Sci Model Simul (2008) 15:67–80
DOI 10.1007/s10820-008-9111-3

Chemomechanics of complex materials: challenges and opportunities in predictive kinetic timescales

Krystyn J. Van Vliet

Received: 15 September 2008 / Accepted: 22 September 2008 / Published online: 11 November 2008

Abstract What do nanoscopic biomolecular complexes between the cells that line our blood vessels have in common with the microscopic silicate glass fiber optics that line our communication highways, or with the macroscopic steel rails that line our bridges? To be sure, these are diverse materials which have been developed and studied for years by distinct experimental and computational research communities. However, the macroscopic functional properties of each of these structurally complex materials pivots on a strong yet poorly understood interplay between applied mechanical states and local chemical reaction kinetics. As is the case for many multiscale material phenomena, this chemomechanical coupling can be abstracted through computational modeling and simulation to identify key unit processes of mechanically altered chemical reactions. In the modeling community, challenges in predicting the kinetics of such structurally complex materials are often attributed to the so-called rough energy landscape, though rigorous connection between this simple picture and observable properties is possible for only the simplest of structures and transition states. By recognizing the common effects of mechanical force on rare atomistic events ranging from molecular unbinding to hydrolytic atomic bond rupture, we can develop perspectives and tools to address the challenges of predicting macroscopic kinetic consequences in complex materials characterized by rough energy landscapes. Here, we discuss the effects of mechanical force on chemical reactivity for specific complex materials of interest, and indicate how such validated computational analysis can enable predictive design of complex materials in reactive environments.

Keywords Chemomechanics · Rough energy landscape · Computational materials science · Kinetic barriers

K. J. Van Vliet (✉)
Department of Materials Science and Engineering, Massachusetts Institute of Technology, Cambridge, MA 02139, USA
e-mail: krystyn@MIT.EDU

1 Introduction

Although computational modeling and simulation of material deformation was initiated with the study of structurally simple materials and inert environments, there is an increasing demand for predictive simulation of more realistic material structure and physical conditions. In particular, it is recognized that applied mechanical force can plausibly alter chemical reactions inside materials or at material interfaces, though the fundamental reasons for this chemomechanical coupling are studied in a material-specific manner. Atomistic-level simulations can provide insight into the unit processes that facilitate kinetic reactions within complex materials, but the typical nanosecond timescales of such simulations are in contrast to the second-scale to hour-scale timescales of experimentally accessible or technologically relevant timescales. Further, in complex materials these key unit processes are "rare events" due to the high energy barriers associated with those processes. Examples of such rare events include unbinding between two proteins that tether biological cells to extracellular materials [1], unfolding of complex polymers, stiffness and bond breaking in amorphous glass fibers and gels [2], and diffusive hops of point defects within crystalline alloys [3].

Why should we consider ways for computational modeling to bridge this gap between microscopic rare events and macroscopic reality? The answer lies chiefly in the power of computational modeling to abstract general physical concepts that transcend compositional or microstructural details: accurate incorporation of mechanically altered rare events can help to predict the macroscopic kinetics that govern phenomena as diverse as creep in metal alloys, hydrolytic fracture of glass nanofibers, and pharmacological drug binding to cell surface receptors (Fig. 1). Modeling of this chemomechanical coupling is especially important and challenging in materials of limited long-range order and/or significant entropic contributions to the overall system energy. Here, we explore the concepts of rare events and rough energy landscapes common to several such materials, and show how mechanical environment defined by material stiffness and applied force can alter kinetic processes in the most complex of these systems: solvated biomolecules. Finally, we point to the potential of such computational analyses to address other complex materials for which breakthroughs in materials design will offer significant technological and societal impact.

2 Putting rare events and rough energy landscapes in context of real materials

2.1 Rare events and rough energy landscapes

Energy landscapes or energy surfaces are graphical representations of the energy of a system as a function of reaction coordinates, $E(\chi)$. These reaction coordinates can represent the physical distance between atomic or molecular coordinates of a material (e.g., distance between atomic nuclei), but more generally represents any relevant order parameter in the material phase space. The energetic basins or minima represent thermodynamically favored configurations, separated by many intermediate states during transitions between these minima. The utility of such free energy landscapes in predictions of material dynamics is that these multidimensional surfaces convey the pathways between local and global energetic minima. The energy basins associated with these minima define the thermodynamics of the system, and the connectivity among these basins defines the chemical reaction kinetics. There exist infinite reaction paths between any two states A and B, but the path of highest activation barrier traverses the saddle point on this $E(\chi)$ surface and is called the transition state. This reaction proceeds at a rate r:

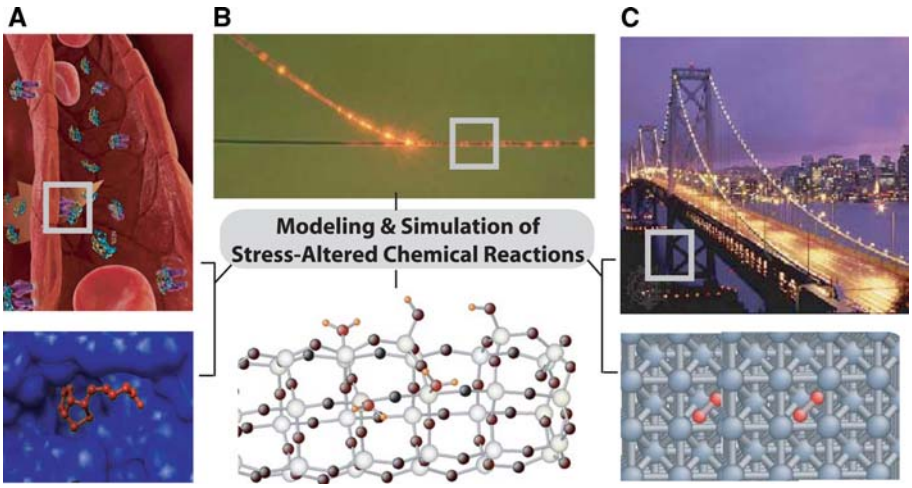

Fig. 1 Chemomechanics of complex materials requires abstraction of molecular-scale reactions under defined mechanical states. This level of abstraction (boxes) is indicated for several disparate macroscale applications, which are all well described as molecular reactions that are altered by the stiffness and/or applied stress state of the material interface. (**a**) In blood vessels, stress altered kinetics of reversible binding of soluble molecules (ligand, red) to cell surface bound molecules (receptor, blue) can be simulated with steered molecular dynamics; (**b**) In fiber optics, kinetics of hydrolytic cleavage (orange) in amorphous silicate glasses (gray and red) can be identified via nudged elastic band methods; (**c**) In structural steel alloys, migration barriers governing diffusion kinetics of carbon (red) in iron crystals (gray) under creep stress can be predicted via ab initio methods

