

Cell and biomolecular mechanics *in silico*

Recent developments in computational cell and biomolecular mechanics have provided valuable insights into the mechanical properties of cells, subcellular components and biomolecules, while simultaneously complementing new experimental techniques used for deciphering the structure–function paradigm in living cells. These computational approaches have direct implications in understanding the state of human health and the progress of disease and can therefore aid immensely in the diagnosis and treatment of diseases. We provide an overview of the computational approaches that are currently used in understanding various aspects of cell and biomolecular mechanics. Our emphasis is on state-of-the-art techniques and the progress made in addressing key challenges in biomechanics.

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Eukaryotic cells, which in view of the intricate nature of their structure are compared with the ‘mother’s work basket’¹, are assemblies of numerous subcellular components with vastly different geometrical, material and biochemical characteristics (Fig. 1a). Understanding how these cells migrate, differentiate, interact with each other, function and die entails resolving mechanics at various spatial and temporal scales^{2–13}. The connection between mechanics and cell function has been researched in various contexts, from studies on diseases such as atherosclerosis and arthritis to tissue engineering^{14–20}. The development of advanced technologies over the past two decades, from high-precision mechanical probes for measuring forces as small as several piconewtons^{8,21,22} to imaging techniques that allow the visualization of a single protein *in vivo*^{23,24}, has provided reliable tools for monitoring the response and evolution of cells, subcellular components and biomolecules under mechanical stimuli. A key challenge in understanding the interplay between mechanics and function *in vivo*, then, is the development of robust frameworks to interpret the trends observed in experiments. The quest to tackle this challenge has spawned various theoretical approaches, ranging from qualitative scaling laws to detailed, predictive computational models for complementing experimental observations. These computational approaches have not only enabled us to gain an understanding of experimental trends but also, more crucially, provided new insights into the connection between cell mechanics and function, as will be described in this article.

TRAVERSING THE LENGTH-SCALE LANDSCAPE

A key step in studying cell mechanics is to develop integrated computational models that capture and simulate the response of cells and subcellular components over a wide range of temporal and spatial scales spanning several decades. An additional level of

complexity arises from the intricate coupling and interplay between structure, function and external stimuli. To put this in perspective, we have illustrated in Fig. 1b the various structures encountered as one traverses the length scales involved in biomechanics. Shown in Fig. 1c is the available computational toolbox in cell mechanics; this is a collection of various computational models that have been used to model cellular, subcellular and biomolecular responses.

Continuum approaches are generally applicable when the smallest length scale of interest is much larger than the length over which the structure and properties of the cell vary. Appropriate coarse graining of local microscopic stress–strain relationships then yields continuum descriptions of material behaviour that apply at macroscopic levels. Figure 2 illustrates commonly used experimental techniques that have been developed to measure the overall mechanical response of individual cells. In each case, we also indicate continuum-based computational models that are commonly used to interpret results from these experiments. However, when the length scale of interest is comparable to the structural features of the system under study, as for example in protein folding and fracture, continuum approaches are inadequate. To understand phenomena at such small scales, microscale approaches such as atomistic and molecular simulations or network theories have to be used.

CONTINUUM-BASED COMPUTATIONAL APPROACHES

Two issues of critical importance in the development of continuum-based approaches are the choice of material laws and the numerical algorithm. The finite-element method is the most common technique used to solve continuum-scale constitutive equations arising in biomechanics. Computational models based on this method have been used to study a wide range of cellular processes at various temporal and spatial scales, from cellular response under localized mechanical stimuli to cell motility^{25,26}. The main advantage of this technique is that both material and geometrical nonlinearities can easily be incorporated. Furthermore, numerical schemes associated with this technique are well developed and efficient and have been implemented in commercially available software. Alternative techniques such as the boundary-element method have also been used in cases when it was more appropriate to do so^{27,28}.

