Micromechanics of engineered and biological systems

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This review paper is concerned with the mechanics issues at the micron scale. The topics considered here are microsystems (microelectromechanical systems – MEMS), microfluidic devices, and biological cells. Mechanics is important for all the three fields. Micromechanics of solids is important for microsystems while microfluid mechanics is essential for microfluidics. Understanding the mechanics of cells requires both and much more. We highlight here some of the major advances and important challenges in all the three fields.

1. Introduction

This review paper focuses on three aspects of mechanics of systems of small size: microsystems (microelectromechanical systems – MEMS – as they are popularly known), microfluidics, and biological cells. The three topics are substantially different from each other but there is significant interplay among them. The critical dimension of micron size is of course common to all three. However, when we consider devices and systems, the size sometimes tends to be much bigger than a micron; and sometimes it can be much smaller than a micron going down to a nanometer when we try to understand a phenomenon or to make an idea work in a device. The bigger than micron size mainly comes because of microsystems. While the critical dimensions of micromachined sensors, actuators, and devices are indeed of micron size, their packaged size tends to be much bigger. Cells are of micron size but their mechano-transduction takes place because of entities much smaller than a micron – down to proteins of nanometer size. Tissues are necessarily bigger than cells and they exhibit behaviour that can be understood from the investigations on the single cells but not all of it. So, it suffices to say that they are all small and hence different from the traditional ‘macro’ phenomena and systems – engineered or biological. Another critical aspect that ties the three topics of this paper together is microfabrication and micromachinery. Without the ability to make intricate structures of small size, to actuate and to control them, these devices would not have come into existence. Without the micromachinery, which includes sensors and actuators, quantitative investigation of the behaviour of cells is unthinkable. To make it all work, we need an understanding of mechanics issues and that is the focus of this paper.

1.1 Microsystems

Here, we use the word ‘microsystem’ rather than ‘MEMS’ because the latter is restrictive as it only conveys mechanical and electrical aspects. Microsystems are good examples of integrated engineered systems of small size. Although this field started in early 1970s, its formal identity came only in late 1980s \cite{1}. In the two recent decades of its intense activity and growth, the emphasis has been on sensors and actuators and some integrated systems. Undoubtedly, rapid advances in microfabrication techniques for silicon and other materials have played a major role in the development of the microsystems field. It is also pertinent

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to note that mechanics too has played an equally important role. The origin of much of the difficulty in simulating and designing a microsystems component or device lies in two things: coupling with other energy domains and scaling effects. There is not a useful microsystems device that operates without involving more than one energy domain. A simple beam-based switch needs actuation to work. If this actuation is electrostatic force, coupling between elastic structures and electrostatic field ensues. A diaphragm-based micro-pump involves a strong coupling between solid and fluid mechanics fields and also couples with a field associated with what actuates it. Often the coupling between the fields is strong and, in some cases, unprecedented at the macroscale. It is important to note that mechanics couples with other energy domains in all these problems. Consequently, new approaches – both analytical and numerical – are warranted to efficiently simulate or design microsystems devices. A key component of this effort is the need for model reduction. As multiple energy domains are solved simultaneously to simulate the behaviour of an integrated microsystems device, usually requiring the solution of two or more coupled partial differential equations in spatial and temporal domains, the computational complexity tends to be very high. The degrees of freedom involved will be large too. The results of such simulations are useful to see if a device works or not but they are not necessarily amenable for gaining insight and for designing efficiently. Hence, microsystems researchers often resort to model reduction. It can be done analytically in some cases [2] but not always. Therefore, techniques for model reduction are developed. Some of these are available today in microsystems design software but there is a lot more to be desired in this direction.

