simulations performed by D. Zak.

Two prototype reaction examples (reversible first-order and irreversible second-order kinetics) were discussed to address issues of rounding when switching from deterministic variables to stochastic (i.e., conversion of real numbers to integers), as well as the thresholds of population sizes and transition probabilities to control accuracy in the first two moments of the population (mean and variance). Other more complex examples were also mentioned. The

BioNetS software was recently published. It can perform various types of simulations in well-mixed environments (exact stochastic Gillespie method, chemical Langevin model, and deterministic ODE model) as well as hybrid deterministic simulation for some reactions coupled with exact stochastic simulation for the rest (Adalsteinsson *et al.*, 2004). The issue of time patching of hybrid schemes was touched upon, and partitioning of reactions was done based on the population size (small populations require stochastic treatment, whereas large populations are treated deterministically). Several examples, including a dimerization reaction in constant volume as well as cell growth and division, a chemical oscillator, and a synthetic gene network, were used for model validation. In a similar spirit, Kiehl *et al.* (2004) proposed hybrid multiscale simulation by combining deterministic with exact stochastic simulation. Emphasis was placed on the time patching between the two types (levels) of models and the algorithm was applied to the lambda phage switch model system.

As another example of hybrid multiscale simulation, recent work combined the Poisson-based τ-leap method of Gillespie with the next reaction method of Gibson and Bruck (2000) for reactions invoking large and small populations (Puchalka and Kierzek, 2004). This two-level method, termed the maximal time step method, is an interesting hybrid multiscale simulation where large disparity in populations can be handled efficiently while the noise is nearly exact. Furthermore, partitioning of reaction sets between the two algorithms is easy to automate. The method was applied to the simulation of glucose, lactose, and glycerol metabolism in *Escherichia coli*. Partitioning reactions as jump and continuous Markov processes, and handling them using the next reaction method and Langevin method, respectively, were also proposed by Salis and Kaznessis (2005). In their approach, reactions modeled using the Langevin method were defined as those that have a large transition probability (occur many times in the time scale of slow reactions) and slightly change the populations of reactants and products.

Burrage *et al.* (2004) provided an overview of the various methods used for modeling of chemical kinetics with emphasis on SODEs. Hybrid schemes, building on the hierarchy depicted in Fig. 3b, were again developed by combining the exact stochastic simulation method of Gillespie, the τ-leap method, and the chemical Langevin equation (first three levels of Fig. 3b). A departure from other recent hybrid simulations mentioned above is that the authors partitioned the reactions into three levels, namely, slow, intermediate, and fast. This partitioning was based not only on propensities but also on population sizes. Furthermore, they emphasized that semi-implicit or implicit solvers should be used for SODEs to cope with possible stiffness, a very reasonable proposal that was also followed by Zak *et al.* (2003). The constraint on the τ-leap time increment of the original method being sufficiently small to avoid negative concentrations (see section on temporal acceleration of KMC methods) was also brought up, and it appears that it limited, at least in part, the computational speed up to less than a factor of 2. Their hybrid simulation was applied to the

expression and activity of LacZ and LacY proteins in *E. coli* consisting of 22 reactions among 23 species. This study highlighted the point made earlier about the original τ-leap method. It would be interesting to study these examples using the new binomial τ-leap method of Chatterjee *et al.* (2005d). Furthermore, it becomes clear that while the proposed partitioning was successful, automatic, generic criteria allowing one to partition on-the-fly reactions into the various levels of models of Fig. 3b are needed. Furthermore, the adverse effect of hybrid schemes on fluctuations of shared species (Takahashi *et al.*, 2004) needs to be addressed.

As temporal upscaling methods for acceleration of KMC simulation become mature and more robust, I expect that they will have a significant impact on the modeling of biological reaction networks.