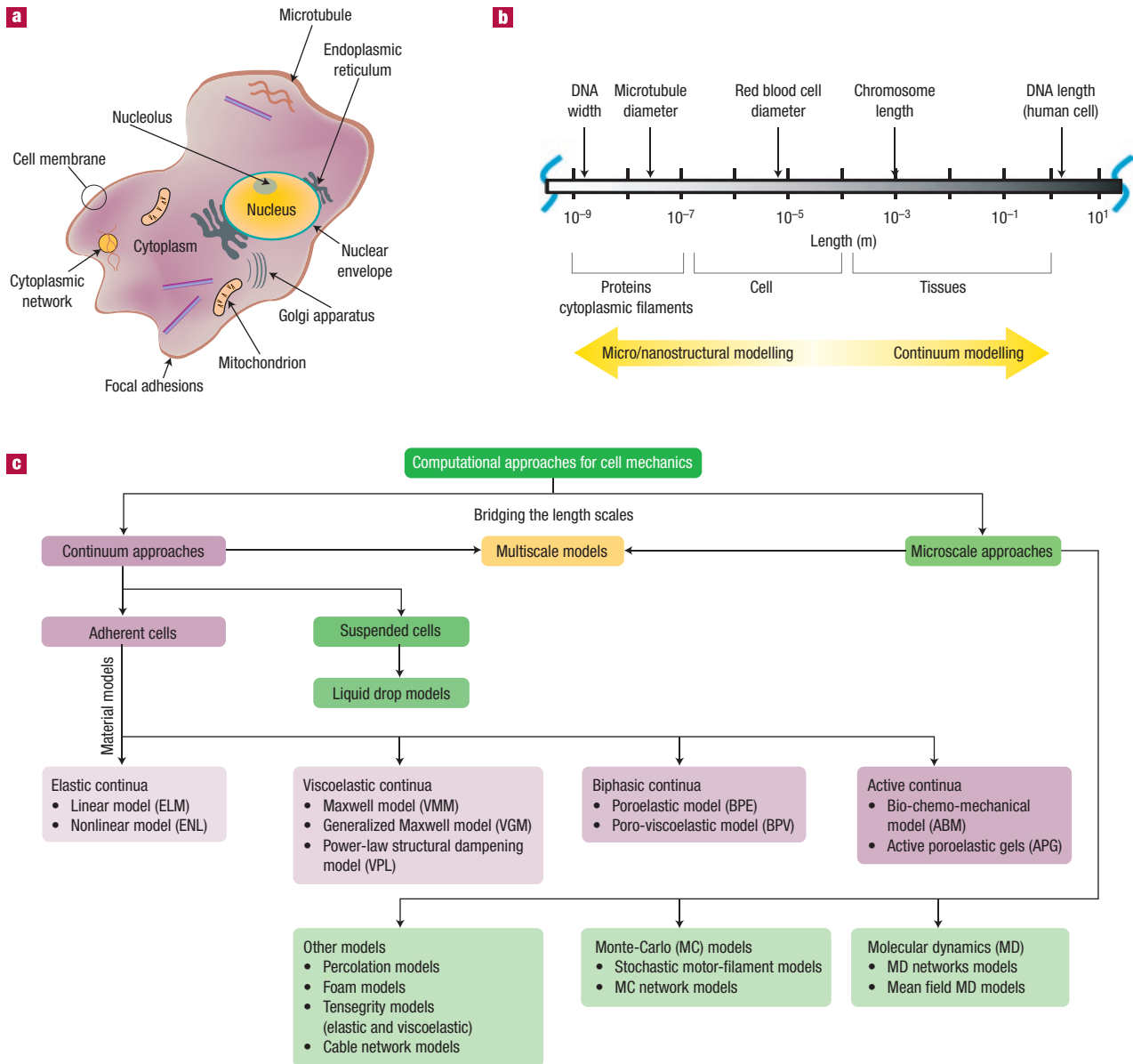


Figure 1 Computational approaches in cell and biomolecular mechanics. **a**, Schematic diagram of a eukaryotic cell and its major components. The cytoskeleton consists of networks of microtubules, filaments, organelles of different sizes and shapes, and other proteins. The cell membrane is a phospholipid bilayer membrane reinforced with protein molecules. **b**, Diagram of the spectrum of length scales encountered in biomechanics. Micro/nanostructural approaches are used in understanding structure and function and their interaction at very small length scales, whereas numerical approaches based on continuum modelling are used at larger scales, as in cell mechanics and tissue engineering. **c**, The complementary computational toolbox encapsulating current computational approaches for living cells.

A key challenge in constructing continuum-based computational models for cell mechanics is choosing material laws capable of faithfully representing complex stress–strain relationships of cells and subcellular components and their alteration as a result of mechanical, biochemical or electrical stimuli. The material constants associated with these models are usually obtained by measuring the response of cells and subcellular structures by using canonical experimental techniques and comparing these experimental results with computational predictions. Examples of this protocol are afforded by the estimation of the stiffness of round endothelial cells and their nuclei by a microplate compression test²⁹.

Appropriate laws for representing cellular behaviour depend on the experimental condition, such as the level and rate of loading, as

well as the cell type. In general, purely elastic models fail to capture certain important behavioural aspects of cells such as motility, whereas purely liquid models cannot predict the resistance of living cells to mechanical stresses. In modelling cytoskeletal mechanics, material laws are typically selected to fit experimental observations over a limited range of loadings and frequencies^{30,31}. Recent experiments performed over a wide range of excitation frequencies reveal that the rheological behaviour of the cytoskeleton follows a relatively simple power-law model called soft glassy rheology^{32–35}. Investigations of the rheology of actin gels containing a single actin crosslinking protein indicate that the power-law behaviour might be an intrinsic feature of actin systems with only one or two binding proteins present³¹. This rheological behaviour is influenced by the mechanical prestress in

the cytoskeleton, which is shown to govern the transition between solid-like and fluid-like behaviour in cells. This effect is manifested as a decrease in the power-law exponent with increasing prestress³⁶. The emergence of this relatively simple power-law behaviour for complex structures such as the cytoskeleton and actin gels has motivated both theoretical and computational efforts to interpret these experimental observations³⁷. Methods that are in current use provide insight into many behavioural aspects of living cells; at the same time, certain observations such as the focused propagation of mechanical stimuli applied to the cell membrane in the cytoskeleton^{38,39} cannot be explained adequately. Unravelling the mechanisms behind these entails the development of new theoretical and numerical models^{40,41}.

Continuum-based approaches have also been used successfully to study the properties of subcellular components, such as the mechanical properties of the nucleus and its associated structures. The nucleus is the defining feature of eukaryotic cells and a site of major metabolic activities, such as DNA replication, gene transcription and RNA processing. Cytoskeleton-mediated deformation of the nucleus has long been considered a pathway through which shear stresses applied to the cell are transduced to gene-regulating signals⁸. The mechanisms underlying this process and details of the mechanical connection between the cell membrane and its nucleus are still far from being understood. Computational models that distinguish between the structural role and response of major subcellular components can help immensely in elucidating these mechanisms^{38,42}. For example, a recent model for an isolated nucleus suggests that local perturbations of the nuclear envelope can be transmitted over a large section of the nucleoplasm⁴². This finding, in combination with the recent observations showing that membrane-bound organelles push the nucleus locally⁴³, suggest a possible pathway through which mechanical forces applied to the cell could lead to gene alteration. However, the proposed computational model, which includes separate components representing the nucleoplasm, the nuclear inner and outer membranes and the nuclear lamina, has a direct implication for understanding the influence of various alterations in the nuclear lamina⁴⁴, such as mutations in the gene encoding lamin A/C and its binding partners, which have been associated with a variety of human diseases^{45,46}. In a similar manner, these computational models can help in measuring the mechanical characteristics of living cells and resolving the apparent discrepancy of the present data^{42,44}.