Scaling effects are many as we move down to the micro size. Although continuum mechanics assumptions do not break down at this scale for deformable solids, a number of problems come to the fore because of the small size. Residual stresses and the stress gradients are common in microfabrication processes. These tend to be very high as compared with the stiffness of the micromechanical structures. Hence, unintended deformations occur if the effects of residual stresses are not properly accounted for. The inhomogeneity of residual stresses is hard to characterize and control in a microfabrication process. The same is true of anisotropic properties of materials. There is often disagreement on basic properties such as Young’s modulus when it is determined with different methods [3]. Stiction is another major problem in deformable structures with features separated by narrow gaps. This is especially so when a deformable structure is released by dissolving a sacrificial (fugitive) layer that holds the releasable structure until the end of the process. The surface tension forces arising from the liquid in the narrow gaps is large enough to pull the deformable structure down and make it stick to the substrate. Moisture and electrical charge accumulation also lead to stiction. Narrow gaps also lead to another complication because the fluid (mostly air surrounding the device) causes squeezed film effects [4]. In general, flow behaviour is intrinsically coupled with the microsystems area. More details on microfluidics follow next.

1.2 Microfluidics

The ever-increasing possibilities of creating structures and patterns on small length scales with ultra-tunable precision have triggered a wide range of scientific investigations involving the transportation and manipulation of fluids in miniaturized devices and systems. These types of investigations, broadly classified under the theme of microfluidics (concerning flow length scales over micrometer ranges) or nanofluidics (concerning flow length scales over nanometer ranges), have rekindled interests in a classical area of fluid dynamics: low-Reynolds-number flows, with a fusion and agglomeration of concepts from molecular physics, surface chemistry, and life sciences. As a commonly acceptable metric, microfluidics refers to the control of small volumes of liquids (fL–μL, 10^{-15}–10^{-6} L). Traditionally, silicon micromachining methods have been used to fabricate micron-scale channels from silicon and glass for transporting these ultra-small fluidic volumes. Other types of materials (such as polycrystalline silicon) are also being extensively used. The latter systems offer potential advantages of faster design times, low cost, the ability to fabricate nanoscale features, and the possibilities of obtaining deformable shapes.

The principal components of the present day microfluidics are lab-on-a-chip devices, which are nothing but miniaturized analytical laboratories, typically consisting of a network of microchannels and reservoirs on small glass or plastic chips. Additionally, these chips may contain electrodes, sensors and electrical circuits, for performing the desired protocols. Such devices are capable of duplicating some specialized functionalities as their larger-sized counterparts in the macroscopic world, such as clinical diagnostics, DNA scanning, cellular analysis, and separation processes. However, with a dramatically reduced sample volume requirement, the lab-on-a-chip concept leads to much shorter reaction and analysis times, higher
throughput, automation, design flexibility, and portability. Modern developments in the design and utilization of microfluidic devices have found many applications, ranging from the life sciences industries for pharmaceuticals and biomedicine (drug design, delivery and detection, diagnostic devices) to industrial applications of combinatorial synthesis (such as rapid chemical analyses and high-throughput screening). In other branches of medicine, new paradigms for noninvasive diagnostics and surgery (possibly implanted or ingested) have also been possible through the developments of microdevices. Such miniaturized micro-total-analysis systems (μTAS) are advantageous in many respects, particularly attributed to the fact that smaller devices are lower in cost, are less energy and material consuming, and are minimally invasive and conveniently disposable without contamination. Furthermore, sophisticated micro analytical systems can be built using individual chip mono-blocks, thereby integrating different complex functionalities together on a small scale in a coherent manner. In the non-biological sector, there are numerous applications as well, including electronic chip cooling and inkjet printing. Inevitably, all these devices would necessitate the handling and processing of small amounts of fluids, and this is where fluid mechanics of small scale systems comes into play.