B. Spatially Distributed Systems

Spatially realistic models are important because most systems, while, not being well mixed, still comprise a small number of molecules deeming stochasticity important. The ramifications of spatial non-uniformity can be substantial. As an example, spatial variations in the receptor concentration on the membrane surface of a living cell, i.e., receptor clustering, can have important effects on downstream signaling (Duke and Bray, 1999; Goldman *et al.*, 2002; Shea *et al.*, 1997). In their review, Meng *et al.* (2004) made the comment that spatiotemporal modeling of biological systems is still infeasible. However, some papers have started to emerge. One of the first examples of spatial KMC in biological systems entails the spatial clustering of membrane receptors in bacterial chemotaxis that may lead to collective activity (Shimizu *et al.*, 2003). This is basically an Ising type of model with first nearest–neighbor interactions that trigger local spatial organization of receptors close to and below the critical temperature. Goldman and co-workers have conducted the first off-and-on lattice simulations of a single type of EGF receptor by allowing dimerization, cluster–cluster collisions, and diffusion of all cluster sizes (Goldman *et al.*, 2002; Gullick *et al.*, 2002). As discussed in Goldman *et al.* (2002), off lattice simulations are very slow even when there is no significant separation of time scales to enable a molecular-level simulation of cell receptor dynamics. Very interesting lattice KMC simulations of diffusion and dimerization events leading to spatial self-organization of the G-protein-coupled receptor family have been carried out by Woolf and Linderman (2003, 2004). Other spatially distributed biological systems modeling using KMC simulation include that of Saxton (1995, 2001) and Shea *et al.* (1997). But none of these papers have really addressed multiscale issues.

Examination of reported values of diffusion and reaction rate constants point to the inherent multiscale challenges encountered in spatiotemporal modeling of

realistic systems using molecular models (Mayawala *et al.*, 2005). What are the multiscale challenges? First, there is a huge disparity in time scales between various transport and reaction events. For example, this disparity is estimated to be at least eight orders of magnitude in the dimerization and auto-phosphorylation events of EFGR on the cell membrane. Second, a microscopic KMC simulation box ($\sim100 \times 100\,\text{nm}^2$ in 2D or $30 \times 30 \times 30\,\text{nm}^3$ in 3D) is far too small to be applied to an entire cell of $\sim10\,\mu\text{m}$ diameter, and periodic boundary conditions may be inadequate for such systems owing to the extremely low density of several features such as surface pits. The disparity in length scales is further attenuated owing to the low density of molecules, which makes the probability of collision too low. This, in turn, results in inefficient sampling and extremely long simulations that currently cannot reach experimental time scales. As a result, only simulations with judiciously chosen parameters, i.e., probabilities of similar magnitude (see Goldman *et al.* (2002)), in model systems have been carried out.

Two CG-KMC simulations for diffusion of non-interacting molecules and simple reaction mechanisms have been proposed apparently independently (Elf *et al.*, 2003; Stundzia and Lumsden, 1996) as the first multiscale spatial models for biological application. These models discretize the space into cells or elements (the latter term is more suitable here, to avoid confusion with biological cells), in exactly the same way as in the CG-KMC simulation described above. Within each element, the local mean field is assumed, and thus, the connection with the Gillespie algorithm is straightforward. A major difference between the aforementioned CG-KMC simulations of Katsoulakis *et al.* (2003a, b) and Katsoulakis and Vlachos (2003) and the work of Stundzia and Lumsden and Elf *et al.* is that in the latter, there is neither an exclusion principle nor interactions between molecules. When the chemistry is nonlinear, strong spatial correlations between molecules usually arise rendering the local mean field approximation inaccurate. Therefore, these CG-KMC models are reasonable only when the diffusion is relatively fast compared with reactions to locally homogenize the concentrations of species and establish local mean field conditions (see Chatterjee *et al.*, 2004a for an example). Under such conditions, these are local mean field models, but they include noise and are thus suitable for small populations. Obviously, this is an area to which significant multiscale efforts are expected to be devoted in future work, in order to enable spatiotemporal modeling of biological systems.

VIII. Systems Tasks

The widespread use of multiscale modeling necessitates the concomitant development of system-level tasks (see Fig. 1) for designing suitable experiments,

estimation of important parameters, reconstruction of entire reaction networks (reverse engineering), metabolic path optimization and control, model-based optimization and control of nanomaterials, to mention a few. A main difference from previous systems tasks work is that one has to extract information from spatiotemporal data of unprecedented resolution that are more noisy. At the same time, one is interested in estimating and controlling additional variables such as population size, intermolecular forces, and spatial correlations, tasks that were inconceivable a few years ago. The systems branch of multiscale simulation is at the embryonic stage, but is expected to grow rapidly. After all, the benefit of multiscale simulation is not only to provide insights into complex systems, but also to enable tasks that lead to improved performance and control. Here, a brief outline of some recent progress on systems-level tasks is provided. Perspectives on systems tasks have appeared recently (Braatz *et al.*, 2004; Christofides, 2001; Kevrekidis *et al.*, 2004).