Systematic application of computational models in conjunction with state-of-the-art experimental techniques has provided a robust protocol for studying the mechanics of cells and nuclei. This protocol has been applied recently to understand the biomechanics of red blood cells (RBCs)^{47–51} (see Fig. 3). The study, which combines experimental techniques based on optical tweezers and detailed three-dimensional computational models, has complemented the theoretical models that relate the metabolic activity of RBCs to their mechanics^{52,53}. This approach makes it easy to identify readily measurable factors that are directly affected by disease. In the particular case of RBC infection by the parasite *Plasmodium falciparum*, which is responsible for most of the mortality caused by malaria⁵⁴, the state of infection is directly related to the mechanics of whole-cell deformation and its cell membrane⁵¹, as illustrated in Fig. 3d. Quantification of the material properties of RBCs was achieved by three-dimensional computational simulations, revealing a tenfold increase in the elastic stiffness of infected RBCs at advanced stages of intracellular parasite development compared with the normal RBC. These findings, in combination with recent studies on the flow of malaria-infected RBCs in microfluidic channels⁵⁵, have provided new insight into the underlying mechanisms of disease progression.

Computational models offer immense scope in the field of viral studies and the connection between infectivity and structure. An example is the recent study on the internal morphological reorganization that HIV and some other retrovirus particles undergo

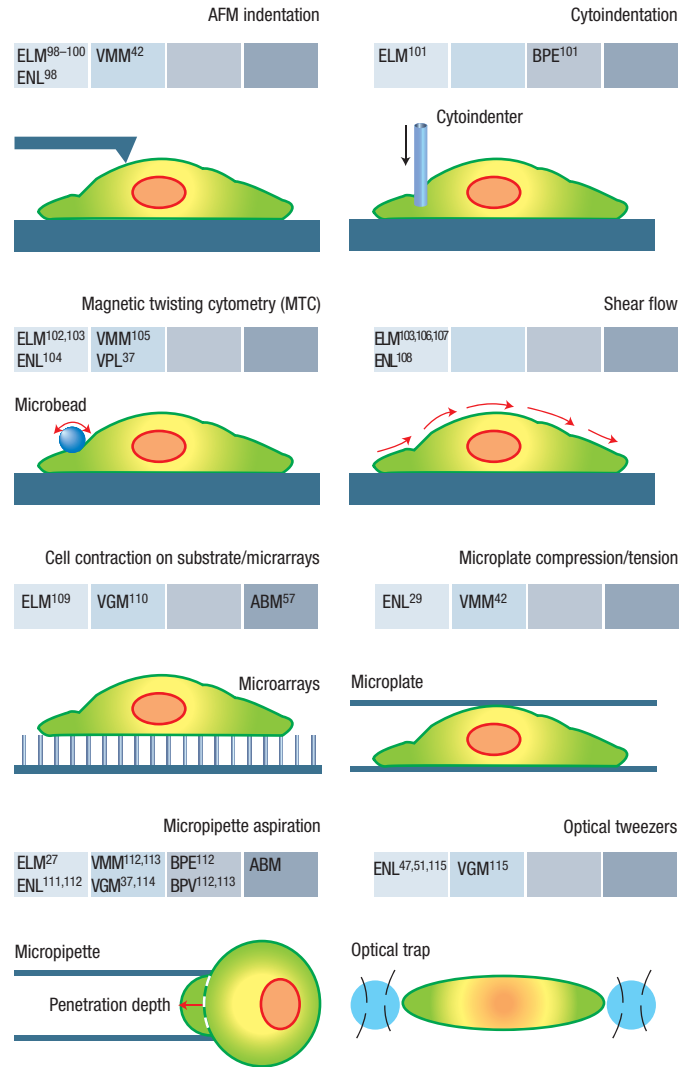


Figure 2 Experimental techniques in cell mechanics and the corresponding continuum-based models. The abbreviations were introduced in Fig. 1c under the ‘continuum approaches’ category. In these computational models, the cell or nucleus is modelled as one homogenous, isotropic material, except in refs 37,42,105,107,110. All the computational models are based on the finite-element method except those in refs 27,114, which are based on the boundary-integral method. The blue boxes denote the overall level of complexity of the model, which increases from light to dark blue.

after budding from a cell⁵⁶. Nano-indentation experiments with an atomic force microscope indicate that immature HIV particles are an order of magnitude stiffer than mature particles; this difference is primarily due to the cytoplasmic tail domain in the HIV envelope. Finite-element simulations used to elucidate the effects of deleting the cytoplasmic tail domain offer strong evidence that changes in mechanical properties, in this case the softening of the viral particle, might be a crucial step in the infection process. Once an understanding of this mechanical change has been gained, attempts to block or change this process may be used as a method of circumventing this intrinsic morphological switch and thus retarding infection.

