Perspective

Equation-Free: The Computer-Aided Analysis of Complex Multiscale Systems

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The best available descriptions of systems often come at a fine level (atomistic, stochastic, microscopic, agent based), whereas the questions asked and the tasks required by the modeler (prediction, parametric analysis, optimization, and control) are at a much coarser, macroscopic level. Traditional modeling approaches start by deriving macroscopic evolution equations from microscopic models, and then bringing an arsenal of computational tools to bear on these macroscopic descriptions. Over the last few years with several collaborators, we have developed and validated a mathematically inspired, computational enabling technology that allows the modeler to perform macroscopic tasks acting on the microscopic models directly. We call this the "equation-free" approach, since it circumvents the step of obtaining accurate macroscopic descriptions. The backbone of this approach is the design of computational "experiments". In traditional numerical analysis, the main code "pings" a subroutine containing the model, and uses the returned information (time derivatives, etc.) to perform computer-assisted analysis. In our approach the same main code "pings" a subroutine that runs an ensemble of appropriately initialized computational experiments from which the same quantities are *estimated*. Traditional continuum numerical algorithms can, thus, be viewed as protocols for experimental design (where "experiment" means a computational experiment set up, and performed with a model at a different level of description). Ultimately, what makes it all possible is the ability to initialize computational experiments at will. Short bursts of appropriately initialized computational experimentation -through matrix-free numerical analysis, and systems theory tools like estimation- bridge microscopic simulation with macroscopic modeling. If enough control authority exists to initialize laboratory experiments "at will" this computational enabling technology can lead to experimental protocols for the equation-free exploration of complex system dynamics.

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The Equation-Free Approach

A persistent feature of many complex systems is the emergence of macroscopic, coherent behavior from the interactions of microscopic agents such as molecules, cells, or individuals in a population. The implication is that macroscopic rules (a description of the system at a coarse-grained, high level) can somehow be deduced from microscopic ones (a description at a much finer level). For laminar Newtonian fluid mechanics, a successful coarse-grained description (the Navier-Stokes equations) was known on a phenomenological basis long before its approximate derivation from kinetic theory. Today, we must frequently study systems for which the physics can be modeled at a microscopic, fine scale; yet, it is practically impossible to derive a good macroscopic description from the microscopic rules. Hence, we look to the computer to explore the macroscopic behavior, based on the microscopic description.

It is difficult to define complexity in a precise, useful way, yet it pervades current modeling in engineering science, in the life and physical sciences (see, e.g., Ottino (2003)), and beyond (e.g., economics). We may not think of laminar Newtonian flow as complex, even though it involves interactions of enormous numbers of fluid molecules with themselves and with the flow boundaries. Such problems are *considered* simple because we have a good model, describing the behavior of the system *at the level we need for practical purposes*. If we are interested in pressure drops and flow rates over humanly relevant space and time scales, we do not need to know the location and velocity of each and every molecule. Similarly, if a stirred chemical reactor can be modeled adequately, for design purposes, by a few ordinary differential equations (ODEs), the immense complexity of molecular interactions involved in flow, reaction, and mixing goes unnoticed. The system is *classified* as simple, because a simple model of the behavior is adequate for practical purposes. This suggests that the scale of the observer, and the practical goals of the modeling, are crucial in classifying a system as simple — or complex.

Macroscopic models of reaction and transport processes come in the form of conservation laws (species, mass, momentum, and energy) closed through constitutive equations (reaction rates as a function of concentration, viscous stresses as functionals of velocity gradients). These models are written *directly* at the scale at which we are interested in practically modeling the system behavior. Because we *observe* the system at the level of concentrations or velocity fields, we sometimes forget that what evolves during an experiment is distributions of colliding and reacting molecules. We know from experience that it is possible to write predictive deterministic laws for the behavior (over space and timescales useful in engineering practice) at the level of concentrations or velocity fields. Knowing the right level of observation at which we can be *practically predictive*, we attempt to write closed evolution equations for the system at this level. The closures may be based on experiment (e.g., through engineering correlations), or on mathematical modeling and approximation of what happens at more microscopic scales (e.g., the Chapman-Enskog expansion). In many problems of current modeling practice, ranging from materials science to ecology, and from engineering to computational chemistry, the physics are known at the microscopic/individual level, and the closures required to translate them to high-level descriptions, are not available. Sometimes we do not even know *at what level of observation* one can be practically predictive. Severe computational limitations arise in trying to bridge the enormous gap between the scale of the available description and the macroscopic, "system" scale at which modeling questions are asked and practical answers are required (see, e.g. Maroudas, 2000; Lu and Kaxiras, 2004). These computational limitations are a major stumbling block in current complex system modeling.