Fluid mechanics at the small scale is often intriguing. It is a vast area of research by itself. In this paper, we will by no means attempt in detailing with all the related issues, but would emphasize on a few salient features that may hold the key towards unveiling several apparently non-trivial facets of this extremely interesting topic. There is, of course, a common synergy behind the central theme of our discussions: as the length scales become smaller, surface effects tend to dominate. Thus, inertia forces turn out to be negligible in comparison to electrostatic, electrodynamic, viscous, or capillary effects. The later effects, therefore, may strongly influence the flow behaviour, in a manner much more emphatic than in classical macro-flows.

Solid mechanics of microsystems and fluid mechanics at the microscale arise in interesting and complex ways when we consider biology at the microscale. We discuss this next.

1.3 Biomechanics of cells

Mechanics and cellular biology were intimately coupled with each other at the inception of both of these fields: it was the same Robert Hooke who hypothesized the fundamental law of mechanics – the Hooke’s law – by relating stress and strain in a solid and also observed the cork cells for the first time and coined the term ‘cell’. Since then mechanics and biology have moved on more or less separately but are now coming together to enrich each other. It is also pertinent to note that Francis Crick, the co-discoverer of the double helix structure of DNA also has the credit of performing one of the earliest mechanics experiments on cells. Thus, there have been instances where researchers saw synergy between biology and mechanics.

Application of mechanics to biology and the development of mechanics for biology have been active at the macroscale for skeletal and bone mechanics, locomotion studies, hemodynamics and blood circulation in living systems, muscle behaviour, and others [5,6]. But biomechanics, in the context of this article, can be described as a field that involves the application, development, and extension of mechanics applied to biological problems at the molecular, cell, and tissue levels. We restrict our discussion to cells here because of the focus on the micromechanics.

Investigations into the mechanics at the cellular level help uncover the fundamental ways in which cells function. The mechanical properties and the forces have been shown to play important roles in cell behaviour and responses. Examples cover both healthy and disease-affected cells. It has been shown that mechanical stretching of transmembrane proteins enhances self-assembly and organization [7]. It is also shown that striation of muscle cells requires a substrate of moderate stiffness: too soft or too hard substrates are ineffective [8]. Another study has found that there is significant difference in the stiffness of healthy red blood cells and the malaria-affected ones [9]. In developmental biology, the application of controlled forces on growing embryos is shown to help in understanding how cells are differentiated at different stages [10].

The sensing of mechanical forces and characterization of mechanical properties at the micro and nanoscales is ably supported by the rapidly growing cell manipulation techniques. There have been good reviews of a variety of techniques for effecting and sensing forces up to femto ($10^{-15}$) N and sensing displacements up to a billionth of a metre [6,11–12]. The theoretical and practical bases for these tools lie in the fields of micro and nanomechanical systems. Thus, the field of microsystems is inextricably tied to the field of cellular mechanics.

2. Computational mechanics in microsystems

Continuum theory of solid mechanics mostly remains unchallenged at the sizes of microsystems.
This is especially true for the elastic regime in which constitutive stress-strain relationship is linear and is far from permanent deformation and failure. This is because elastically deformable structures in microsystems devices have to operate reversibly and repetitively. Nonlinearities in structural behaviour such as large displacements and rotations, contact, and stress-stiffening are present. But none of these pose as significant a problem in simulating these devices as the coupling of the elastic domain with other force fields does. The phenomena that do not matter at the macroscale become significant at the micro sizes. The result of the coupling and scaling effects is seen in electrostatically actuated micromechanical structures. Here, the structural deformation interacts nonlinearly with the static electric field ensuing between electrical conductors and dielectrics. As has been argued well in the literature, electrostatic force scales vary favourably at the microscale and therefore numerous microsystems devices use this. Many such devices are commercially available and yet not all problems associated with their simulation are completely resolved. We consider them in the next section.