A. Sensitivity and Identifiability Analyses

One of the most important tools in complex systems modeling and analysis is sensitivity analysis (SA) (Tomlin *et al.*, 1997; Varma *et al.*, 1999). In order to carry out SA, system responses (R) have to be defined first. These responses are system specific, and some may be experimentally measurable whereas others may not. For example, in developing gas-phase combustion mechanisms, the ignition delay time, the flame speed, flammability limits, and concentrations of major and some radical species are common responses. These responses are actually obtained with different types of experiments, such as shock tubes, flame-propagation experiments in wide tubes, continuous flow jet stirred reactor or one-dimensional burner flame species measurements. In a typical catalytic reactor on the other hand, conversion and selectivity are two key responses. Pollutant mole fractions, explosion limits for safety, and hot spots are just some additional responses. Lastly, in advanced materials and pharmaceuticals growth, the primary concerns are different: making the right material (e.g., the correct polymorph) with specific particle morphology (habit), high growth rate, appropriate roughness, controllable fraction of defects, etc. is the main goal.

I expect that SA of stochastic and multiscale models will be important in traditional tasks such as the identification of rate-determining steps and parameter estimation. I propose that SA will also be a key tool in controlling errors in information passing between scales. For example, within a multiscale framework, one could identify what features of a coarse-level model are affected from a finer scale model and need higher-level theory to improve accuracy of the overall multiscale simulation. Next a brief overview of SA for deterministic systems is given followed by recent work on SA of stochastic and multiscale systems.

1. Sensitivity Analysis of Deterministic Systems

SA determines the change in a response R as a result of a perturbation in one of the parameters P of the model. Parameters of a model can be any conceivable ones. For example, in a MD simulation, parameters could be all factors appearing in the intermolecular potential. Since the magnitude of various parameters can be very different, it is common to compute a normalized sensitivity coefficient (NSC) defined as

$$\text{NSC}_{ij} = \frac{\mathrm{d}\ln R_i}{\mathrm{d}\ln P_j} = \frac{P_i}{R_j}\frac{\mathrm{d}R_j}{\mathrm{d}P_i} \approx \frac{P_i}{R_j}\frac{R_j(P_i + \Delta P_i) - R_j(P_i)}{\Delta P_i} \tag{9}$$

The last approximate equality is simply a forward finite difference approximation of the derivative (higher order, more accurate approximations can obviously be used). The partial derivative simply indicates the slope, i.e., the change in a response for an infinitesimal change in a parameter. When the partial derivative is computed by differentiation of the response function, the SA is termed *local* SA. On the other hand, when the parameter is changed and the response is recomputed by solving the entire problem, the SA is termed *brute force*. Brute force SA is straightforward. However, a perturbation must be performed for each parameter, leading to prohibitive computational costs, especially when the number of parameters is large and the simulation is expensive. This is typically the case with multiscale codes.

2. Sensitivity Analysis of Stochastic and Multiscale Models

SA of SODEs describing chemically reacting systems was introduced early on, in the case of white noise added to an ODE (Dacol and Rabitz, 1984). In addition to expected values (time or ensemble average quantities), SA of variances or other correlation functions, or even the entire pdf, may also be of interest. In other words, in stochastic or multiscale systems one may also be interested in identifying model parameters that mostly affect the variance of different responses. In many experimental systems, the noise is due to multiple sources; as a result, comparison with model-based SA for parameter estimation needs identification of the sources of experimental noise for meaningful conclusions.

One of the difficulties in performing SA of stochastic or more generally multiscale models is that a closed form equation does not often exist. As a result, brute force SA has so far been the method of choice, which, while possible, is computationally intensive. As suggested in Raimondeau *et al.* (2003), since the response obtained is noisy, one has to introduce relatively large perturbations to ensure that the responses are "reliable," so that meaningful SA results are obtained. For most complex systems, local SA may not be feasible. However, I do not see this being an impediment since SA is typically used to rank-order the

importance of model parameters (see section on parameter estimation for a different use of SA).