$$r = k\,[\mathrm{A}]\,[\mathrm{B}] \tag{1}$$

where k is the rate constant of the transition from A to B:

$$k = \nu \quad \exp\left(-E_\mathrm{b}/RT\right) \tag{2}$$

and E_b is the minimum activation barrier the system must overcome to transition from A to B, and ν is the attempt frequency (e.g., atomic collision frequency). The existence of local and global minima of defined connectivity in this phase space demonstrates why certain systems may be kinetically trapped in local minima for hours, whereas others are able to achieve states predicted by thermodynamic or global minima within seconds. Rare events or transitions are those with relatively high activation barriers, which consequently occur at exponentially lower rates. Physical examples of rare events include nucleation and migration of many-atom defects in crystals or amorphous solids, and large conformational changes in solvated proteins [4–7].

The challenge in actually using the concept of energy landscapes to predict such material transitions is that the free energy landscape of real materials is typically not known *a priori*. Figure 1a illustrates a very simple one-dimensional energy landscape between two states or configurations, showing that the transition to a configuration of lower energy (local minimum) requires sufficient input energy to overcome a single transition barrier. Although the energy differences between configurations A and B can be calculated directly through various methods (e.g., ab initio approximations of the Schrodinger equation describing material configurations at the level of electronic structure [8–10]), it is computationally costly to use such approaches to map out an entire landscape for a material comprising hundreds to thousands of atoms. Thus, simplified descriptions of one-dimensional paths between conformations of interest (Fig. 2a) are often constructed using empirical force fields, identifying

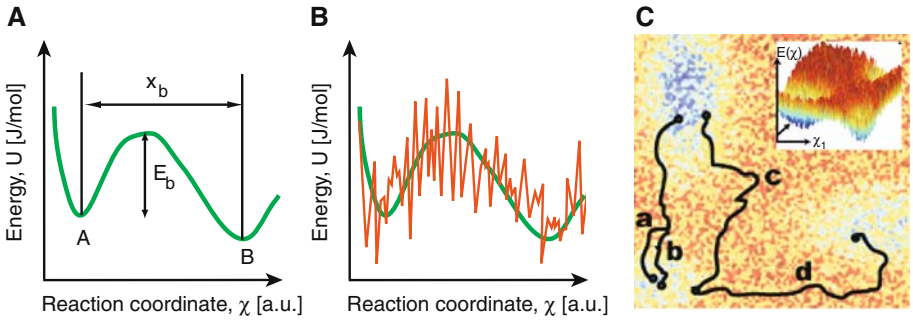

Fig. 2 Transition states and rough energy landscapes. (**a**) Kinetics for a material reaction described by a simple one-dimensional energy landscape with well-separated transition states A and B can be described via transition state theory, with energy barriers E_b and energetic distances x_b that define reaction rates k; (**b**) Structurally complex materials often exhibit so-called rough energy landscapes, with access to many energetically competitive minima between states A and B; (**c**) More realistically, these landscapes are three-dimensional (inset), such that two similar configurations/energy states can diverge to attain different final states (compare *a* and *b*) and two dissimilar configurations/energy states can converge to attain similar final states (compare *c* and *d*) Adapted from Ref. [50]

minimum energy paths between the two states of interest via nudged elastic band (NEB)-type approaches [11,12], or even by drawing from experimental measurements of reaction times that set relative barrier heights according to Eqs. (1) and (2) [13–15]. Energy landscapes described as "rough" exhibit many local minima of comparable barrier heights (Fig. 2b), such that neighboring conformations of lower barriers are rapidly sampled whereas neighboring conformations of higher barriers are rarely accessed.

Often, the concept of energy landscapes is not invoked to directly predict properties from quantitatively accurate $E(\chi)$ for complex materials, but to understand that systems with multiple energetic minima will exhibit multiple timescales of relaxation to the local and global energetic minima. For example, thermal fluctuations in conformations within glasses, colloids, polymers, and functional states of proteins have long been conceptualized as sampling of neighboring conformations in a high dimensional energy landscape [16]. Thus, a decrease in temperature forces the material system to sample conformations of lower energy barriers; this trapping within many local minima effectively freezes out sampling of larger conformational changes of higher barriers. The most physically relevant and experimentally accessible transitions in complex materials, however, are typically these high-barrier or "rare events" such as crack nucleation and protein unfolding. As Fig. 2c illustrates qualitatively, the roughness of the three-dimensional energy landscape causes the transition states and reaction rates that are sampled to depend quite strongly on the initial configuration of the system: small differences in the initial trajectory can lead to large differences in the minima that are sampled, and likewise two very different paths in phase space can require the same activation energy. For complex materials, then, the computational challenge is to adequately sample the ensemble of initial configurations and the frequency of rare events, in order to predict mechanisms of chemical reactions or macroscopic kinetic consequences of those reactions. Next, we will consider the increasing complexity of rough energy landscapes in highly alloyed crystals, glasses, and solvated proteins.

2.2 Diving in to rough energy landscapes of alloys, glasses, and biomolecules

Elemental metallic crystals such as body-centered cubic iron exhibit long range translational and rotational order, and as such have well-defined energy minima corresponding to the

underlying atomic lattice. The energy landscape of such Fe crystals is thus relatively smooth, notwithstanding the magnetic spin state of the atoms, and the activation barriers for nucleation of vacancies within the lattice can be determined directly via density functional theory (DFT) [3,17–21]. The diffusion of single vacancies within the lattice must overcome an activation barrier, but in this case the energetic barrier of the diffusive unit process—atomic hopping to adjacent lattice sites—is defined by transition pathways that are essentially limited to $< 100 >$ and $< 111 >$ crystallographic directions. Such barriers can then be calculated readily through NEB approaches that identify a minimum energy path consisting of intermediate configurations between state A (vacancy in one defined lattice site) and state B (vacancy in adjacent lattice site), where energies of these intermediate states can be calculated from ab initio methods such as DFT [3,22,23].