Our objective is to develop a computational approach for studying the *simple* collective, coarse-grained behavior of any *complex*, multiscale system, when we know in principle how to model such systems at a very fine scale (e.g., through molecular dynamics). We assume that we do not know how to write *simple* model equations at the right macroscopic scale for their collective, coarse grained behavior. We will argue that, in many cases, the derivation of macroscopic equations can be circumvented: by using short bursts of appropriately initialized

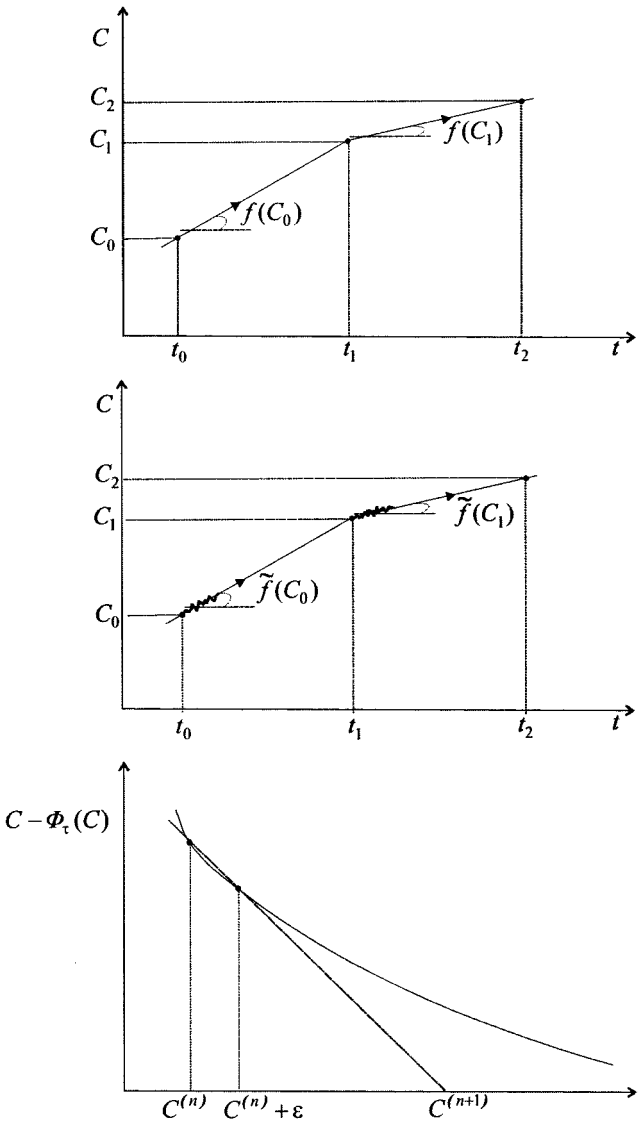

Figure 1. Forward Euler (a) as a template for projective integration using the results of short experiments (b); fixed-point iteration for a timestepper (c).

microscopic simulation, one can effectively solve the macroscopic equations *without ever writing them down*, and build a direct bridge between microscopic simulation and traditional continuum numerical analysis. It is, thus, possible to enable microscopic simulators to directly perform macroscopic, systems level tasks. The main idea is to consider the microscopic simulator as a (computational) experiment that one can initialize and run at will. The results of such appropriately designed, initialized, and executed brief computational experiments, allow us to *estimate* the same information that a macroscopic model would let us *evaluate* from explicit formulas.

The heart of the approach can be conveyed through a simple example (see Figure 1). Consider

$$\frac{dc}{dt} = f(c)$$

as a model of a reactant concentration in a stirred reactor. Given a finite amount of information (the state at the present time, c(t=0)), we can predict the state at a future time. Consider the simplest computational scheme for this, forward Euler

$$c_{n+1} \equiv c([n+1]\tau) = c_n + \tau f(c_n).$$

Starting with the initial condition c_0, we *go to the equation* and *evaluate* $f(c_0)$, the slope of the trajectory c(t); we use this value to make a prediction of the system state at the next time step c_1. We then repeat the process. Consider how the equation is used: given the state we *evaluate* the time derivative; then, using mathematics (in particular, Taylor series and smoothness to create a local linear model of the process in time), we make a prediction of the state at the next time step. A numerical integration code will "ping" a subroutine to obtain the time-derivative of the current state. The code will then process this value, and use local Taylor series to make a prediction of the next state. Three simple things are important to notice. First, the *task* at hand (numerical integration) does not need a closed formula for f(c) — it only needs f(c) evaluated at a particular sequence of values c_n. Whether the subroutine evaluates f(c) from a single-line formula, uses a table lookup, or solves a large subsidiary problem, from the point of view of the integration code, it is the same thing. Second, the sequence of values c_n at which we need the time derivative evaluated is not known *a priori*. It is evaluated as the task progresses, *from processing results of previous function evaluations.* We know protocols for designing experiments to accomplish tasks, such as parameter estimation (Box et al., 1978). In the same spirit, we can think of the Euler method, and of explicit numerical integrators in general, as *protocols for specifying where to perform function evaluations,* based on the task we want to accomplish (computation of a temporal trajectory). Lastly, the form of the protocol (the Euler method here) is based on mathematics, particularly on smoothness (Taylor series). The trajectory is locally approximated as a linear function of time; the coefficients of this function are obtained from the model using *function evaluations.*

Suppose now that we do not have the equation, but *we have the experiment itself*: we initialize the stirred reactor at concentration c_0, run and record the time series of c(t). With the results of a short run (over, say, 1 min), we can *estimate* dc/dt at t=0, and predict (using the Euler method), where the concentration will be in, say, 10 min. Now, instead of waiting for 9 min for the reactor to get there, we stop the experiment and immediately start a new one: reinitialize the reactor *at the predicted concentration;* run for one more minute, and use forward Euler to predict what the concentration will be 20 min down the line. We are substituting short, appropriately initialized experiments, and *estimation* based on the experimental results, for the function evaluations that the subroutine with the closed form f(c) would return. We are in effect doing forward Euler again; but the coefficients of the local linear model are obtained using experimentation *on demand* (Cybenko, 1996) rather than function evaluations of an *a priori* available model.