In our group we have used SA in lattice 2D and 3D KMC in order to identify key parameters for parameter estimation from experimental data (see corresponding section below). Finite difference approximations of NSC were employed (Raimondeau et al., 2003; Snyder and Vlachos, 2004). Drews et al. (2003a) motivated by extraction of parameters for Cu electrodeposition, obtained an expression for the sensitivity coefficient, analogous to Eq. (9), that minimizes the effect of noise on the NSC assuming that the variance of the stochastic correction is unaffected by the perturbation.

In order to elucidate some of the issues in SA of stochastic systems, the gene-expression model proposed in Thattai and van Oudenaarden (2001) and Ozbudak et al. (2002) for transcription and translation, shown schematically in
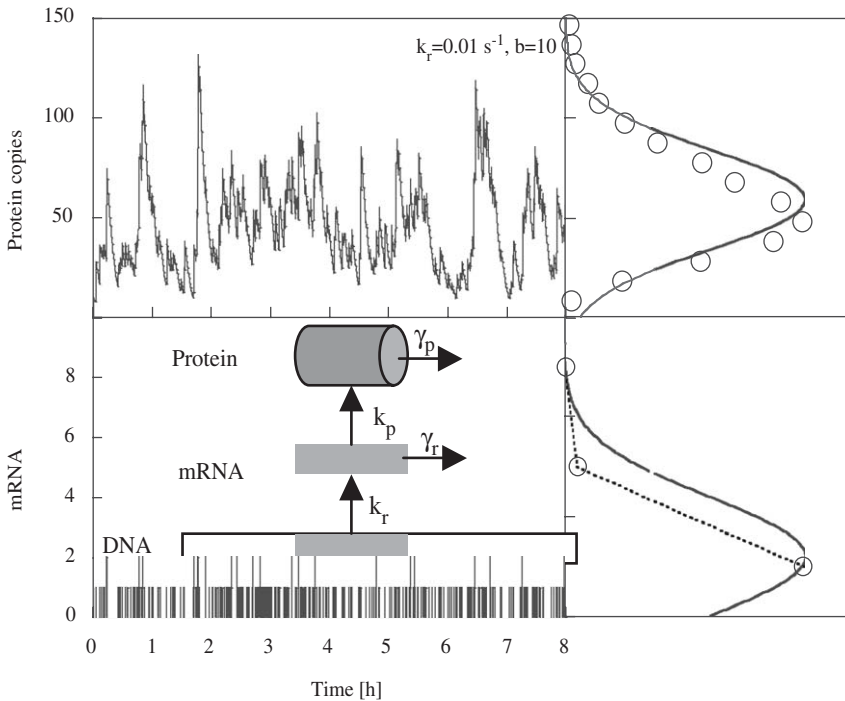

Fig. 14. Simulation of gene expression depicting the number of protein copies and mRNA as well as the corresponding pdf. While a normal distribution describes reasonably the population of protein, the pdf of the mRNA, whose population is very low, is far from Gaussian (solid lines on the right panels). The parameters are: transcript initiation rate $k_r = 0.01 \, \text{s}^{-1}$, decay rates of $\gamma_r = 0.1 \, \text{s}^{-1}$ and $\gamma_p = 0.002 \, \text{s}^{-1}$, and $b = 10$. The deterministic steady-state values are $\langle r \rangle = 0.1$, $\langle p \rangle = 50$. The inset is a schematic of the gene expression process.

the inset of Fig. 14, is studied. At the deterministic, continuum level, the concentrations of mRNA (r) and protein (p) are given by the following ODEs:

$$\frac{\mathrm{d}r}{\mathrm{d}t} = k_r - \gamma_r r \tag{10}$$

$$\frac{\mathrm{d}p}{\mathrm{d}t} = k_p r - \gamma_p p \tag{11}$$

where γ denotes the rate of decay ($\ln(2)/\gamma$ is the half-life time) and k is the rate constant for transcription or translation. The steady-state solution is $\langle r \rangle = k_r/\gamma_r$ and $\langle p \rangle = k_p k_r/(\gamma_p \gamma_r) = b k_r/\gamma_p$, where $b = k_p/\gamma_p$ is the average number of proteins produced per transcript. For this linear system, it is relatively easy to show that the variance over the mean (termed the Fano factor) is given by

$$\frac{\langle \delta p^2 \rangle}{\langle p \rangle} = 1 + k_p/(\gamma_p + \gamma_r) \tag{12}$$

Typically, γ_p/γ_r is small (the mRNA is unstable compared to the protein).