Now contrast this case of simple bcc Fe with the simplest approximation of high-carbon ferritic steel. As ubiquitous as this alloy is in failure-critical industrial applications, the additional chemical complexity created by a thermodynamic supersaturation of Fe self-vacancies and interstitial carbon immediately impedes such straightforward calculations of self-diffusivity. Ab initio formation energies of point defect clusters indicate that vacancies will be predominantly sequestered as point defect clusters such as divacancy-carbon clusters [3]. There exist many possible paths and unit processes of self-diffusion for even this triatomic defect cluster: a single vacancy could dissociate from the cluster along specific directions, the divacancy pair could dissociate from the carbon, etc. The minimum energy paths and associated activation barriers for each possible final state could still be computed via NEB, albeit at considerable computational expense for realistic carbon concentrations of up to 1 wt%C in body-centered cubic iron to form hardened structural steels.

Next, consider a glass such as amorphous silica. Silica is a naturally occurring material, comprising silicate tetrahedra (SiO_4) in the crystalline form of quartz; it is the most abundant material in the Earth's crust and the key component of fiberoptic and dielectric-thin—film communication platforms. It is well known that water reduces the strength of silica through several mechanisms, including hydrolytic weakening of quartz due to interstitial water [24–26] and stress corrosion cracking of amorphous silica due to surface water [17,19–21]. This interaction is representative of a broader class of chemomechanical degradation of material strength, including stress corrosion and hydrogen embrittlement in metals, and enzymatic biomolecular reactions. Owing to the large system size required to recapitulate such amorphous structures, atomistic reactions and deformation of such materials are typically studied via molecular dynamics (MD) simulations based on approximate empirical potentials. To study the unit process of this degradation in this glass, here the process of a single water molecule attacking the siloxane bonds of amorphous silica [25], the lack of long-range order confers an immediate challenge, as compared to crystalline analogues: where will this failure occur? That is, simulations of hydrolytic fracture must identify which of the thousands of distinct silica bond configurations, which are strained yet thermodynamically stable just prior to fracture, will be most susceptible to failure and thus should be simulated in detail. In direct simulation, either via molecular dynamics or quasi-static deformation by energy minimization, no information is available *a priori* to determine how far from stability the system is located and what failure mechanism will be activated. The system must be driven beyond the instability point and then allowed to explore the energy landscape in order to find a lower energy failed configuration. In the amorphous case, there are numerous instability points and a matching number of failed configurations. Therefore, the failure behavior will be highly dependent on the time available to explore the energy landscape (in molecular dynamics) or on the number of search directions attempted during minimization (in NEB identification of minimum energy paths). Here, efficient searching of these strained

regions of interest, or failure kernels, can be identified by recourse to computational modeling and simulation methods we have developed for crystalline materials: namely, the identification of an unstable localized vibration mode in the material [27]. In the context of dislocation nucleation in metallic crystals, we have previously described this unstable mode as the λ-criterion [28–30]which can be computed from eigenvectors and stresses calculable for each atom (for MD simulations) or material region under affine strain (for continuum simulations); we located the failure kernel of homogeneous dislocation nucleation at crystallographic locations where $\lambda_{\min} = 0$. This unstable mode identification thus isolates independent regions of the many-atom amorphous material that are most strained and thus most susceptible to bond failure. For silicate glass nanofibers under applied stress (Fig. 1b), we have found that the size of this failure kernel depends on the cutoff chosen for this vibrational amplitude but can be as small as 200 atoms within the very complex amorphous glass; this system size discourages use of ab initio methods to study the failure processes in detail, but makes efficient use of classical and reactive empirical potentials that are currently in development for silicate glasses, water, and organic molecules.

Proteins and other biomacromolecules can also be idealized as complex materials. The chemical reactions among such proteins and protein subunits define fundamental processes such as protein folding (the prediction of three-dimensional protein structures from knowledge of lower-order structural details) and reversible binding of drug molecules to cell surface-bound molecules. From a computational modeling and simulation perspective that recapitulates *in vitro* or *in vivo* environments, accurate prediction of mechanically altered chemical reaction kinetics between biomolecules must consider several challenges. For molecular dynamics (MD) or steered MD (SMD) simulations, these challenges include protein solvation in aqueous media, definitions of solution pH via protonation of specific amino acid residues comprising the protein, and the many configurations that will be accessed due to enhanced entropic contributions of long organic molecules. The structure-function paradigm of biology states that small changes in protein structure can confer ample changes in function of that protein. Although the structure of many proteins has been experimentally determined and shared on the Protein Data Bank (PDB) public database, it is important to note that these "solved structures" are ensemble or time-averaged snapshots of the many configurations a protein will access even when exploring a global energetic basin at body temperature. Recent experiments on photoreceptor proteins have demonstrated that very small-scale variations in configurations of a protein structure (root-mean-square deviation $<< 0.1$ nm) can have large functional consequences in the activation response of such proteins to light [31]. The effects of such small configurational changes in the initial simulated structure are typically neglected in modern simulation of protein dynamics, and instead the community has focused on simulations of increasing duration to access rare events such as unfolding over timescales approaching 100 ms or to access forced unbinding at increasingly realistic (slow) velocities < 10 m/s [32–34].

These increased timescales of observation are an important and reasonable goal for predictive protein simulations. However, in light of the rough or high-dimensional energy landscape of proteins (see Fig. 2c), the strong dependence of energetic trajectories on the initial configuration, and thus on the inferred reaction kinetics, warrants additional consideration. For example, the equilibrium dissociation constant K_D is a key parameter that represents the ratio between the unbinding rate or off-rate k_{off} and binding rate or on-rate k_{on} of a ligand-receptor complex. The off-rate $k_{off}$is expressed in units of $[s^{-1}]$, and is the inverse of the lifetime of the complex τ. In particular, integrated computational and experimental studies of forced unbinding of complementary macromolecules (e.g., ligand-receptor complexes such as Fig. 1a) can reveal key energetic and kinetic details that control the lifetime of the bound

complex. The reversible binding of such complexes is a rare event that can be altered by two distinct mechanical cues: applied mechanical forces that may result from fluid shear flow or other far-field stresses, or the mechanical stiffness of materials to which the molecules are tethered.