A basic assumption in commonly used computational models is that the cellular material is passive in nature. Recent studies have attempted to remedy this by incorporating the inherently active nature

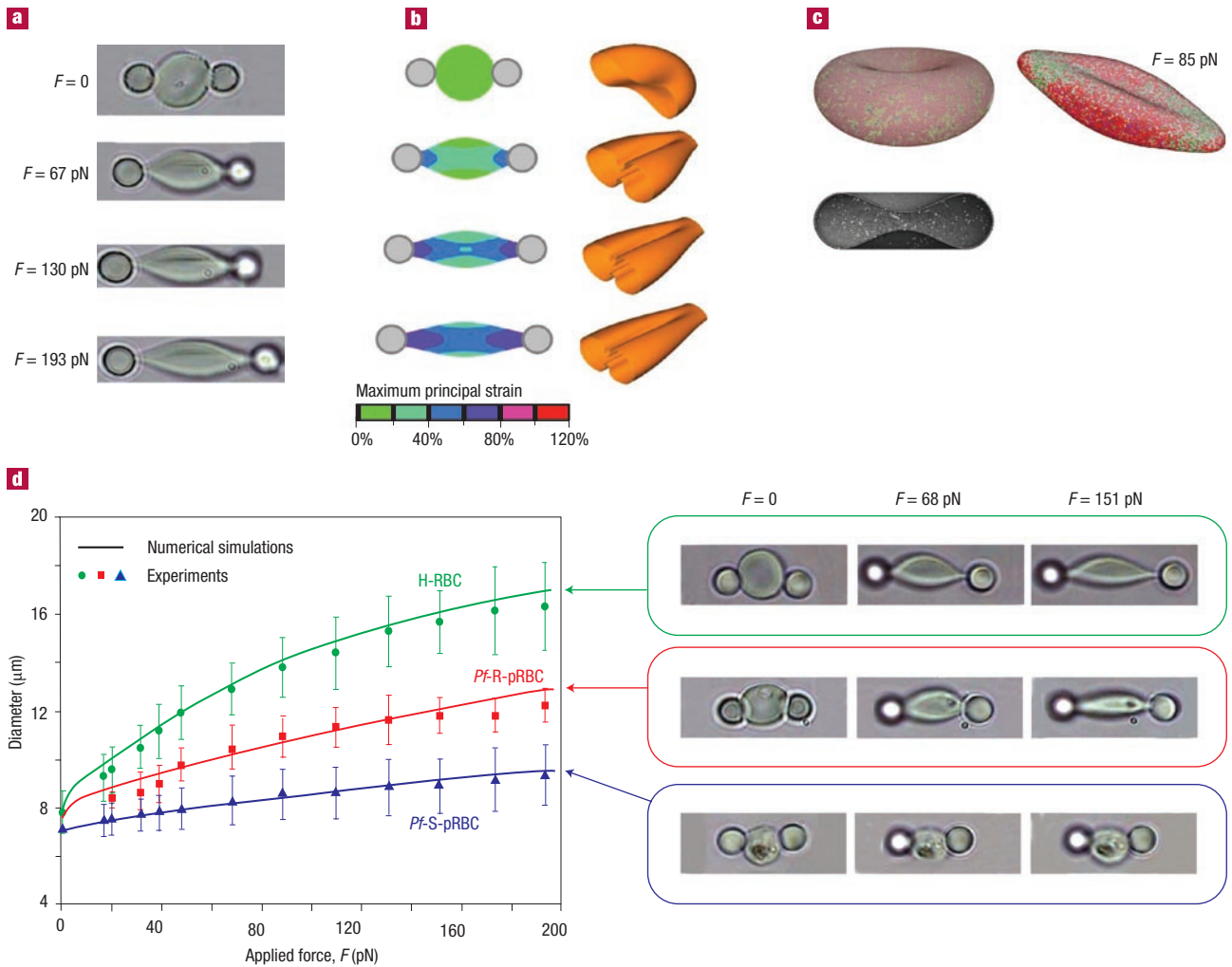


Figure 3 Biomechanics of the human RBC in health and disease. **a**, Optical microscopy images of a normal RBC in an optical tweezers experiment at four levels of applied force. **b**, Numerical simulations of the optical tweezers experiment with the use of a three-dimensional finite-element model. Distribution of the maximum principal strain (left) and the deformed configurations of the RBC (right) are shown at the same levels of loading as in **a**. **c**, Alternative computational model for stretching of RBC based on spectrin molecular-level modelling (the overall geometry and the cross-section of the model are shown). The deformed configuration of a RBC subjected to a stretching force of 85 pN is also shown. The predicted deformed configuration is consistent with that obtained with the three-dimensional finite-element model as well as the experimental observations. **d**, Biomechanics of RBC infected by the malaria-inducing parasite *P. falciparum*. During asexual development, the stiffness of the RBC increases steadily. Left: variation of the axial diameter of RBC with applied force in an optical tweezers experiment for normal RBCs (H-RBC, $n = 7$) and RBC infected by *P. falciparum* at the ring stage (Pf-R-pRBC, $n = 5$) and the schizont stage (Pf-S-pRBC, $n = 23$). The error bars show the standard deviation from the mean for each experiment for n cells. The solid lines are from three-dimensional finite-element simulations of an optical tweezers stretching experiment of RBC with an effective shear modulus of the cell membrane equal to $5.3 \mu\text{N m}^{-1}$ (H-RBC), $16 \mu\text{N m}^{-1}$ (Pf-R-pRBC) and $53.3 \mu\text{N m}^{-1}$ (Pf-S-pRBC). Right: optical images of H-RBC, Pf-R-pRBC and Pf-S-pRBC at three levels of applied force. (**a** and **b** are reprinted with permission from ref. 48; **c** is reprinted with permission from refs 49 (left) and 50 (right); **d** is reprinted in part with permission from ref. 51.)