Single stochastic trajectories obtained using Gillespie's KMC algorithm are shown in Fig. 14 for the protein and the mRNA levels vs. time. The corresponding pdfs are also shown. Figure 15 shows the dependence of copies of mRNA and proteins along with the variance of proteins on k_r. Using the steady solution of deterministic equations, the NSC with respect to k_r (chosen parameter for illustration) can be easily computed to be 1. In order to exploit the accuracy of computed NSCs, central second-order and forward or backward
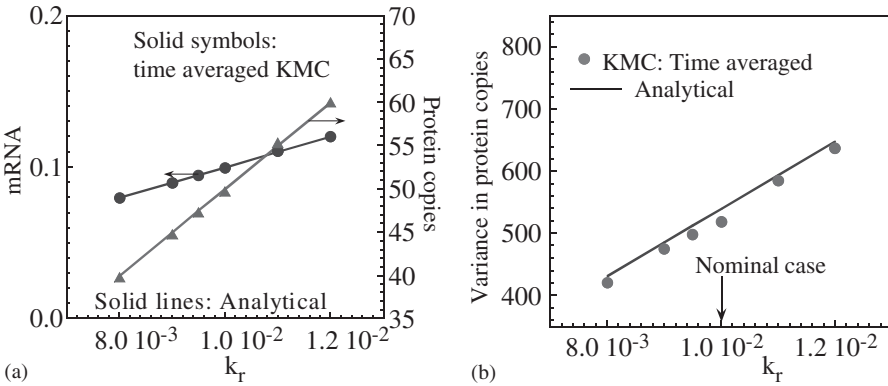

FIG. 15. (a) Expected values of mRNA and protein from a KMC simulation computed as time averaged (filled symbols), along with the corresponding values from the deterministic gene-expression model (solid lines) as a function of k_r. (b) Corresponding variance in protein copies. Time-averaged population and variance are in very good agreement with the analytical solution for this linear model despite the low number of protein and mRNA copies. The rest of the parameters are those of Fig. 14.
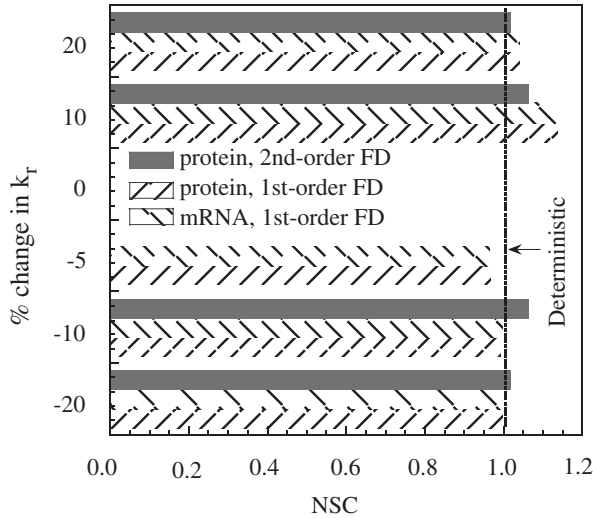
FIG 16. NSC for protein and mRNA copies for different size perturbations in k_r when time-averaged concentrations are used. First-order (forward or backward) and central finite difference approximations are used. The deterministic NSC for both species is 1 (vertical dashed line).

first-order finite difference approximations were employed, and the results are depicted in Fig. 16. Owing to the inherent noise, the different methods make little difference in the value of NSC, at least using steady-state data from a single KMC trajectory and the perturbation sizes indicated (expected values are typically computed from a total of 10^6–10^9 MC events to ensure very good statistics). That is, there is no specific, clear-cut trend regarding accuracy in computing NSCs. From a fundamental point of view, it is obviously desirable to understand how many simulations and what simulation sizes are needed to improve accuracy. Future work should explore this issue in detail.