Many elements of this example are contrived and may appear laughable. The point, however, remains: it is possible to do forward Euler integration, using short bursts of appropriately initialized experiments *if it is easy to initialize such experiments at will.* An "outer" process (design of the next experiment, setting it up, measuring its results, processing them to design a new experiment) is wrapped around an "inner" process (the experiment). The outer wrapper is motivated by the task that we wish to perform (here, long-time integration), and is based on traditional, continuum numerical analysis. The inner layer is the process itself. It is clear that systems theory components (data acquisition and filtering, model identification, Ljung (1999)) are vital in forming the connection between the outer layer and the inner layer (the task we want to accomplish and the system itself).

Now, we complete the argument: suppose that the inner layer is not a laboratory experiment, but a *computational* model, such as a lattice kinetic Monte Carlo, kMC. Instead of running the kMC model for long times, and *observing* the evolution of the concentration, we can exploit the procedure described earlier, perform only short bursts of appropriately initialized microscopic simulation, and use their results to evolve the macroscopic behavior over much longer timescales. The conceptual point is: even if we do not have the right macroscopic equation for the concentration, we can still *perform its numerical integration* without obtaining it in closed form. The skeleton of the wrapper (the integration algorithm) is the same one we would use if we had the macroscopic equation; but, now function evaluations are replaced by short computational experiments with the microscopic simulator. If a large separation of timescales exists between microscopic dynamics (here, the time we need to run kinetic Monte Carlo to estimate dc/dt), and the macroscopic evolution of the concentration, this procedure may be significantly more economical than direct simulation.

Passing information between the microscopic and macroscopic scales at the beginning and the end of each computational experiment is a vitally important issue. It is accomplished through a *lifting operator* (macro- to micro-) and a *restriction operator* (micro- to macro-), as discussed below (Theodoropoulos et al., 2000; Kevrekidis et al., 2003, and references therein). Detailed, fine-level dynamics are typically given in terms of microscopically and stochastically evolving distributions of interacting "agents" (molecules, cells); the evolution rules could be molecular dynamics (classical, or Car-Parrinello, (Car and Parrinello, 1985)), MC or kMC, Brownian dynamics, etc. The macroscopic dynamics are described by closed evolution equations, typically ordinary (for macroscopically lumped), or partial differential and integrodifferential equations. The *dependent variables* in these equations are frequently *a few, lower order moments* of the evolving distributions (such as concentration, the zeroth moment). The proposed computational methodology consists of the following elements:

(a) Choose the statistics for describing the long-term behavior of the system, and their representation. For example, in a gas simulation at the particle level, the statistics would probably be density and momentum (zeroth and first moment of the particle distribution over velocities), and we might choose to discretize them in a computational domain via finite elements. We call this the macroscopic description $\mathbf{u}$. These choices suggest possible *restriction* operators $\boldsymbol{M}$, from the microscopic-level description $\mathbf{U}$, to the macroscopic description: $\mathbf{u} = \boldsymbol{M}\mathbf{U}$;

(b) Choose an appropriate *lifting* operator $\boldsymbol{\mu}$, from the macroscopic description $\mathbf{u}$, to a set of (possibly one) consistent

microscopic descriptions **U**. For example, in a gas simulation using pressure etc., as the macroscopic-level variables, $\boldsymbol{\mu}$ could make random particle assignments consistent with the macroscopic statistics. $\boldsymbol{\mu M} = I$, i.e., lifting from the macroscopic to the microscopic, and then restricting (projecting) down again, should have no effect, except roundoff.

(c) Start with a macroscopic condition (e.g., concentration profile) $\mathbf{u}(t_0)$;

(d) Transform it through lifting to *consistent* microscopic realizations $\mathbf{U}(t_0) = \boldsymbol{\mu}\mathbf{u}(t_0)$;

(e) Evolve these realizations using the microscopic simulator for the desired short macroscopic time T, generating the value(s) **U**(T).

(f) Obtain the restrictions $\mathbf{u}(T) = \boldsymbol{M}\mathbf{U}(T)$, and average over them.

This constitutes the *coarse time-stepper*, or *coarse time-T map*. If this map is accurate enough, we showed earlier how to use it in a two-tier procedure to perform *Coarse Projective Integration* (Gear and Kevrekidis, 2003; Gear, 2001; Gear et al., 2002).