of the cell. For instance, computations that take into account the role of activity in mediating and controlling cell function have recently been proposed and used to simulate cell contractility⁵⁷ (Fig. 4). The proposed model, which accounts for dynamic reorganization of the cytoskeleton, is capable of predicting and simulating important experimentally observed characteristics, such as the high concentration of stress fibres at focal adhesions where the cell grips the substrate and the dependence of the forces generated by the cell on the compliance of the substrate (Fig. 4b). The use of computational models that incorporate activity, and thus coupling between material properties and mechanical state, provides invaluable insight into the dynamic structure of the cytoskeleton⁵⁸ and the interplay between mechanics and function at

the single-cell level. Moreover, these ‘active continua’ models can help in addressing one of the key challenges in cell mechanics discussed previously: measuring the material characteristics of living cells⁵⁷.

MICROSCALE SIMULATIONS FOR MODELLING AT SUBCELLULAR SCALES

The macroscopic response of living cells to stimuli is ultimately governed by active processes and biochemical reactions, which occur at much smaller length scales^{3,5,6}. At the single-molecule level, the mechanical characteristics and structure of individual biomolecules critically determine their ability to function⁵⁹⁻⁶². At the same time, overall cell and tissue behaviour emerges from collective interactions

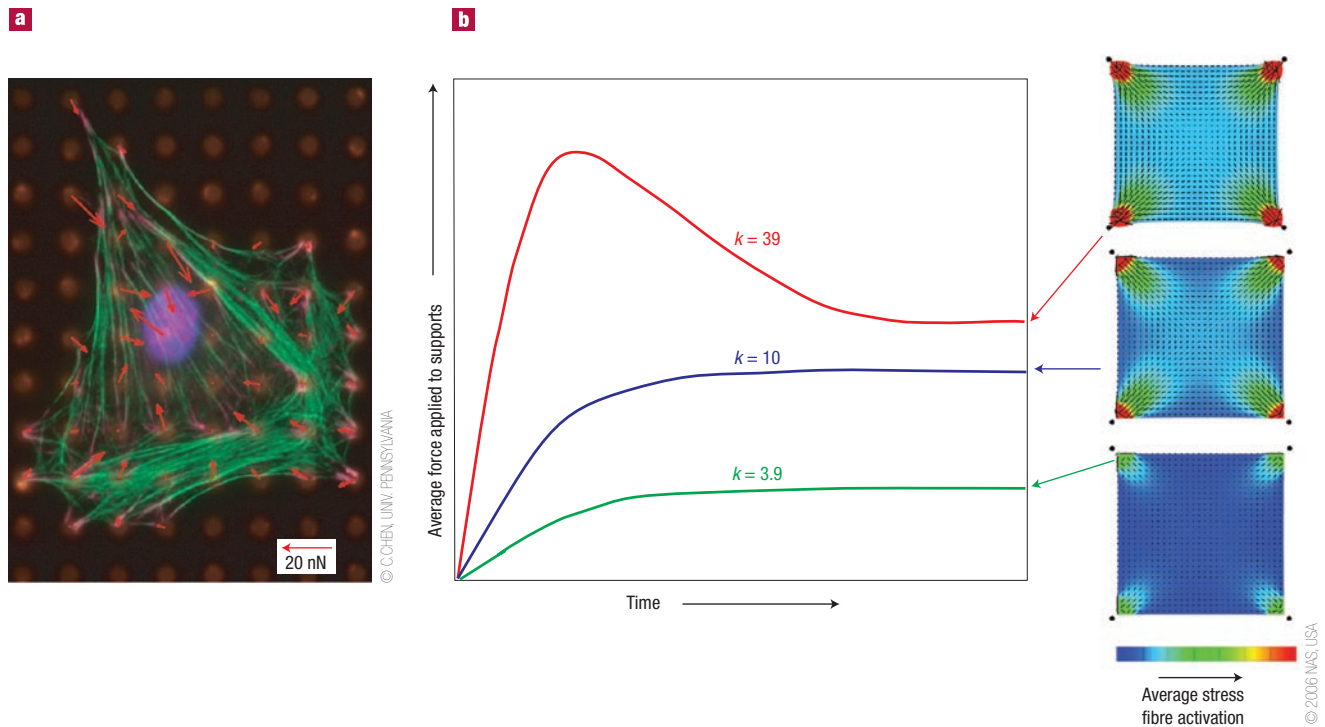


Figure 4 Bio-chemo-mechanical model for cell contractility. **a**, A fibroblast cell on a bed of microneedles. The actin fibres are stained green. The arrows show the force exerted on the microneedles. **b**, Time evolution of the force exerted by a square cell on an array of four posts plotted for three values of the normalized support stiffness, k . The distribution of the average stress fibre activation over all orientations at steady state is also shown. The filled circles indicate the original positions of the cell corners. (Figure reprinted in part with permission from ref. 57.)

between structures within the complex biomolecular networks. The paramount need to further the structure–function paradigm has led to significant advancements in computational techniques for probing the characteristics of subcellular structures. Existing microstructural and nanostructural approaches can be classified into three broad categories, as illustrated in Fig. 1c. Molecular dynamics models developed from deterministic algorithms are more commonly used for studying the behaviour of single biomolecules. Monte-Carlo methods, in contrast, comprise a class of stochastic computational algorithms in which the system under study can evolve by accessing alternative states as it moves towards an equilibrium conformation. Some studies have also used a hybrid molecular dynamics–Monte-Carlo approach in understanding the mechanics of biomolecules⁶³.