Other widely used actuation techniques in microsystems devices are magnetic and electrothermal. Magnetic actuation, although thought to be unfavorably scalable to microsystems at the inception of the field, has now come back. The issue of requiring large currents to generate significant forces has been solved by using external magnetic field generated by powerful permanent magnets and, in some cases, having wound coils to get large magnetic fields in narrow areas. Fortunately, the coupling here is not strong enough to warrant any special techniques that are different from their macro-scale equivalents. Electro-thermal actuation, however, is different. If it is generating out-of-plane deformations, analysis of bimorph-type actuation is sufficient and is not involved. When it comes to in-plane actuation, sequential electrical, thermal, and elastic domain coupling needs to be solved. Among other things, temperature-dependent mechanical properties matter in this case. We consider this later in this section.

Modeling dissipation in mechanical structures is still a current issue in the dynamic simulation of micromechanics. Fluids squeezed in narrow gaps, thermoelastic damping, and surface energy are to be carefully accounted for. The need for careful modeling of dissipation arises because of the desire to achieve high quality factors, i.e., acutely sharp resonance peak in the frequency response of the microscale dynamic systems. It is also discussed in this section after describing the coupled electrostatic-mechanical and electrothermal-mechanical effects.

2.1 Coupled electrostatic-elastic simulations

A parallel-plate capacitor suffices to explain the coupled nature of the electrostatic forces and elastic behaviour of a deforming body. Imagine that one plate of the capacitor is fixed while the other end is made translatable by restraining it with a linear spring of spring constant, \( k \). Upon applying an electric potential \( V \) between the plates, the attractive electrostatic force acts on the movable plate and is given by \( \varepsilon AV^2/(2g^2) \) where: \( \varepsilon \) is the permittivity of the medium between the plates, \( A \) and \( g \) are the area of overlap and the gap of separation between the plates. Since the gap changes as the plate moves, the displacement, \( x \), is to be shown in the expression for the electrostatic force. The displaced linear spring has a force of \( kx \). As can be seen in this simple example, the equation equilibrium between the electrostatic force, \( \varepsilon AV^2/(2(g_0 - x)^2) \), and the elastic force, \( kx \), is nonlinear. Here, we have used \( g_0 \) to indicate the gap before the voltage is applied. This nonlinearity is so severe that catastrophic collapse, called electrostatic pull-in, occurs after the applied electric potential crosses a certain threshold appropriately called the pull-in voltage. At that critical voltage, the moving plate collapses onto the fixed plate. Furthermore, if there is a thin dielectric layer above the fixed plate, the plate remains in that pulled-in position until the voltage is lowered down to a pull-up voltage. When the displacement of the plate is plotted against the applied voltage, we see an apparent hysteresis [13]. This simple phenomenon becomes increasingly complex as we move to 2D and 3D continua with involved geometry such as what layered or anisotropically etched silicon micromechanical structures would have.

The equations governing the general 3D bodies in which coupled electrostatic and elastic fields exist are shown for a general geometry in figure 1. The electrostatic force, being a force that acts on the surface, appears as the coupling term in the elastic deformation equation. This can be seen in the equations in figure 1. What might not be immediately apparent is how the elastic structure influences the electric field. This arises because the deformation of the elastic structure changes the surface charge distribution, \( \psi_s \). Hence, the electrostatic problem has to be solved for the new deformed geometries of the conductors and dielectrics. This force is once again applied to the elastic structure to obtain its deformation, and then the process is repeated until both the governing equations are
solved self-consistently. The process is iterative and requires repeated analysis of the two domains to get a converged solution. Note that the re-meshing for the electrostatic calculation is necessary whenever the deformed geometry of the conductors and dielectrics changes. All this takes considerable computation time and today’s microsystems simulation software take a few hours to compute the pull-in voltage for practically useful microsystem components.