The lifting step (creating microscopic distributions, conditioned on a few of their lower moments, going back to Ehrenfest, 1911) is clearly not unique: consider for example, creating a distribution of particles on a lattice that has prescribed average and pair probabilities. A preparatory step (e.g., through simulated annealing) may be required to arrange the particles on the lattice consistently with the prescribed constraints. Through such appropriate preparation, one can even lift prescribed pair-correlation functions to consistent particle assemblies. Constrained dynamics algorithms, like SHAKE (Ryckaert, 1977), can also be thought of as lifting procedures.

An important point made in Figure 2a is that an initial interval must elapse before estimating the time derivative of the macroscopic variables from the microscopic simulation. In the microscopic dynamics, every particle evolves while interacting with other particles, and the moments of the distribution evolve in a coupled manner. Remarkably, practically predictive models are usually written in terms of *only a few* moments of these evolving distributions. This is only possible because the remaining higher-order moments quickly become functionals of the few, lower-order, slow, "master" moments —our observation variables. This occurs over timescales that are short, compared to the macroscopic observation timescales. In this separation of timescales (and concomitant space scales), lies the essential reduction step, underpinning effective simplicity and practical determinism. The long-term observable dynamics of the system evolve on a low-dimensional, strongly attracting, *slow manifold* in moments space; this is, effectively, a quasi-steady state approximation (Bodenstein, 1913). This manifold is parameterized by our observation variables (typically, the lower distribution moments, such as concentration), in terms of which we write macroscopic equations. The expected values of the remaining moments can be written as an (unspecified) function of the coarse variables; that is, the graph of the manifold. A good example is provided by Newtonian viscosity: when one starts a molecular simulation, the stresses are not instantaneously proportional to velocity gradients — but for Newtonian fluids, they become so within a few collision times, i.e., over times much shorter than the macroscopic observation times, over which the Navier-Stokes equations become valid approximations. The coarse variables are, therefore, *observation variables*. If the fine scale simulation, conditioned on values of the observation variables, is initialized "off manifold" it only takes a fast initial transient to approach a neighborhood of this manifold. Through the restriction operator, we observe the dynamics on the hyperplane spanned by our chosen observation variables. After the system quickly relaxes to the manifold, we estimate the time-derivative of the observation variables, and use it in projective integration. The dynamics of the full system will then, after lifting and a short integration, spontaneously establish (by bringing us to the manifold) *the missing closure*, that is, the effect of the full description on the

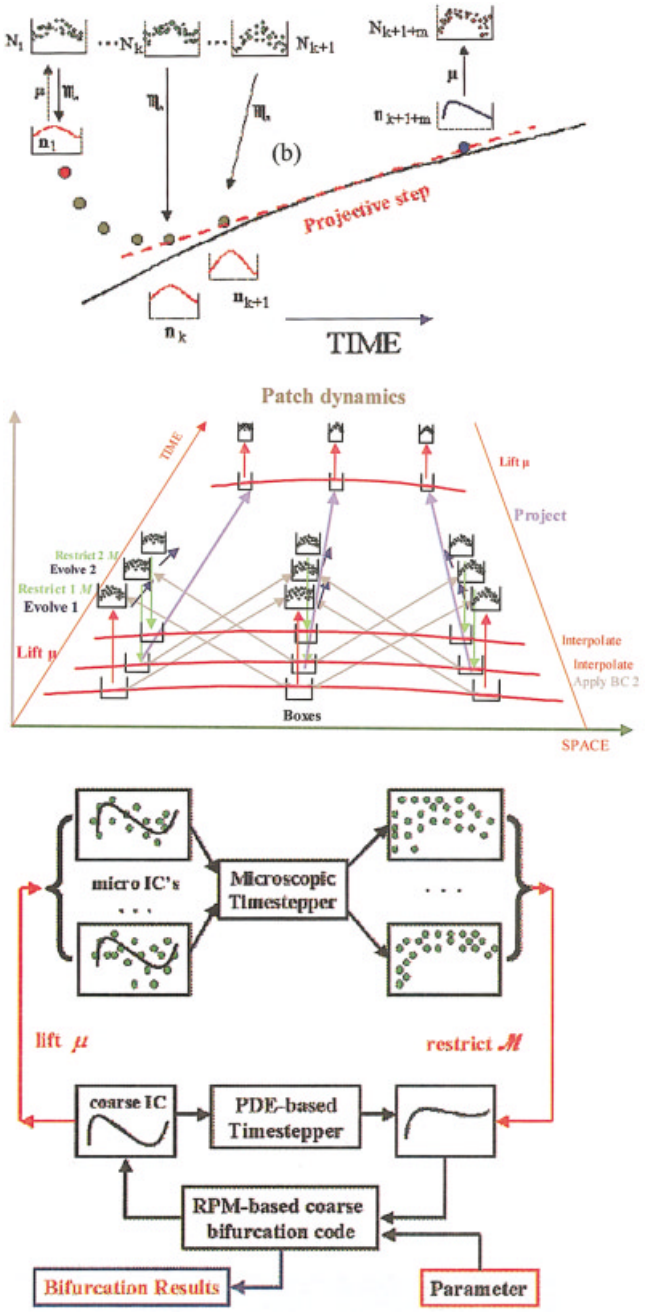

Figure 2. (a) Coarse projective integration; (b) patch dynamics; and (c) coarse timestepper-based bifurcation computations (see text).

observed dynamics. A direct conceptual analogy arises with center manifolds in dynamical systems (parameterized using eigenvectors of the linearization, Guckenheimer and Holmes, 1983), or inertial manifolds for dissipative PDEs (Constantin et al., 1988; Temam, 1990). Normal forms and (approximate) inertial forms are thus analogous to macroscopic equations for the coarse observation variables.