In the following section, we will consider the effects of both initial configuration and effective mechanical stiffness of molecules to which ligands are tethered, as these relate to the inferred energetic and kinetic properties of a particularly strong and useful biomolecular complex, biotin-streptavidin. Steered molecular dynamics simulations of this forced unbinding show why the mechanical stiffness effect was noted as a possibility but not calculated explicitly in the pioneering work of Evans. These simulations also show that tether stiffness and initial configuration should be carefully considered both in the interpretation of biophysics experiments and in the design of ligand-functionalized drug delivery materials.

3 Forced unbinding of biomolecular complexes

Three decades ago, Bell established that the force required to rupture the adhesion between two biological cell surfaces F_R should increase with the rate of loading $dF/dt = F'$:

$$\mathrm{F_R} = \mathrm{k_B T / x_b ln}\left(\left[F'\mathrm{x_b}\right] / \left[\mathrm{k_B T k_{off}}\right]\right) \tag{3}$$

where k_B is Boltzmann's constant, T is absolute temperature, x_b is the energetic distance between the bound and unbound states in units of χ, and is sometimes termed the unbinding width. This model has since been applied to the rupture between individual molecules such as adhesive ligands to cell-surface receptors, and Evans and Ritchie have attributed this rate-dependent rupture force of the molecular complex as a tilt in the one-dimensional energy landscape [35,36]. They and many others, including our group, have demonstrated that the dynamic strength of this bond can be measured experimentally by several methods that quantify the rupture force at defined loading rates $F_\mathrm{R}\left(F'\right)$ [36–39].

Although such experiments are far from equilibrium, in that the dissociation of the molecular pair is forced by the applied loading rate, Eq. (3) shows that the equilibrium bond parameters k_{off} and x_b should be obtainable via extrapolation and slope of acquired F_R vs. ln F', respectively. Here, it is presumed that the loading rates are sufficiently slow that at least some details of the rough energy landscape $E(\chi)$ are accessed. One of the most commonly employed experimental methods used to obtain these so-called dynamic force spectra is molecular force spectroscopy or dynamic force spectroscopy, an atomic force microscopy (AFM)-based approach that measures the force-displacement response between a ligand tethered to an AFM cantilevered probe and its receptor presented at an opposing surface (such as a rigid, flat mica surface or a compliant living cell surface) [40]. In such experiments, the loading rate F' is expected to alter the observed rupture force according to Eq. (3), and could be defined as the product of the velocity of the ligand v and the stiffness of the force transducer to which the ligand is attached k_s, or $F' = k_s v$.

3.1 Does stiffness matter? Why k_s perturbs the accessible molecular rupture forces

Upon compiling experimental results from several groups acquired over several years for a single molecular complex, biotin-streptavidin, we noticed that Bell's prediction was qualitatively accurate but that various researchers reported significant differences in F_R at the same ostensible loading rate F'. Biotin-streptavidin is a well studied biomolecular complex because, under equilibrium conditions and in the absence of applied load, the binding lifetime

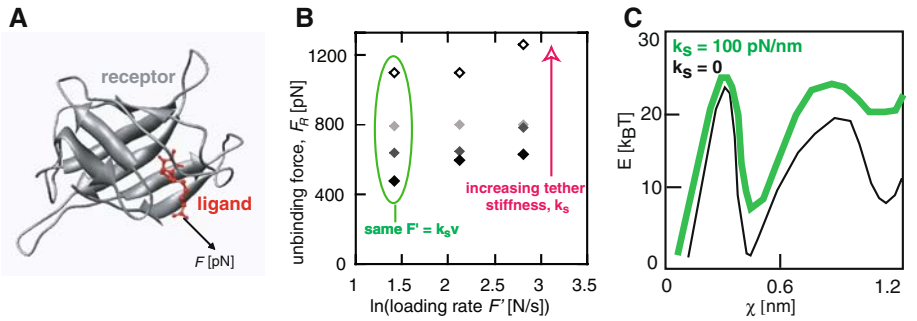

Fig. 3 Effects of tether stiffness on biomolecular rupture force. (**a**) Biotin ligand is displaced from the streptavidin receptor pocket via a transducer of stiffness ks moving at constant velocity v; (**b**) the observed rupture forces depend on loading rate as expected from Bell's model, but also on k_S; (**c**) This stiffness-dependence can be attributed to direct alteration of the energy landscape of the complex, even before load is applied to the biotin ligand. Adapted from Ref. [1]

of the biotin ligand to the streptavidin receptor is long (as compared to other ligand-receptor and antibody-antigen complexes. Thus, this complex has become a tool to bioengineers who use the complex to effectively "glue" other molecules together with nearly covalent bond strength, and to biophysists who use the complex as a benchmark for long binding lifetimes τ.

However, when we observed that experimentalists using the same AFM approach and biotin-streptavidin preparations measured the same rupture forces for 100-fold differences in loading rate, or 150 pN differences in rupture force for the same applied loading rate [1], we developed a matrix of steered molecular dynamics simulations to identify possible sources of this discrepancy. These simulations are described fully in [1], in which we acquired the structure of this complex from the PDB, solvated the protein in simple-point charge (SPC) water with ions to mimic charge neutrality of physiological buffers, and then selected a single configuration of this complex from the so-called "equilibration trajectory" of an unconstrained MD simulation of 100 ns duration. This configuration was not strictly equilibrated in terms of representing the global minimum of the protein structure, of course; instead, it was chosen at a timepoint in the trajectory which we deemed to be sufficient to enter an energetic minimum in the admittedly rough energy landscape (20 ns), according to our protocol for objectively choosing an initial configuration of proteins as we outlined in Ref. [41]. We then conducted SMD simulations (Fig. 3a), applying a simulated loading rate via a Hookean spring connected to the ligand, and achieved the same magnitude of $F' = k_S v$ for pairs of low k_s/ high v, and high k_s/ low v(Fig. 3b).