Doyle and co-workers have used sensitivity and identifiability analyses in a complex genetic regulatory network to determine practically identifiable parameters (Zak et al., 2003), i.e., parameters that can be extracted from experiments with a certain confidence interval, e.g., 95%. The data used for analyses were based on simulation of their genetic network. Different perturbations (e.g., step, pulse) were exploited, and an identifiability analysis was performed. An important outcome of their analysis is that the best type of perturbations for maximizing the information content from hybrid multiscale simulations differs from that of the deterministic, continuum counterpart model. The implication of this interesting finding is that noise may play a role in systems-level tasks.

3. Hierarchical Approaches to Sensitivity Analysis

A hierarchical approach could be an efficient way of reducing the CPU requirements for performing systems-level tasks. In my experience, mean field or

continuum models, while not as accurate, provide a qualitatively picture of sensitivity when the model itself is qualitatively correct (Raimondeau *et al.*, 2003; Snyder and Vlachos, 2004). Mean field-based SA could be used in various ways. First, SA of a mean field model could identify key processes controlling a system. Second, optimization of parameters of a stochastic model can be done by first optimizing the parameters of the mean field model. These optimized parameters could serve as a good initial guess for optimizing the parameters of a KMC or multiscale model. The advantage of this hierarchical approach is that it narrows down the parameter space where an optimum parameter search has to be conducted for a stochastic or multiscale model. Obviously, this idea is based on the premise that the optimum set of parameters of the stochastic or multiscale model is close to that of the corresponding continuum model. This looks to be the case in several examples explored by our group so far. However, it is expected to fail when mean field models are qualitatively different from stochastic or multiscale models.

The evolution equation of the sensitivity of the chemical master equation, along with a first-order deterministic approximation of the sensitivity of the mean, was recently derived in Haseltine (2005). In a similar spirit, the SA evolution equations in MD simulations were developed in Stefanovic and Pantelides (2001). Haseltine *et al.* suggested computing the mean using the KMC method and the sensitivity evolution of the mean through the deterministic first-order approximation. This is an improvement over simply using the SA of the mean field model mentioned above. The advantage of this hierarchical, hybrid approach is that the sensitivity is a smooth function of time, an important aspect for many systems tasks, and less expensive to compute. For the examples considered in a batch reactor by Haseltine (2005), the deterministic approximation gave a smooth evolution of the sensitivity that works very well for linear systems, and shows moderate deviations from the exact sensitivity for nonlinear systems. From the prolegomena it is clear that hierarchical methods have significant potential for accomplishing systems tasks at reduced computational cost.

B. Parameter Estimation from Experimental Data and Finer Scale Models

One question that arises is: if one uses multiscale simulation to predict systems behavior from first principles, then why does one need to carry out parameter estimation from experimental data? The fact is that model predictions using even the most accurate QM techniques have errors. In the foreseeable future, one would have to refine parameters from experiments to create a fully quantitative multiscale model. Furthermore, for complex systems, QM techniques may be too expensive to carry out in a reasonable time frame. As a result, one may rely on estimating parameters from experimental data. Finally, an important, new class of problems arises when one has to estimate parameters of

a coarser scale model in order to minimize the difference in predictions (in some proper measure) from the ones of the finer scale model.

Parameter estimation is a very mature subject for continuum, deterministic models and is an integral part of reverse engineering. In general, a cost function, such as the Euclidean distance between modeling results and experimental observables, is formulated. For deterministic systems, this is sufficient. For multiscale models, however, a cost function for expected values may not be enough. For example, in a stochastic simulation one would like to fit the entire pdf, described by a Fokker–Planck equation. However, the pdf is known only for a limited number of rather trivial problems, and its calculation is computationally impractical. Practically, one may extend the approach of deterministic systems to stochastic or multiscale models by including, aside from expected values, additional quantities such as variances. While this is possible, including variance into the objective function requires hundreds to thousands of trajectories, rendering parameter estimation very time-consuming (Fullana and Rossi, 2002). In passing, I should note an overview of parameter estimation of stochastic differential equations based on maximum approximate likelihood ideas given in Nielsen *et al*. (2000). Some additional complications in parameter estimation are due to the large number of parameters of multiscale models and the noisy results arising from molecular models. The introduction of high throughput experiments or combinatorial methods opens up the possibility of creating massive data sets for parameter estimation. However, one may not be able to extract useful information for all parameters. It is important that the relevant parameters get extracted.