What is described above is a simple relaxation approach to the simultaneous solution of the coupled equations. By taking the sensitivities of the quantities in one field with respect to the quantities in the other, a Newton’s algorithm is often used to increase the speed of computation [14]. A combination of finite element and boundary element methods (FEM and BEM) is also used to solve this problem. This is because the electrostatics problem is an infinite domain problem. That is, the electrostatic equation is to be solved over the infinite domain from which the space occupied by the conductors is subtracted. In figure 1, we show the infinite domain as a sufficiently large bounding box at the boundaries of which the electric field is presumed to be sufficiently low and all the charges reside only on the surfaces of the conductors. Instead, if we consider the integral form of the governing equations of the electrostatic problem, the problem size reduces considerably as only the surfaces of the conductors need to be meshed in the boundary element method. The computational algorithm switches between BEM (for the electrostatic problem) and FEM (for the elastic deformation problem) in a staggered manner.

Instead of the staggered approach, recently, a monolithic approach to a simultaneous solution of the two governing equations is proposed. The key to this new method is the application of electrostatic force not as a surface force but as a body force by using Maxwell’s stress tensor [15–18]. This is given by

\[
\sigma_M = \varepsilon (\nabla V \nabla V - 0.5(\nabla V \cdot \nabla V)I)
\]

and hence \( \nabla \cdot \sigma_M \) applies at each point of the 3D continuum as a body force. As a result, there is no need for re-meshing in each iteration if
the electrical permittivity is smoothly interpolated in the entire region of the empty space, dielectrics, and conductors within the bounding box shown in figure 1. This approach increases the computational efficiency. Furthermore, it is useful in optimization-based design and can handle dielectric materials embedded within the domain.

The nonlinear coupling between electrostatic and elastic domains also gives a rich dynamic behaviour wherein chaotic motion can also be observed [19]. There are no reports of chaotic behaviour effectively used in microsystem device but it does become an important issue in the operation of the device and in its control. The chaotic response aside, simulating the nonlinear behaviour has important practical consequences in tunable capacitors [20], mechanical filters whose frequencies can be adjusted [21], radio frequency switches, etc. Here, for example, in the case of switches one would need to compute the time for pull-in and pull-up. A simple structure such as a cantilever too shows involved behaviour in terms of its pull-in geometries. With a voltage higher than the pull-in voltage, the beam does not just touch the electrically insulated ground substrate but zips onto it under certain circumstances. When it pulls up too, it can undergo different transformational states among zipping, tip-contact, and complete pulled up configurations [22].

The coupled simulation of electrostatically actuated micromechanical structures also needs to consider the residual stresses and their gradients (which is not so difficult), fluidic effects, and thermoelastic damping. The latter two are discussed in subsection 2.3.

2.2 Electro-thermal-elastic simulations

Many transduction mechanisms in microsystems require electric current to be passed through them. This means that there will be Joule heating and the ensuing thermally-induced deformations. Since most of the properties vary with temperature, it causes additional difficulties in simulation. Thermal forces can also be advantageous and can be used for actuation. Indeed, thermal force is quite large as compared with electrostatic force for the same applied voltage.

Simulation of electro-thermal microactuators requires a sequential or simultaneous analysis of three energy domains: electrical, thermal, and elastic. The governing equations of electrical current and thermal conduction are both diffusion equations. Solving them sequentially will suffice if electrical conductivity dependence on the temperature can be neglected. Thermal analysis, by itself, is complicated at the microscale because of insufficient knowledge about the heat transfer coefficients for convection and shape factors for radiation. One needs to model the fluid surrounding the deforming solid to obtain the heat transfer coefficients. But most often, microsystems researchers are content with borrowing empirical formula from the macro-scale literature. Because of the narrow gaps involved in micromechanical structures, one cannot be sure if conduction through air is to be modeled or convection. This issue is also not given importance in many a thermal simulation. Convection through vertical surfaces of essentially thin microsystem components is sometimes significant. Improper modeling of convection is known to give qualitatively different deformation patterns from those reality [23]. Hence, using a 3D model in numerical computations is imperative. When the elastic structure touches itself or another structure, as it happens in switches and other microsystems devices, thermal boundary conditions change suddenly. This causes additional complications. The basic issue of the type of boundary for the interface between the microsystem component and its substrate is debatable. We normally assume that there is a large thermal mass at that interface and impose Dirichlet (fixed temperature) boundary condition. But it will not be true if there are many such components located close to each other. Then, we may need a zero heat flux or a mixed boundary condition. On top of all of these, the knowledge of the temperature dependence of material properties is neither accurate nor complete.