We were initially surprised that we obtained very different rupture forces F_R for pairs of simulations conducted for different spring constants and velocities but the same resulting F', differing as much as 60 pN for F' on the order of 1000 pN/s; this difference was well in excess of our standard deviation of replicate simulations for the same configuration under the same loading conditions, differing only in the initial velocities of atoms within the complex. We also confirmed this finding with AFM force spectroscopy experiments on biotin-streptavidin, at admittedly lower loading rates, and observed the same result: the velocity of two AFM cantilevers of differing stiffness k_s could not be altered to attain the same rupture force at a given loading rate defined as $F' = k_s v$. However, more careful consideration of our findings showed a clear and independent effect of this tether stiffness k_s on the observed rupture force. We conceptualized this effect as a direct perturbation of the energy landscape, superposing an additional energetic term $E = k_s \chi^2$ to the existing potential of the complex. Importantly,

this energy landscape is perturbed *even before any external force is applied*, and effectively changes the accessible energy states and trajectories accessible to the complex.

Although Evans had previously noted the possibility of stiffness directly altering the nature of the energy landscape [42], he had not included this term explicitly in his model of molecular unbinding kinetics without any loss of accuracy in the interpretation of his own experiments. Why did this tether stiffness contribute so strongly to our simulations and AFM force spectroscopy experiments, but so little to Evans et al.'s experiments on the same complex? Figure 3c shows that the magnitude of this stiffness effect naturally scales directly with the stiffness of the force transducer stiffness, as superposed on a one-dimensional energy landscape that has been based on several measurements and simulations of the bound states of this particular complex. In Evans et al.'s biomembrane force probe-based experiments on this complex, the stiffness of the biomembranes was so low ($k_s < 10\,\mathrm{pN/nm}$) that the energy landscape was not noticeably perturbed. In contrast, in our AFM-based experiments with cantilevers of stiffness $k_s \sim 100\,\mathrm{pN/nm}$, there is noticeable alteration of the initial landscape, such that the barriers to dissociation of the complex are increased with increasing ks. Naturally, SMD-based simulations of the complex employ springs of even larger stiffness ($k_s \sim 1000\,\mathrm{pN/nm}$) in order to force the dissociation in accessible simulation timescales, and perturb the initial landscape of the complex to an even greater extent.

Note that the actual rupture force of the complex is unchanged by this tether stiffness, but rather the observed rupture force F_{obs} increases with increasing tether stiffness. For biophysical applications, the actual rupture force of the complex F_R can thus be computed from this summed effect:

$$\mathrm{F_{obs}} = \mathrm{F_R} - \mathrm{k_s x_b}/2 = \mathrm{k_B T}/\mathrm{x_b} \ln\left(\left[F' \mathrm{x_b}\right] / \left[\mathrm{k_B T k_{off}}\right]\right) \tag{4}$$

However, for practical and biological applications, this direct contribution of tether stiffness to the applied force required to dissociate the complex presents the following implication. The force required to dissociate a ligand from its target (such as a cell surface receptor), and thus the binding lifetime of that complex, will depend directly on the stiffness of the material to which the ligand is tethered (e.g., the conjugating biomolecules between the drug ligand and a solid support) and, by extension, to the stiffness of the material to which the receptor is tethered (e.g., the mechanical compliance of the cell surface region that presents the receptor protein).

3.2 Enough is enough: practical requirements of rare event sampling in MD

As noted, MD simulations have been utilized to model protein behavior and function for over 30 years, in fact as long as Bell's model has been known [43,44]. The timescale limitation of such atomistic simulations has been addressed by the development of Steered Molecular Dynamics (SMD), a variation on classical MD in which rare events such as ligand-receptor unbinding are induced by mechanical force. One key goal of simulations that faithfully recapitulate experiments is to consider replicate simulations that explore the variation as well as the magnitude of simulated parameters and extracted properties of individual and complexed molecules. However, here we must ask for the sake of tractability, when have we simulated "enough" of the ensemble, given that we will never full access the entire ensemble via direct simulation?

MD studies typically utilize a single, long-timescale trajectory to draw conclusions about biomolecular properties such as complex stabilization, binding pathways, and ligand-receptor unbinding [45–47]. However, proteins *in vitro* and *in vivo* show considerable variation in

measured properties; protein properties including rupture forces and photoactivity are typically distributions and cannot be adequately characterized by a single measurement, but can depend critically on small configurational differences that are accessible for a given protein structure [31]. Therefore, it is reasonable that simulations should aim to sample the property *distribution* if they are to be representative of natural or experimental systems, especially if the goal is to compare simulation results at two different conditions. Encouragingly, a few simulation-focused researchers have begun to report MD simulated results for multiple initial configurations [48,49]. For more in the community to consider this initially daunting approach, however, it is very helpful to know how many initial configurations are necessary to capture sufficient variation without incurring excessive computational expense.

We have considered this sufficient number for the biotin-streptavidin complex, seeking to identify whether there were configurational subsets that gave rise to higher or lower rupture forces under identical applied loading conditions [50]. We first created configurational subsets of the solvated complexes that differed by less than some cutoff root-mean-square deviation among atoms (e.g., RMSD $<$ 10 A), and then applied the same loading rate details to each configurational member of the cluster; to the centroid configuration within each cluster (of median RMSD); and to one of the cluster centroids while varying only the initial velocity of the atoms as set by the simulated temperature and a random number generator. As Fig. 4 shows, the variation in rupture force observed for these three different cases was quite similar, demonstrating that at least for this particular case, configuration is not a strong determinant of observed rupture force. More generally, though, we created randomized subsets of size N $=$ 4 to N $=$ 40, to identify the sufficient number of simulations required to reproduce this distribution of observed rupture forces. In retrospect, statistical analysis of epidemiology, economic forecasts, and even polymer rheology would have predicted what we observed: in order to capture the full distribution of rupture forces and correctly identify the mean value, we needed to simulate at least 30 configurations. In fact, a statistical rule of thumb is that approximately 30 samples are needed to adequately characterize the mean of an underlying distribution, because for this sampling number the sampling distribution approaches a normal distribution [51]. Thus, we can conclude that, in the absence of a correlation between configuration and observed molecular property, at least 30 replicate simulations will be necessary to ensure adequate characterization of the observed property. We find that the relative error in our simulation output F_R is equal to the relative error of the calculated final parameter k_{off}, and so 30 replicate simulations at each loading rate would be appropriate. If this number of initial configurations is intractable due to system size, however, the confidence interval of the simulated predictions could be calculated and reported. Consideration of such qualifications by the atomistic simulation community, particularly for predictive modeling of amorphous and biomolecular systems, should help to inform our interpretation of brute-force simulated dynamics.