Alternative approaches using tensegrity-based discrete models^{64–66}, cell-foam approximations^{67,68} and cable network models^{69,70} have provided valuable insight and quantitative predictions of the mechanics of cells. In its original formulation the tensegrity model was more suited to a description of the static behaviour of adherent cells. However, recent extensions to this formulation that incorporate viscoelasticity and prestressing have been proposed^{66,71}. These models are capable of capturing and predicting key features of the frequency-dependent cytoskeletal behaviour and thus permit extensions to studies on active cells.

Network models based on Monte-Carlo and molecular dynamics simulations have been used to study the whole-cell equilibrium and large-scale deformations of RBCs^{49,50,72}; a set of results is shown in Fig. 3c. At the length scale of individual biomolecules, both molecular dynamics and Monte-Carlo simulations are increasingly being used in studying the folding, misfolding^{73–77} and mechanics^{62,78–80} of single biomolecules and proteins. Figure 5 shows a set of results based on recent studies on the mechanics of collagen, which constitutes about

one-quarter of all proteins in the human body. The deformation map of the collagen fibril presented in Fig. 5c was obtained by relating the macroscopic mechanical response of fibrils to its distinctive structure and amino-acid composition by using multiscale modelling approaches based on atomistic and molecular simulations. These calculations have provided a unique insight into the characteristics of collagens by considering different nanostructure designs and details of the molecular and intermolecular properties. Figure 6 shows the results based on molecular dynamics simulations on collagen-like model peptides, which illustrates the mechanics and dynamics of collagenase cleavage near imino-poor sites as well as the effects of hyperglycaemia on collagenolysis. The free-energy profile presented in Fig. 6c suggests that folding to an ideal triple-helical structure at the site of a Gly→Ser mutation in collagen sequences associated with some forms of osteogenesis imperfecta is unfavourable⁸¹. In contrast, Fig. 6d suggests that glycation affects the accessible conformational states of collagen, shedding light on how hyperglycaemia, and hence diabetes, may affect collagenolysis. These data provide new insight into events and factors underlying the formation of misfolded proteins and therefore the mechanisms of collagen degradation — a critical factor in the progress of several human diseases such as arthritis and atherosclerotic heart disease. In another example, Monte-Carlo simulations and NMR were coupled to construct a coarse-grained energy landscape for α -lactalbumin in the absence of urea to obtain information about the folded states of associated proteins^{60,82}.

MULTISCALE COMPUTATIONAL APPROACHES FOR BRIDGING THE GAP

Understanding the structure–function paradigm entails the simultaneous resolution of the cell and subcellular characteristics over a wide range of spatial and temporal scales. For this purpose,