Owing to all the above issues, electro-thermal-elastic analysis is not straightforward. Here, there are no unresolved conceptual issues but the numerical solution involves a lot of computation. Hence, there is a need for fast algorithms and better modeling capabilities to account for convection and radiation with few degrees of freedom and without having to model the fluid around the solid.

2.3 Dissipation in microsystems

Micromechanical structures are essentially dynamic systems because they move. Due to their internal structure and external environment, they do dissipate considerable energy that is put into them. Many dissipation mechanisms exist and almost all of them become important for microsystems and, more importantly, nanoelectromechanical systems (NEMS). Modeling dissipation is important in these systems because of the desire to achieve high quality factors (a consequence of minimal losses) and the demonstrated possibilities of achieving them through miniaturized mechanical
structures. The other reasons are achieving accurate predictive capability for the component-level and system-level behaviour of the devices. Due to the lack of accurate methods to estimate energy dissipation mechanisms, the experimentally determined quality factors have large discrepancy with the simulated values. It is thus currently an active area of research.

Dissipation mechanisms in microsystems can be classified into five types: bulk or internal damping, surface loss mechanisms, viscous losses to the surroundings, anchor losses, and package-related losses. Internal damping may be due to defects [24], phonon-mediated dissipation among different internal vibration modes [25], and thermoelastic damping. Of these three, thermoelastic damping, a special situation of the second, has received considerable attention in recent years.

Thermoelastic dissipation of energy is a consequence of irreversible heat flow between high and low temperature regions of a deformed structure. In a micromechanical structure, local thermal gradients arise because of the mechanical strain: regions with compressive strain get hotter because of increased internal vibrations while tensile strain regions become relatively colder. This was first explained by Zener [26] for thin beams and his approximation to the quality factor is quite good even in light of recent experimental data. But it is not accurate enough when it comes to micro and nanomechanical vibrating structures where there is persistent effort to increase the quality factor. Therefore, Lifshitz and Roukes [27] set aside the assumptions made by Zener, simultaneously solved the temperature profile, and obtained a slightly better estimate of the quality factor but nevertheless exact solution under the small-amplitude harmonic excitation and other assumptions made by them. According to Zener, more than 98.6% of dissipation occurs through the first mode of flexural vibration of the harmonically excited beam. Recently, it was found that when a micro or nanomechanical beam is excited arbitrarily and through large motions (as it happens in electrostatically actuated structures), more than one mode needs to be considered. And more importantly, modal solution for the temperature profile is not accurate and only a complete numerical solution matches the experimentally obtained quality factor data [19].

It is rather interesting that only a single material property, the linear thermal expansion coefficient \( \alpha \), controls thermoelastic damping. For slender structures undergoing transverse flexural vibrations, Euler–Bernoulli beam modeling is deemed to be adequate at present. So, by adding an extra term to the well-known beam equations and solving a one-dimensional (in the depth direction across the cross-section of the beam) heat conduction equation, thermoelastic damping can be included in numerical simulation.

\[
\rho A \frac{\partial^2 w}{\partial t^2} + \frac{\partial^2}{\partial x^2} \left( EI \frac{\partial^2 w}{\partial x^2} + E\alpha T \right) = F(x, t)
\]

\[
\frac{\partial T}{\partial t} = \kappa \frac{\partial T}{\partial y} + y \frac{E\alpha T_0}{\rho C_p} \frac{\partial w}{\partial t}.
\]

where

- \( \rho \) = mass density
- \( A \) = area of cross-section
- \( w \) = transverse displacement of the beam
- \( E \) = Young’s modulus
- \( F \) = any other external force
- \( T \) = temperature
- \( y \) = distance in the depth direction across the cross-section of the beam
- \( \kappa \) = thermal diffusivity
- \( C_p \) = specific heat at constant pressure
- \( I \) = moment of inertia of the beam
- \( I_T = \int_A y T \, dA \) = thermal contribution to the beam’s inertia.