Rawlings and co-workers proposed to carry out parameter estimation using Newton's method, where the gradient can be cast in terms of the sensitivity of the mean (Haseltine, 2005). Estimation of one parameter in kinetic, well-mixed models showed that convergence was attained within a few iterations. As expected, the parameter values fluctuate around some average values once convergence has been reached. Finally, since control problems can also be formulated as minimization of a cost function over a control horizon, it was also suggested to use Newton's method with relatively smooth sensitivities to accomplish this task. The proposed method results in short computational times, and if local optimization is desired, it could be very useful.

Since complex systems most probably exhibit complicated surfaces with multiple minima, convergence may not be obtained using local searching techniques, and the probability of obtaining the global optimum with local optimizers is low. Alternatively, one can employ global-type optimization methods, such as simulated annealing and genetic algorithms. While these techniques are often successful in determining the global minimum, they require hundreds of thousands of function evaluations, i.e., KMC or multiscale simulations. Such a task is impractical. To overcome this challenge we have proposed to develop reduced models or surfaces approximated by low-order degree polynomials using solution mapping or surface response methods typically

employed in design of experiments. This idea leads to a relatively smooth surface that can be used in optimization (Raimondeau *et al.*, 2003). Hierarchical parameterization where the mean field model parameters are estimated first and serve as an initial guess for optimization of the molecular or multiscale model parameters offer an attractive approach for constructing accurate surfaces.

The first application of hierarchical SA for parameter estimation included refinement of the pre-exponentials in a surface kinetics mechanism of CO oxidation on Pt (a lattice KMC model with ~6 parameters) (Raimondeau *et al.*, 2003). A second example entailed parameter estimation of a dual site 3D lattice KMC model for the benzene/faujasite zeolite system where benzene–benzene interactions, equilibrium constants for adsorption/desorption of benzene on different types of sites, and diffusion parameters of benzene (a total of ~15 parameters) were determined (Snyder and Vlachos, 2004). While this approach appears promising, the development of accurate but inexpensive surfaces (reduced models) deserves further attention to fully understand its success and limitation.

C. Model Reduction and Control

Online multiscale model-based control is beyond current computer capabilities owing to the computational intensity of multiscale simulation. Two approaches are proposed to enable control at the nanometer scale using multiscale simulation. The first entails a suitable model reduction, where the full multiscale model is effectively mapped into an approximate surface that is subsequently used in process design and control. Toward this goal, proper-orthogonal decomposition was explored to derive a small number of modes (space dimension), i.e., spatially global eigenfunctions, to form a basis that captures spatiotemporal computer data. While this is indeed possible, we have found that the noise of KMC or multiscale simulations renders model reduction challenging Raimondeau and Vlachos (2000). In a way, microscopic surface processes have slower dissipation mechanisms than fluid-phase processes, and as a result, noise-induced phenomena, such as nucleation, demand many modes for accurate reduction. It appears then that a second strategy based on optimum design, where one designs the system using a multiscale model to behave in a desirable manner, may be more suitable than online control. This is also underscored by the current lack of easy implementation of sensors and actuators operating at the nanoscopic scale the way their macroscopic counterparts work at the large scale. While materials engineering could possibly overcome this problem in the future, at least in part, manipulating a few input and output coarse variables may still remain the only viable way for many processes. A similar view is shared by Braatz and co-workers (2004). However, further work is needed to delineate the necessity of online control and the suitability of various model reduction tools for this task.

Aside from proper orthogonal decomposition, alternative model reduction strategies have also been explored. For a simple reaction network with a species in QSS, a reduced description of the master equation has been successful by applying the projection operator formalism (Shibata, 2003), and subsequently applied to a simple gene expression network. An advantage of this theoretical study is that it provides insight into how the noise of the eliminated species affects the population of the other species. However, extension of such theoretical analysis to complex reaction networks is not straightforward. Reduction of the master equation was also carried out, and the reduced model was used to determine open-loop temperature profiles for epitaxial growth (Gallivan and Atwater, 2004; Gallivan and Murray, 2003, 2004).