Low-order distribution moments have traditionally been the observation variables of choice. In principle, however, any set of variables that parameterizes this low-dimensional slow manifold can be used as observation variables with the appropriate lifting and restriction operators. Working with more observation variables than necessary reduces computational efficiency, it is analogous to using a finer mesh than necessary for the accuracy required in solving a problem. Intelligently chosen *order parameters* usually provide a much more parsimonious basis set on which to observe the dynamics, and apply our computational framework. There is a clear analogy here with *empirical eigenfunctions* (Holmes et al., 1998), used for model reduction in the discretization of dissipative PDEs. The detection of good observables, capable of efficiently parameterizing this manifold through statistical analysis of simulation results (Coifman et al., 2004) is a crucial enabling technology for our computational framework.

In coarse projective integration, we exploit the smoothness *in time* of the unavailable macroscopic equation in order to project (jump) to the future. In the case of macroscopically (spatially or otherwise) distributed systems, one can also exploit smoothness of the unavailable macroscopic equation *in space* in order to perform the microscopic simulations only over a few, appropriately coupled, small computational boxes called *teeth*. This is illustrated in Figure 2b:

(a) Coarse variable selection (same as above, but now the variable $\mathbf{u}(x)$ depends on "coarse space" x. For simplicity, we consider only one space dimension).

(b) Choice of lifting operator (same as above, but now we lift entire profiles of $\mathbf{u}(x)$ to profiles of $\mathbf{U}(\mathbf{y})$, where $\mathbf{y}$ is microscopic space corresponding to the macroscopic space x. This lifting involves, therefore, not only the variables, but the space descriptions too. The basic idea is that *a coarse point* in x corresponds to an interval (a "box" or "tooth" in $\mathbf{y}$).

(c) Prescribe a macroscopic initial profile $\mathbf{u}(x,t_0)$ — the "coarse field". Particularly, consider the values $u_i(t_0)$ at a number of macro-mesh points; the macroscopic profile arises from interpolation of these values of the coarse field.

(d) Lift the "mesh points" x_i, and the values $u_i(t_0)$ to profiles $\mathbf{U}_i(\mathbf{y}_i)$ in the microscopic domains ("teeth") corresponding to the coarse mesh points x_i. These profiles should be conditioned on the values u_i, and also on certain boundary conditions motivated by the coarse field (e.g., be consistent with coarse slopes at the boundaries of the "teeth," computed from the coarse field).

(e) Evolve each of these boxes for a short time based on the microscopic description, and through ensembles that enforce the coarsely inspired boundary conditions (see, e.g. Li et al., 1998) and, thus, generate $\mathbf{U}_i(\mathbf{y}_i, T)$.

(f) Obtain the restriction from each tooth to coarse variables $u_i(T) = \boldsymbol{M}\, \mathbf{U}_i(\mathbf{y}_i, T)$.

(g) Interpolate between these to obtain the new coarse field $\mathbf{u}(x,T)$.

Up to this point, we have the *gaptooth scheme*: a scheme that computes in small domains (the "teeth") which communicate over the gaps between them through "coarse field motivated" boundary conditions. We can now proceed by combining the gaptooth scheme with projective integration ideas to

(h) repeat the process (lift within the teeth, compute boundary conditions, evolve microscopically, restrict to macroscopic variables and interpolate) for a few steps, and then

(i) Project coarse fields "long" into the future. For a projective forward Euler, this would involve the chord between two successive coarse fields to estimate the right-hand-side of the unavailable coarse equation, and then an Euler "projection" of the coarse field long into the future.

(j) Repeat the entire procedure starting with the lifting **(d)** above.

This leads to *patch dynamics:* a computational framework in which simulations using the microscopic description over short times and small computational domains ("patches" in space-time) can be used to advance the macroscopic dynamics over long times and large computational domains (Kevrekidis, 2000; Kevrekidis et al., 2003; Gear et al., 2003; Samaey et al., 2003). Initializing microscopic computations conditioned on macroscopic variables is an important component of coarse projective integration; similarly, imposing macroscopically motivated boundary conditions to microscopic computations is an important element of gaptooth and patch dynamics.