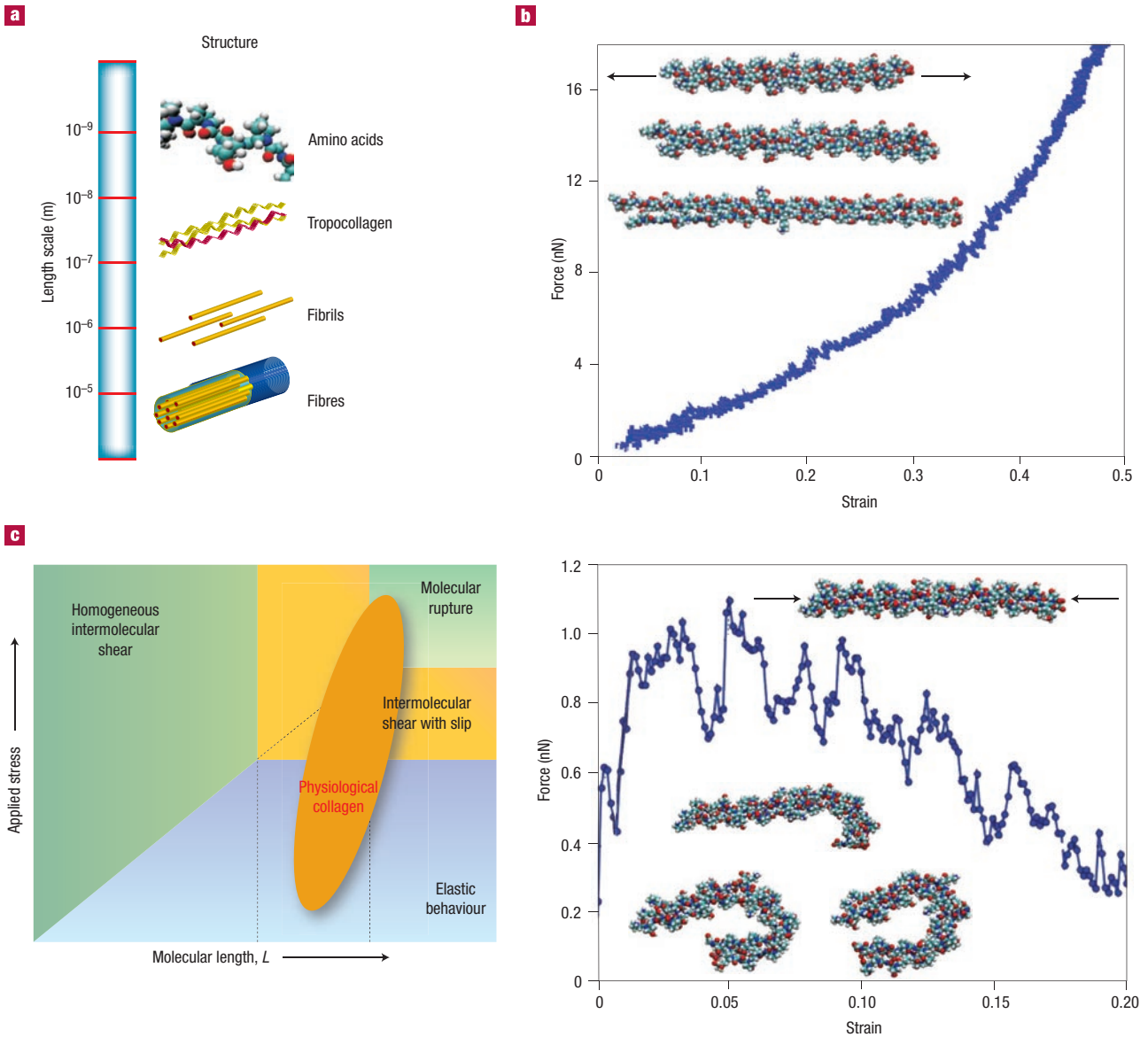


Figure 5 Biomechanics of collagen. **a**, Hierarchical structure of collagen. **b**, Force–strain response of a single tropocollagen molecule under uniaxial stretching (top) and under compression (bottom). Insets show snapshots at various levels of deformation. The maximum load that can be sustained by the tropocollagen molecule under pure compression is predicted to be much lower than that under tension because of buckling. The simulations also reveal the underlying mechanisms of strain-hardening of the tropocollagen molecule under stretching. **c**, Deformation map of collagen fibrils obtained with a multiscale modelling scheme based on atomistic and molecular simulations. The results reveal that the mechanical response is governed by two critical length scales. The physiological collagen range is also shown ($L = 300$ nm). (**a** and **c** are reprinted in part with permission from ref. 62; **b** is reprinted in part with permission from ref. 80.)

pure continuum approaches are inadequate, and large-domain or long-duration microscale approaches might be prohibitively expensive. To address this issue, efforts have been made towards bridging the gap between microscopic and macroscopic simulations by development of multiscale approaches. Separate calculations are performed at different length scales and the results are combined to produce a full characterization. A major challenge in this process is in coupling the microscale and macroscale computations such that the correct mechanics and activity are simulated. A significant complication arises from the strongly nonlinear interactions as macroscopic mechanical effects provoke signal pathways, which may give rise to both local effects and non-local cell-wide changes. Even when considering properties and responses at macroscopic length

scales, it is imperative to take into account the cumulative effects of active microscopic processes.

Multiscale approaches developed in the field of cell mechanics can be classified into two categories. In the first, atomistic simulations at subcellular, microscopic or single-molecule level are used as input to coarse-grained mesoscopic computational models. These mesoscale models can then be coarse-grained further to predict averaged properties at continuum scales. A critical component of this two-step procedure is the judicious exchange of information between the multiscale descriptions. Multiscale computational schemes developed for modelling lipid bilayers^{83–85}, cell adhesion to extracellular matrix^{86–88}, cell motility^{89,90} and the mechanics and fracture of collagen⁶² are successful realizations of these approaches