One of the objectives of model reduction is the possibility of carrying out model-based control. Some initial, promising efforts along this direction have already appeared. Control of surface roughness and growth rate in hybrid KMC/stagnation flow simulations of epitaxial growth mentioned above was demonstrated by employing integral control in Lou and Christofides (2003a, b, 2004). In particular, the overall approach employed real-time estimators from KMC (using multiple, small KMC simulation boxes), filters to reduce the noise of KMC, and error compensators followed by feedback controllers. In an alternative approach, a time stepper method was used to derive an optimal control policy for reactions (modeled by the LB technique or a well-mixed KMC model to stabilize an unstable open-loop state) or to derive a local linearization of a stochastic model that was subsequently employed in linear control theory (Armaou et al., 2004; Siettos et al., 2003).

Systems approach borrowed from the optimization and control communities can be used to achieve various other tasks of interest in multiscale simulation. For example, Hurst and Wen (2005) have recently considered shear viscosity as a scalar input/output map from shear stress to shear strain rate, and estimated the viscosity from the frequency response of the system by performing short, non-equilibrium MD. Multiscale model reduction, along with optimal control and design strategies, offers substantial promise for engineering systems. Intensive work on this topic is therefore expected in the near future.

D. BIFURCATION

Many systems exhibit nonlinear behavior. This is another systems-level task that is computationally very demanding. Application of bifurcation analysis to simple and complex chemistry hybrid stochastic (KMC)-deterministic (ODE) models has been presented by our group (Raimondeau and Vlachos, 2002b, 2003; Vlachos et al., 1990) for various catalytic surface reactions. Prototype hybrid continuum-stochastic models that exhibit bifurcations were recently explored by Katsoulakis et al. (2004). It was found that mesoscopic

models based on the stochastic averaging principle are excellent approximations of fully stochastic models when there is disparity in relaxation times of microscopic (fast) and flow (slow) processes. Multiple states in tropical convection model prediction were reported in Majda and Khouider (2002). Kevrekidis and co-workers have been successful in applying time steppers in constructing bifurcation diagrams of stochastic simulation such as KMC (e.g., Makeev *et al.*, 2002). One of the advantages of their method is that unstable branches and bifurcation points can be computed, a task that is difficult with direct KMC simulation. On the other hand, it is expected that the stabilization has an adverse effect on understanding metastability and transitions between states of small systems.

IX. Outlook

The multiscale simulation framework presented here is generic and can be applied across multiple disciplines and problems of chemical sciences. Obviously, specific scientific problems may be amenable to special twists. While substantial progress in multiscale analysis has already been achieved, the emerging field is still at an embryonic stage; many exciting developments are expected in the next decade. The area of systems tasks is by far the least developed. However, the significantly increasing number of presentations at the AIChE meeting (in area 10d) is an indicator of the explosion of the new field and the exciting contributions of the systems community to the design and control of complex systems via multiscale modeling and simulation. A central theme in multiscale modeling, as one moves from finer to coarser scales, is model reduction. While universal approaches to model reduction may not exist or even be desirable, robust reduction methodologies along with methods of assessing the resulting errors of coarse graining for various types of multiscale simulation are needed.

I believe that growth in a number of critical areas of technological importance to the nation, such as nanotechnology, biotechnology, and microengineering, will be accelerated and catalyzed by the new multiscale modeling and computational paradigm. In all these and other areas of chemical sciences, as alluded to in the introduction, multiscale analysis could have the most significant engineering impact in top-down and reverse engineering modes. While multiscale analysis research is multidisciplinary and is currently conducted, in many cases, in a collaborative manner, training of future undergraduate and graduate students on these topics is also important. Graduate and undergraduate education is at a crossroads (Cussler *et al.*, 2002; Dudukovic, 2003), and modern and in many cases undeveloped tools need to be taught in efficient ways for preparing students for the modeling challenges arising from the new technologies. To achieve this goal, there is a clear need for revision of core courses to incorporate

elements of multiscale analysis and for development of new multiscale modeling and simulation courses.

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