The methods we discussed can, under appropriate conditions, drastically accelerate the direct simulation of the coarse-grained, macroscopic behavior of certain complex multiscale systems. Direct simulation, however, is but the simplest computational task one can perform with a system model. It corresponds to physical experimentation: we set parameter values and initial conditions, let the system evolve on the computer and observe its behavior, just like a laboratory experiment. Depending on what we want to learn, however, there exist much more interesting and efficient ways of using the model and the computer. Consider the location of steady states: fixed point algorithms, like Newton-Raphson, are a much more efficient way of finding steady-states than direct integration (given a good initial guess). Such algorithms can locate both stable and unstable steady-states (the latter would be extremely difficult or impossible to find with direct simulation). "*The Jacobian of the solution is a treasure trove, not only for continuation, but also for analyzing stability of solutions, for detecting bifurcations of solution families, and for computing asymptotic estimates of the effects, on any solution, of small changes in parameters, boundary conditions and boundary shape*" (Brown et al., 1980). Beyond stability and sensitivity analysis, having the steady-states and using Taylor series in their neighborhood (Jacobians, Hessians), one can design stabilizing controllers, observers, solve optimization problems, etc. There is a vast arsenal of algorithms (and codes implementing them) for the *computer-aided analysis* of system models, going much beyond direct simulation. However, these algorithms are applicable to macroscopic equations. Smoothness and Taylor series expansions are vital in formulating and implementing most of these algorithms. When the model comes in the form of microscopic and stochastic simulators at a much finer scale — without a closed formula for the equation, i.e., without a "righthand side" for the time derivative-, this arsenal of continuum numerical tools appears useless. Fortu-

nately, the same coarse timestepping idea we used to accelerate direct simulation of an *effectively simple* multiscale system can be used to enable its coarse-grained computer-assisted analysis, even without explicit macroscopic equations.

To illustrate this, we return to our simple scalar example in Figure 1. We are given a black box timestepper for this equation: a code which, initialized with $c_n(t=n\tau)$ integrates the equation for time τ and returns the result $c_{n+1}=c(t=[n+1]\tau)$. We use the notation

$$c_{n+1} = \Phi_\tau(c_n).$$

We can find a steady state for the equation by calling the timestepper repeatedly (integrate forward in time) until the result does not change any more. Indeed a steady state of the equation is a *fixed point* for the timestepper, $x^* = \Phi_\tau(x^*)$. Yet this iteration will only find *stable* steady states, and the rate of convergence to them depends on the physical dynamics of the problem. The method of choice for finding a steady state (given a good initial guess) would be a Newton-Raphson iteration, which would converge quadratically to nonsingular steady states.

$$\left[\frac{df}{dc}\right]_{c^{(n)}} (c^{(n+1)} - c^{(n)}) = -f(c^{(n)}).$$

Can we trick an integration code into becoming a fixed point solver ? In other words, if we do not have the equation for f(c), but can computationally evaluate the timestepper, can we still do Newton for the steady state ? The answer is illustrated in Figure 1c: we use the computationally evaluated timestepper to solve the fixed point problem

$$G(c) \equiv c - \Phi(c) = 0.$$

Calling the timestepper for an initial condition $c^{(n)}$ gives us $\Phi(c^{(n)})$ and the residual, $G(c^{(n)})$. Lacking a formula to compute the linearization, we call the timestepper with a nearby initial condition, $c^{(n)}+\epsilon$. This gives us $\Phi(c^{(n)}+\epsilon)$, and the difference (using Taylor series) is approximately $(d\Phi/dc)\cdot\varepsilon$. This estimate of the action of the Jacobian can then be used in a secant method to compute the next iterate $c^{(n+1)}$ of the steady-state search. Notice again the crucial issue of being able to initialize a simulator at will; after $c^{(n+1)}$ is estimated from the nearby integrations and the secant procedure, we can immediately call the timestepper with initial condition $c^{(n+1)}$ and iterate the process. We have not done much more than estimating derivatives through differencing. Yet forward integration can now be used (through a computational superstructure, a "wrapper" that implements what we just described in words) to converge to *unstable* steady states, and eventually to compute bifurcation diagrams. We have enabled a simulation code to perform a task (fixed-point computation) for which it had not been designed (Theodoropoulos et al., 2000).

This procedure may initially appear hopeless in higher dimensions (e.g., for the large sets of ODEs arising in PDE discretizations). Fortunately, recent developments in large scale computational linear algebra (the so-called matrix free solvers and eigensolvers) address precisely this point. Integrating with two nearby initial conditions (m-vectors, differing by the m-vector $\boldsymbol{\epsilon}$), and taking the difference of the timestepper results provides an estimate of $\mathbf{D\Phi}\cdot\boldsymbol{\epsilon}$, the inner product of the m×m Jacobian matrix of the timestepper (which is not available in closed form), and the known m-vector $\boldsymbol{\epsilon}$. Matrix-free iterative algorithms (for example, Newton-Krylov/GMRES methods, based on the timestepper) can then be used to solve for the steady state (e.g., Kelley, 1995; Saad, 2003). Matrix free eigensolvers (e.g., subspace iteration methods, based on the timestepper) can be used to estimate the part of the spectrum of the linearization close to the imaginary axis, which is relevant for stability and bifurcation computations of the unavailable equation (Lehoucq et al., 1998). We see once more that the quantities necessary for computer-aided analysis (residuals, action of Jacobians) can be *estimated* by appropriately designed short calls to the timestepper and subsequent postprocessing of the results, even if the equation is not available in closed form.