4 Potential advances for chemomechanical analysis of other complex materials

Several other complex materials can benefit from computational analyses that establish links between chemical kinetics and mechanics. Consider the example of cement, a material so inexpensive and commonly used (1.7 billion tons/year, with 5 billion tons/year estimated by 2050 [52]) that few would initially consider its study as high-impact, and fewer still would even know the composition and structure of this ubiquitous material. Despite its status as the most widely used material on Earth, cement remains an enigma in the fundamental science of materials and a key international target of environmentally sustainable development. Cement is the solid composite material that forms at room temperature from mixing a grey

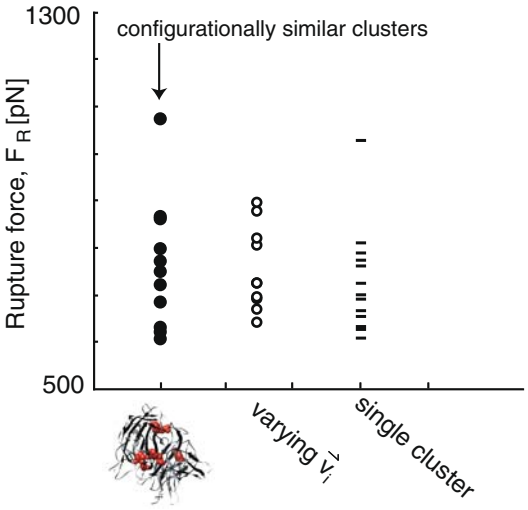

Fig. 4 Configurational variations may not be predictive of property variations. (**a**) Rupture force distributions are quite similar when obtained via steered molecular dynamics of configurationally distinct groups (clusters) of biotin-streptavidin; a single cluster for which every member was simulated; or a single configuration for which initial atomic velocities were randomly varied. This indicates an absence of configuration-property correlation for this particular complex and property, so 30 randomly selected configurations will capture the actual distribution of this property. Adapted from Ref. [49]

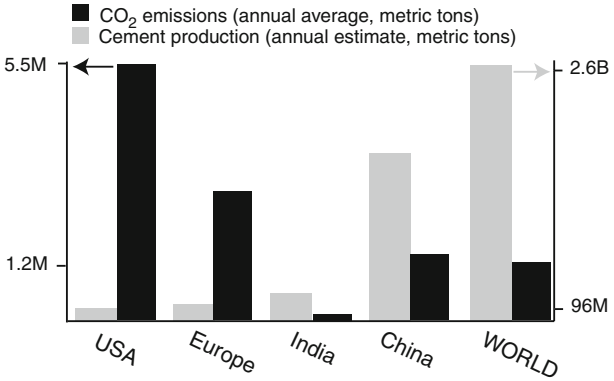

Fig. 5 National production of cement and CO_2 in metric tons are inversely related as of 2007, but are projected to increase rapidly in industrializing nations such as India and China. Predictive modeling and simulation of cement chemomechanics can contribute to new compositions and/or processing temperatures and pressures that lower the CO_2 production associated with cement production. Data source for cement production and carbon dioxide: Cement Industry Environmental Impact Assessment (2005) and US Geological Survey (2007), respectively

Portland cement powder with water, is the most widely used material on Earth at $1\,m^3$/person/year, typically in the form of concrete comprising cement and stone aggregates. Each ton of cement produced results in an emission of 750 to 850 kg of carbon dioxide, amounting to a per capita emission of some 250 kg of CO_2 per cubic meter of concrete consumed. As shown in Fig. 5, cement production for infrastructural applications is currently most prevalent in industrializing nations such as India and China.

The composition and structure of Calcium-Silica-Hydrate (C-S-H), the basic molecular unit of cementitious materials, continues to defy quantitative characterization. Cement is a nanocomposite material, and is called "liquid stone" because it gels by a poorly understood, exothermic and confined aqueous reaction between calcium/silicate powders and water. As

the processing of the currently used cement compositions requires reduction of calcium carbonate ($CaCo_3$, limestone) to CaO prior to reaction with water, every produced ton of cement contributes approximately 1 ton of CO_2 to the atmosphere, representing $> 5\%$ of the global CO_2 emission on earth and an estimated "environmental burden cost" of \$100 ton [52].

Experimental efforts to alter cement chemistry and processing without altering the kinetic rates of gelation and final stiffness and strength of cementitious composites are ongoing, but have been largely iterative: the structure of the C-S-H constituents and the details of the gelation over hour-scale gelation reactions are unknown. Importantly, the mechanical properties of the C-S-H nanoparticles have recently been identified through nanoscale indentation experiments and differ in packing density [53–55]. Here, computational modeling and simulation can offer valuable insight into structural predictions and dynamics of hydrated C-S-H layers and nanoparticles that impact curing times in defined ambient environments, susceptibility to hydrolytic fracture, and ultimate compressive strength of such complex materials.

What would the benefit of such fundamental modeling and simulation efforts in such an established material be? The chief advances would focus on reduced energy required to create CaO, achieved through either new cement compositions requiring less Ca or more likely through new processing routes to synthesize or reduce CaO. If materials research efforts could predict cementitious materials that reduced CaO concentrations (e.g., by identifying alternative divalent ions) and/or processing temperature/time (while maintaining critical gelation times and compressive strength), the CO_2 savings could be sufficient for the world to meet Kyoto Protocol targets. Alternatively, if cement compositions could be modified to include noxious gas-getting nanoparticles such as TiO_2, again with predictive alteration of the kinetics of gelation and the compressive strength of the fully cured gel, the very surface of the buildings rising rapidly in India and China could be used to meliorate air quality in congested cities. These are not blue-sky promises, but the foreseeable result of computational studies focused on complex nanocomposites critical to physical infrastructure. The above considerations of stress-altered reactions in other complex materials such as alloys, glasses, and biomolecules will be important examples and case studies to guide accurate benchmarking of such models.