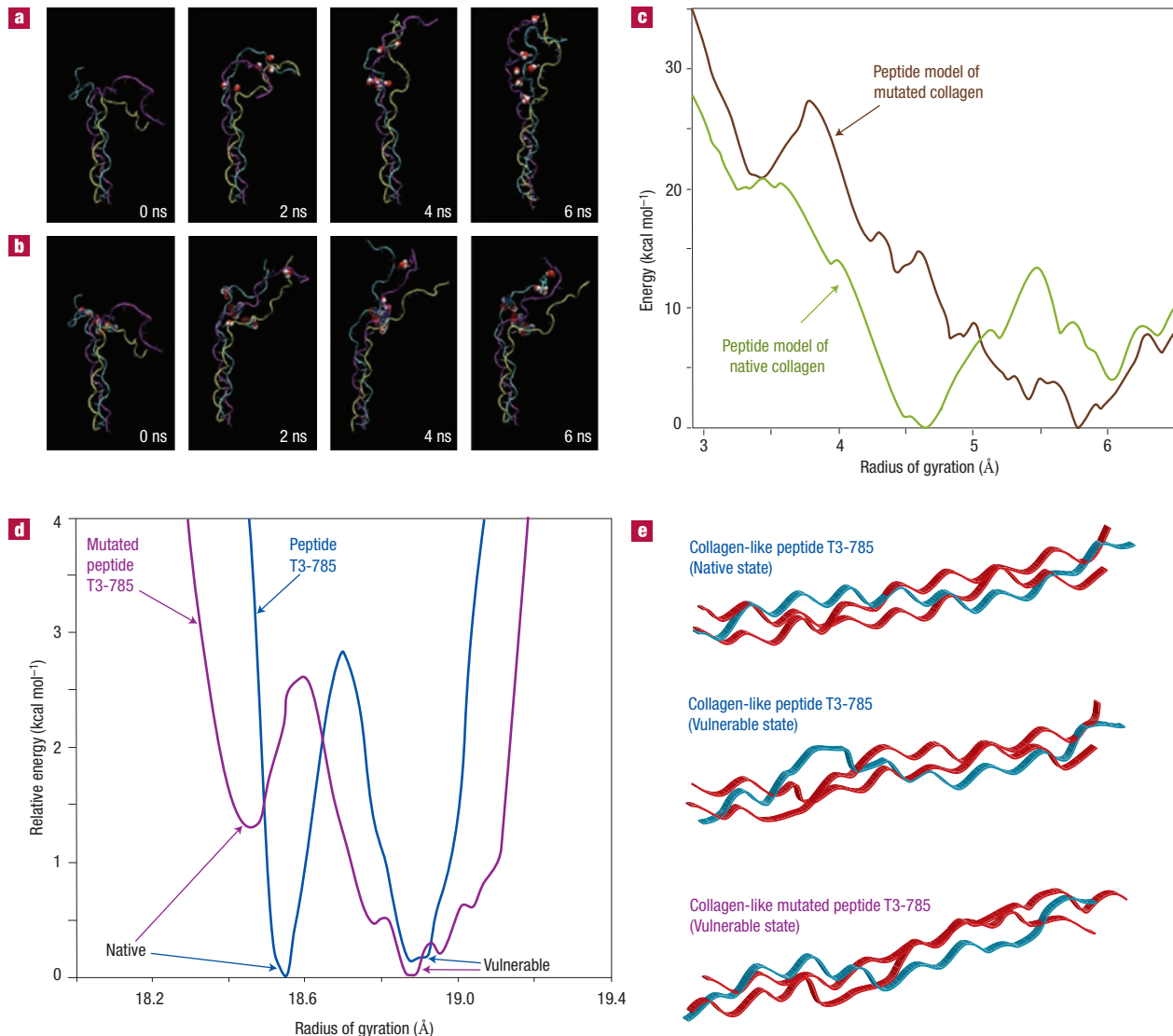


Figure 6 Role of mutation on protein folding. **a, b**, Folding trajectories (shown at 2-ns intervals) of peptide models of native collagen and of a mutant bearing a Gly→Ser substitution that models a mutation found in several forms of osteogenesis imperfecta. In **b** the relatively large Ser side chains prevent the peptide chains from packing closely together at the site of the mutation. **c**, Free-energy profiles for folding of the peptide models. For the peptide model with Gly→Ser mutation, the calculated free energy of the more compact state at 3.4 Å is more than 20 kcal mol⁻¹ higher than that of the state at 5.7 Å, suggesting that folding to an ideal triple-helical structure at the site of mutation is unfavourable. **d**, Free-energy profiles for folding of the peptide T3-785 models. These data suggest that imino-poor segments from collagen can exist in two states: the native state corresponds to the crystallographically observed conformation, whereas in the vulnerable state the imino-poor segments of collagen are partially unfolded. For glycosylated collagens (mutated peptide T3-785), the energy of the vulnerable state is almost 1.3 kcal mol⁻¹ lower than that of the native state, suggesting that most of the glycosylated collagen molecules exist in a vulnerable state. **e**, Representative structures from states in **d**. (**a** and **b** are reprinted in part with permission from ref. 77; **c** is reprinted in part with permission from ref. 77. **d** and **e** are reprinted in part with permission from ref. 73.)

(see Fig. 5c), providing a template for extensions of this approach to other applications. In the second multiscale approach the results from continuum computations at the single-cell or subcellular level are used as input to study behaviour and response at the tissue or organ level. These multiscale computations have been used in studying various aspects of the circulatory system, from the mechanical properties of the heart muscle due to ageing and plaque to cardiovascular circulatory mechanics⁹¹. Another example of the application of such multiscale approaches is in understanding the underlying mechanisms of morphogenesis, which is a complex developmental phenomenon that involves cell growth, division, rearrangement and flow in a well-defined manner⁹².

CONCLUDING REMARKS AND PERSPECTIVES

Variations in microstructural sequences at the single-molecule level ultimately influence macroscopic properties of the whole cell and critically influence the energy landscape characterizing the conformational changes as biomolecules perform various functions. Knowledge of this landscape obtained by means of computational methods can eventually be used to engineer proteins with desired characteristics. Macroscale mechanical stress and external stimuli also trigger microscale responses. Established continuum-based models can provide accurate details of stress and strain distributions induced at the cell level, which in turn can aid in predicting the

distribution and transmission of forces to the cytoskeletal and subcellular components. This can then assist in the refining of more accurate microscale models.

Active cytoskeletal reorganization and prestress have now been recognized as driving forces behind cell deformation, motility and function. Most work in this respect has focused on experimental investigations. Recent theoretical work has involved deriving closed-form continuum models for active cytoskeletal dynamics, taking into account energy expenditure and input through coupling between microtubule structures and motor activity^{93,94}. We envisage that coupling this formalism to computational finite-element-based schemes, by incorporating prestressing and polymerization kinetics, will provide the critical step needed towards understanding the mechanics of active and deformable cellular systems as described recently for human RBCs⁹⁵. The application of active models to understanding the role of mechanics in the development and onset of atherosclerotic lesions has also been demonstrated recently⁹⁶. A novel illustration of the rapid progress made in this regard is a continuum-based model of neutrophil mechanics that takes into account the mechanical characteristics of individual cytoskeletal components and the role of active force production⁹⁷. The success of this approach arises from the fact that the proposed protocol is able to identify the dominant factors contributing to active force generation. Such detailed modelling can serve as a framework within which experimental data can be analysed efficiently and can also provide directions for further experimentation.

In conclusion, despite the recent developments in algorithms and rapid enhancements in computing speed and efficiency, computational approaches are yet to be thoroughly exploited. Current efforts towards the development of novel multi-physics and multiscale approaches are envisaged to lead to new applications in several fields such as computational biophysics, nanobiotechnology, tissue engineering and medicine. Considering the ease of application, improved computing speed and the versatility of computational approaches, we expect rapid and exciting developments in cell and biomolecular mechanics in the years to come, which could potentially affect the life of thousands of people around the world.

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