Independently of complex and multiscale computations, these software wrappers have the potential to enable *legacy codes* (large scale, industrial dynamic simulators) to perform tasks, such as stability/bifurcation and operability analysis, controller design and optimization, for which they have not been designed. Our inspiration comes from precisely such a wrapper: the recursive projection method of Shroff and Keller (1993), which enables large scale direct simulators (even slightly unstable ones) to become convergent fixed-point solvers.

Clearly, the same type of superstructure can turn *coarse timesteppers* into *coarse fixed point algorithms*, and *coarse bifurcation algorithms* (Figure 2c). Coarse residuals and the action of coarse slow Jacobians and Hessians can be estimated in a matrix-free context by calls to the coarse timestepper. Coarse equation solvers and coarse eigensolvers can, thus, be implemented and many aspects of the computer-assisted analysis of the unavailable macroscopic equation can be performed. Motivated by the connection to matrix-free numerical analysis methods, we call the timestepper and coarse-timestepper based computer-assisted analysis *equation free computation* (Kevrekidis *et al., 2003*).

The scope of the approach is very general. We have used coarse projective integration, and coarse bifurcation computations in problems ranging from the kMC modeling of catalytic surface reactions (Makeev et al., 2002a,b, 2004; Rico-Martinez et al., 2004), and MD simulations of the folding of a peptide fragment (Hummer and Kevrekidis, 2003) to individual-based models of evolving diseases (Cisternas et al., 2004) and *e-coli* chemotaxis (Setayeshgar et al., 2004). Beyond simulation and stability, equation-free computation has been used to perform linear stabilizing controller design for kMC, LB-BGK and BD simulators (Siettos et al., 2003a,b; Armaou et al., 2004); coarse optimization (Armaou and Kevrekidis, 2003), as well as coarse feedback linearization (Siettos et al., 2004); coarse *reverse* integration (Gear and Kevrekidis, 2004); coarse dynamic renormalization (Kevrekidis *et al,* 2003; Chen *et al.* 2004); and effective medium computations (Runborg et al., 2002; Moeller et al., 2003). Wrappers for large-scale codes like gPROMS (accelerating rapid pressure swing absorption computations), have been devised (Siettos et al., 2003c). As experience is accumulated, and the methods develop, more problems may become accessible to equation-free computer aided analysis.

Most of the discussion so far was formulated in a deterministic context; yet many systems of interest are described by stochastic models. Every outcome of computations with such models is in principle different; noise destroys determinism at the level of a single experiment. Determinism is often restored, however, at a different level of observation: the distribution of the outcomes. One might be able to make deterministic predictions about, say, the expectation and the standard deviation of a sufficiently large ensemble of replica (computational) experiments. Once again, higher-order moments of a probability distribution (whose evolution is governed by a Fokker-Planck-type equation) get quickly slaved to lower-order moments, and one can be *practically predictive* if one looks at an appropriately coarse-grained level. For the right observables, the coarse timestepper is constructed by simulating a large enough ensemble of realizations of the stochastic problem. An important category of problems can be approximated by dynamics on low-dimensional free-energy surfaces, parametrized by a few well chosen coarse variables (reaction coordinates). In the statistical mechanics of molecular systems the ability to be "practically predictive" with just a few *meaningful reaction coordinates* is intimately connected with separation of timescales. Formally, such coordinates could be defined with the help of the leading eigenfunctions of a Frobenius-Perron operator for the detailed problem (Schuette et al., 1999); yet this is practically unachievable. Instead, physical intuition, experience and data analysis is often used to suggest collective coordinates, which hopefully provide dynamically relevant measures of the progress of a reaction. Projecting the full dynamics on such well-chosen reaction coordinates will then retain the macroscopically relevant features of the dynamics, with only simplified representations of noise and memory (Zwanzig, 2001, Haenggi et al., 1990). Short bursts of appropriately initialized molecular dynamics can again be used to estimate on demand the drift and the noise terms of effective Langevin or Fokker-Planck equations in these variables (e.g., Kupferman and Stuart, 2004; Givon et al., 2004); to find minima and saddles; and to construct approximate propagators for the density on this surface, without deriving or writing this effective equation in closed form.

In our discussion we have outlined the possibilities opened by the equation-free framework. There are many theoretical and practical difficulties. Some are the usual problems of error monitoring, and control of the standard macroscopic algorithms made more difficult by the microscopic environment; some are particular to complex/multiscale timesteppers (consistent initialization through lifting; estimation and filtering involved in restriction operators; imposition of macroscopically inspired boundary conditions); some arise from the coupling (choice of good observation variables). We will mention one special feature here. To adaptively determine the *level of coarse-graining* at which we can be practically predictive, the coarse timestepper can be computed with different numbers of coarse variables (e.g., surface coverages only, vs. surface coverages *and* pair probabilities for lattice simulations of surface reactions). Matrix-free, timestepper-based eigensolvers can then be used to estimate the slow eigenvalues and corresponding eigenvectors for the timestepper, which should be tangent to the slow manifold (embodying the missing closure). Gaps in this spectrum, and the components of the corresponding eigenvectors can be used to probe the number and nature of coarse variables that should be used to observe the system dynamics (i.e., to locally parameterize the manifold).