5 Summary and outlook

Here we have discussed the challenge of predictive modeling and simulation for materials of increasing structural complexity. Although the materials are dissimilar in both structure and application, the key dobstacles to informative computational studies of stress-altered reaction kinetics are strikingly similar. Prediction of transition states and associated kinetics in materials with high-dimensional or rough energy landscapes require careful consideration of sufficient system size, identification of strained regions of interest, effects of conjugate variables such as force transducer stiffness, and sufficient sampling of initial configurations. From alloys to glasses to biomolecules, these requirements of predictive modeling and simulation serve to connect the rich and largely unexplored terrain of chemomechanically coupled behavior in and between materials. Just as these concepts are interesting within the material application of interest, they are also inspirational for new materials and material processes that can potentially improve material performance while reducing associated environmental burdens.

References

1. Walton, E.B., Lee, S., Van Vliet, K.J.: Extending Bell's model: how force transducer stiffness alters measured unbinding forces and kinetics of molecular complexes. Biophys. J. **94**, 2621–2630 (2007)
2. Silva, E.C., Tong, L., Yip, S., Van Vliet, K.J.: Size effects on the stiffness of silica nanowires. Small **2**(2), 239–243 (2006)
3. Forst, C.J., Slycke, J., Van Vliet, K.J., Yip, S.: Point defect concentrations in metastable Fe–C alloys. Phys. Rev. Lett. **96**(17) (2006)
4. Andrews, B.T., Schoenfish, A.R., Roy, M., Waldo, G., Jennings, P.A.: The rough energy landscape of superfolder GFP is linked to the chromophore. J. Mol. Biol. **373**(2), 476–490 (2007)
5. Gruebele, M.: Rough energy landscape of folded and unfolded proteins. Abstr. Pap. Am. Chem. Soc. **227**, U267–U267 (2004)
6. Wang, J., Huang, W.M., Lu, H.Y., Wang, E.K.: Downhill kinetics of biomolecular interface binding: Globally connected scenario. Biophys. J. **87**(4), 2187–2194 (2004)
7. Onuchic, J.N., Wolynes, P.G.: Energy landscapes, glass transitions, and chemical-reaction dynamics in biomolecular or solvent environment. J. Chem. Phys. **98**(3), 2218–2224 (1993)
8. Simka, H., Willis, B.G., Lengyel, I., Jensen, K.F.: chemistry predictions of reaction processes in organometallic vapor phase epitaxy. Progress in Crystal Growth and Characterization of Materials **35**(2–4), 117–149 (1997)
9. Wesolowski, T., Muller, R.P., Warshel, A.: Ab initio frozen density functional calculations of proton transfer reactions in solution. J. Phys. Chem. **100**(38), 15444–15449 (1996)
10. Kim, K., Jordan, K.D.: Comparison of density-functional and Mp2 calculations on the water monomer and dimer. J. Phys. Chem. **98**(40), 10089–10094 (1994)
11. Henkelman, G., Uberuaga, B.P., Jonsson, H.: A climbing image nudged elastic band method for finding saddle points and minimum energy paths. J. Chem. Phys. **113**(22), 9901–9904 (2000)
12. Henkelman, G., Jonsson, H.: Improved tangent estimate in the nudged elastic band method for finding minimum energy paths and saddle points. J. Chem. Phys. **113**(22), 9978–9985 (2000)
13. Sorensen, M.R., Brandbyge, M., Jacobsen, K.W.: Mechanical deformation of atomic-scale metallic contacts: Structure and mechanisms. Phys. Rev. B **57**(6), 3283–3294 (1998)
14. Pincet, F., Husson, J.: The solution to the streptavidin-biotin paradox: the influence of history on the strength of single molecular bonds. Biophys. J. **89**, 4374–4381 (2005)
15. Merkel, R., Nassoy, P., Leung, A., Ritchie, K., Evans, E.: Energy landscapes of receptor–ligand bonds explored with dynamic force spectroscopy. Nature **397**, 50–53 (1999)
16. Coureux, P.-D., Fan, X., Sojanoff, V., Genick, U.K.: Picometer-scale conformational heterogeneity separates functional from nonfunctional states of a photoreceptor protein. Structure **16**, 863–872 (2008)
17. Kellou, A., Grosdidier, T., Aourag, H.: An ab initio study of the effects and stability of vacancies, antisites and small radius atoms (B, C, N, and O) in the B2–FeAl structure. In: Fisher, D.J. (ed.) Defects and Diffusion in Metals—An Annual Retrospective VII, vol. 233–234, pp. 87–95. Defect and Diffusion Forum (2004)
18. Lau, T.T., Foerst, C.J., Lin ,X., Gale, J.D., Yip, S., Van Vliet, K.J.: Many-body potential for point defect clusters in Fe–C alloys. Phys. Rev. Lett. **98**(21):215501 (2007)
19. Legris, A.: Recent advances in point defect studies driven by density functional theory. In: Fisher, D.J. (ed.) Defects and Diffusion in Metals—An Annual Retrospective VII, vol. 233–234, pp. 77–86. Defect and Diffusion Forum (2004)
20. Mizuno, T., Asato, M., Hoshino, T., Kawakami, K.: First-principles calculations for vacancy formation energies in Ni and Fe: non-local effect beyond the LSDA and magnetism. J. Magn. Magn. Mater. **226**, 386–387 (2001)
21. Simonetti, S., Pronsato, M.E., Brizuela, G., Juan, A.: The C–C pair in the vicinity of a bcc Fe bulk vacancy: electronic structure and bonding. Phys. Status Solidi B Basic Solid State Phys. **244**(2), 610–618 (2007)
22. Becquart, C.S., Souidi, A., Domain, C., Hou, M., Malerba, L., Stoller, R.E.: Effect of displacement cascade structure and defect mobility on the growth of point defect clusters under irradiation. J. Nucl. Mater. **351**(1–3), 39–46 (2006)
23. Domain, C.: Ab initio modelling of defect properties with substitutional and interstitials elements in steels and Zr alloys. J. Nucl. Mater. **351**(1–3), 1–19 (2006)
24. Cao, C., He, Y., Torras, J., Deumens, E., Trickey, S.B., Cheng, H.P.: Fracture, water dissociation, and proton conduction in SiO2 nanochains. J. Chem. Phys. **126**(21):211101 (2007)
25. Zhu, T., Li, J., Yip, S., Bartlett, R.J., Trickey, S.B., De Leeuw, N.H.: Deformation and fracture of a SiO2 nanorod. Mol. Simul. **29**(10–11), 671–676 (2003)

26. McConnell, J.D.C.: Ab initio studies on water related species in quartz and their role in weakening under stress. Phase Transit. **61**(1–4), 19–39 (1997)
27. Silva, E., Van Vliet, K.J., Yip, S.: Effects of water on chemomechanical instabilities in amorphous silica: nanoscale experiments and molecular simulation. PhD Thesis, Silva, MIT, unpublished results (2007)
28. Van Vliet, K.J., Li, J., Zhu, T., Yip, S., Suresh, S.: Quantifying the early stages of plasticity through nanoscale experiments and simulations. Phys. Rev. B **67**(10)(2003)
29. Li, J., Zhu, T., Yip, S., Van Vliet, K.J., Suresh, S.: Elastic criterion for dislocation nucleation. Mater. Sci. Eng. A Struct. Mater. Prop. Microstruct. Process. **365**(1–2), 25–30 (2004)
30. Li, J., Van Vliet, K.J., Zhu, T., Yip, S., Suresh, S.: Atomistic mechanisms governing elastic limit and incipient plasticity in crystals. Nature **418**(6895), 307–310 (2002)
31. Coureux P.-D., Fan, Z., Stojanoff, V., and Genick,U.K.: Picometer-scale conformational heterogeneity separates functional and nonfunctional states of a photoreceptor protein. Structure **6**:863–872 (2008)
32. Puklin-Faucher, E., Gao, M., Schulten, K., Vogel, V.: How the headpiece hinge angle is opened: new insights into the dynamics of integrin activation. J. Cell Biol. **175**(2), 349–360 (2006)
33. Wriggers, W., Mehler, E., Pitici, F., Weinstein, H., Schulten, K.: Structure and dynamics of calmodulin in solution. Biophys. J. **74**(4), 1622–1639 (1998)
34. Sheng, Q., Schulten, K., Pidgeon, C.: Molecular-dynamics simulation of immobilized artificial membranes. J. Phys. Chem. **99**(27), 11018–11027 (1995)
35. Evans, E., Ritchie, K.: Dynamic strength of molecular adhesion bonds. Biophys. J. **72**(4), 1541–1555 (1997)
36. Merkel, R., Nassoy, P., Leung, A., Ritchie, K., Evans, E.: Energy landscapes of receptor–ligand bonds explored with dynamic force spectroscopy. Nature **397**(6714), 50–53 (1999)
37. Lee, S., Mandic, J., Van Vliet, K.J.: Chemomechanical mapping of ligand–receptor binding kinetics on cells. Proc. Natl. Acad. Sci. USA **104**(23), 9609–9614 (2007)
38. Hinterdorfer, P., Baumgartner, W., Gruber, H.J., Schilcher, K., Schindler, H.: Detection and localization of individual antibody-antigen recognition events by atomic force microscopy. Proc. Natl. Acad. Sci. USA **93**(8), 3477–3481 (1996)
39. Stroh, C.M., Ebner, A., Geretschlager, M., Freudenthaler, G., Kienberger, F., Kamruzzahan, A.S.M., Smith-Gil, S.J., Gruber, H.J., Hinterdorfer, P.: Simultaneous topography and recognition Imaging using force microscopy. Biophys. J. **87**(3), 1981–1990 (2004)
40. Van Vliet, K.J., Hinterdorfer, P.: Probing drug–cell interactions. Nano Today **1**(3), 18–25 (2006)
41. Walton, E.B., Van Vliet, K.J.: Equilibration of experimentally determined protein structures for molecular dynamics simulation. Phys. Rev. E **74**(6):061901 (2006)
42. Evans, E.: Looking inside molecular bonds at biological interfaces with dynamic force spectroscopy. Biophys. Chem. **82**, 83–87 (1999)
43. McCammon, J.A., Gelin, B.R., Karplus, M.: Dynamics offolded proteins. Nature **267**, 585–590 (1977)
44. McCammon, J.A., Karplus, M.: Simulation of protein dynamics. Annu. Rev. Phys. Chem. **31**:29–45 (1980)
45. Craig, D., Gao, M., Schulten, K., Vogel, V.: Structural insights into how the MIDAS ion stabilizes integrin binding to an RGD peptide under force. Structure **12**(11), 2049–2058 (2004)
46. Isralewitz, B., Izrailev, S., Schulten, K.: Binding pathway of retinal to bacterio-opsin: a prediction by molecular dynamics simulations. Biophys. J. **73**(6), 2972–2979 (1997)
47. Kosztin, D., Izrailev, S., Schulten, K.: Unbinding of retinoic acid from its receptor studied by steered molecular dynamics. Biophys. J. **76**(1), 188–197 (1999)
48. Curcio, R., Caflisch, A., Paci, E.: Change of the unbinding mechanism upon a mutation: a molecular dynamics study of an antibody–hapten complex. Protein Sci. **14**(10), 2499–2514 (2005)
49. Paci, E., Caflisch, A., Pluckthun, A., Karplus, M.: Forces and energetics of hapten-antibody dissociation: a biased molecular dynamics simulation study. J. Mol. Biol. **314**(3), 589–605 (2001)
50. Krishnan, R., Walton, E.B., Van Vliet, K.J.: in review (2008)
51. Mendenhall, W., Beaver, R.J., Beaver, B.M.: Introduction to Probability and Statistics. 12th ed., Thomson Higher Education, Belmont, CA (2006)
52. Chaturvedi, S., Ocxhendorf, J.: Global environmental impacts due to concrete and steel. Struct. Eng. Int. **14**(3), 198–200 (2004)
53. Ulm, F.J., Constantinides, G., Heukamp, F.H.: Is concrete a poromechanics material?—a multiscale investigation of poroelastic properties. Mater. Struct. **37**(265), 43–58 (2004)
54. Jennings, H.M., Thomas, J.J., Gevrenov, J.S., Constantinides, G., Ulm, F.J.: A multi-technique investigation of the nanoporosity of cement paste. Cem. Concr. Res. **37**(3), 329–336 (2007)
55. Constantinides, G., Ulm, F.J.: The effect of two types of C-S-H on the elasticity of cement-based materials: Results from nanoindentation and micromechanical modeling. Cem. Concr. Res. **34**(1), 67–80 (2004)