Handshaking between microscopic solvers and continuum numerical analysis consists mainly of components traditionally studied in systems theory. System identification, based on the results of computational experimentation with the fine scale model is the most important component. Separation of timescales underpins the low-dimensionality of the macroscopic dynamics. The dynamics of the hierarchy of distribution moments constitute a singularly perturbed system, and brief detailed simulation is used to establish the missing closure. Adaptive tabulation (Pope, 1997) can be used to economize in the design of experiments, and the importance of data assimilation and statistical analysis tools to identify nonlinear correlations has already been stressed. The use of observer theory (e.g., Luenberger, 1964; Krener, 2003) and realization balancing (e.g., Moore, 1981; Lall et al., 2002) arises naturally: the microscopic system dynamics are observed on the macroscopic variables, but are realized through the microscopic simulator. Techniques for filtering (Kalman and Bucy, 1961) and variance reduction (e.g., Melchior and Oettinger, 1995) will play an important role in making equation-free computations practical (Li et al., 2003).

Equation-free methods constitute alternative ensembles for performing microscopic (molecular dynamics, kMC) simulations. These ensembles are motivated by macroscopic numerical analysis, rather than statistical mechanics. We are currently exploring the applicability of these "numerical analysis motivated" ensembles in accelerating equilibrium computations (grand canonical MC computations of micelle formation, Kopelevich et al., 2004a,b). It is particularly interesting to consider ensembles motivated by the augmented systems arising in multiparameter continuation. In such ensembles, like the *pathostat* (Siettos et al., 2004), based on pseudoarclength continuation, both the variables *and* the operating parameters themselves evolve, so that the system traces both stable and unstable parts of bifurcation diagrams.

An increasing number of experimental systems appears in the literature for which finely spatially distributed actuation–coupled with sensing- is available; chemical reactions addressed through light (Sakurai et al., 2002; Wolff et al., 2001) and colloidal particles manipulated through electric fields (Ristenpart et al., 2003) constitute such examples. When experiments can be initialized at will, the methods we discussed can be applied to laboratory–rather than computational–experiments. Continuum numerical methods will then become experimental design protocols, tuned to the task we wish to perform. This way, mathematics might be performed directly on the physical system, and not on the (approximate) equations modeling it.

Many of the mathematical and computational tools combined in this exposition (e.g., system identification, or inertial manifold theory) are well established; we borrowed them, in our synthesis with tools developed in our group, as necessary. Innovative multiscale/multilevel techniques proposed over the last decade include the quasi-continuum methods of Phillips and coworkers (Phillips, 2001; Ortiz and Phillips (1999)); optimal prediction methods of Chorin and coworkers (Chorin *et al*., 1998, 2000); coupling of continuum fields with stochastic evolution by Oettinger and coworkers (Oettinger, 1996; Laso and Oettinger, 1993); kinetic-theory based solvers by Xu

and Prendergast (Xu and Prendergast, 1994; Xu, 2001), the modification of equation-free computation in the context of conservation laws by E and Engquist (2003); and lattice coarse graining by Katsoulakis et al., 2003 (see the review by Givon et al., 2003, and the discussion in Kevrekidis et al. (2003)). In the context of molecular dynamics simulations, the idea of using multiple, possibly coupled replica runs to search conformation space forms the basis of approaches, such as parallel replica MD (Voter, 1998), SWARM-MD (Huber and van Gunsteren, 1998), coarse extended Lagrangian dynamics (Iannuzzi et al., 2003; Laio and Parrinello, 2002), and simple averaging over multiple trajectories (Yeh and Hummer, 2002; Snow et al., 2002).

It is fitting to close by citing from a 1980 article entitled "Computer-Aided Analysis of Nonlinear Problems in Transport Phenomena" by Brown, Scriven and Silliman (Brown et al., 1980): "*The nonlinear partial differential equations of mass, momentum, energy, species and charge transport, especially in two and three dimensions, can be solved in terms of functions of limited differentiability -no more than the physics warrants- rather than the analytical functions of classical analysis. . . . Organizing the polynomials in the so-called finite element basis functions facilitates generating and analyzing solutions by large, fast computers employing modern matrix techniques*". These sentences celebrate the transition from analytical solutions (of explicitly available equations) to computer-assisted solutions. The solutions are not analytically available for our class of complex/multiscale problems either; but now the equations themselves are not available, and they are solved in a computer-assisted fashion using appropriate computational experiments at a different level of system description. The similarity of the list of important elements is remarkable: The right basis functions, dictated by the physics (discretizations of the right coarse observation variables); large, fast computers (now massively parallel clusters, each CPU computing one realization of trajectories for the same "coarse" initial condition); and modern matrix techniques (now matrix-free iterative linear algebra). The approach bridges traditional numerical analysis, computational experimentation with the microscopic simulator, and systems theory; its most vital element is the simple fact that a code can be initialized at will.

If one has good macroscopic equations, one should use them. However, when these equations are not available in closed form (and such cases arise with increasing frequency in contemporary modeling) the equation-free computational enabling technology we outlined here may hold the key to the engineering of *effectively simple* systems.

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