However, many assumptions still remain in the analysis and numerical simulations carried out so far. For example, only a beam analysis is carried out as opposed to continuum analysis. Temperature gradients are considered only in the depth direction and not along the beam. While the relaxation of these assumptions takes us to more accurate estimates of the quality factor, the numerical complexity continues to increase. Note that the elastic, electrostatic (or other if the actuation is not electrostatic), and thermal conduction equations need to be solved for obtaining proper dynamic response of a micromechanical vibrating structure. The effect of convection and radiation and relaxation time constants at those length scales is yet to be ascertained.

Surface loss mechanisms depend on surface roughness, adsorbed particles, and monolayers [28]. What might have been second order effects at the macroscale turn out to be non-negligible at the microscale. Another, more dominant, dissipation mechanism is viscous damping. Not all microsystems devices are vacuum-packaged. In some, the cost is prohibitive and some others, some amount of damping is necessary to prevent sustained oscillations so as to increase the bandwidth and resolution of the device. When there is air, it gets squeezed in narrow gaps that are prevalent in micromechanical structures. This necessitates
the invoking of isothermal compressible Reynolds equation, which is used widely in lubrication theory. Much work is done on this topic and [2] may be consulted for a good review. At one simplistic level, an extra term may be added to the beam equation above or one can consider the full numerical solution of the Reynolds equation. Microsystem simulation software can handle this equation simultaneously with the elastic field equation. However, complications do exist when a vertically vibrating structure has perforations for which additional flow needs to be considered [4].

Anchors, places where micromechanical structures attach to their substrates, are not as rigid as they are supposed to be. Hence, dissipation of energy takes place through these anchors too. Another recent observation is that additional dissipation routes arise because of packaging of the microsystem components wherein the diced chip, the die, is attached to a packaging substrate [29]. Here, a rigid die attachment can minimize the dissipation but compromises the vibration isolation of the device. Hence, careful design is necessary to achieve a trade-off. The anchor and package related losses are slightly more traditional phenomena as compared with the other dissipation mechanisms. Apparently, everything matters when desired quality factor is exceeding one million!

While this section considered the analysis (simulation) aspects, the next section takes a design perspective.

3. Mechanics-based design perspective in microsystems

Microfabrication is an expensive proposition and it is also time-consuming. One cannot rely upon trial-and-error methods to conceive a design intuitively and/or by using prior experience and then make it and test to see if it is good enough. The same applies to simulation-based design because coupled simulation too is computationally expensive. Hence, trial-and-error design is not recommended nor is viable. In order to ease this problem, two techniques – both rooted in mechanics – are often used. They are synthesis techniques and reduced-order modeling, which we discuss next.

3.1 Synthesis of microsystems

Synthesis, simply put, is the inverse of analysis. In analysis, when a design is on hand, we simulate (analyse) it to see how well it meets the functional and performance specifications. In synthesis, on the other hand, we come up with a design for given specifications. Mathematically, the synthesis problem is posed as an inverse problem of analysis. Most algebraic or differential equations are amenable for this albeit not without difficulties. Optimization is a useful tool for synthesis. Many optimal synthesis methods have been developed for microsystems [30]. Among these, topology optimization methods can address the problem at a more abstract level than the others.

Design for a microsystem, or for that matter most other engineering systems, is the process of determining the sub-systems or components and their geometrical form and materials. Topology optimization has the capability to do this at the component level for specified requirements posed in the form of an objective function and constraints. And, it can do so with minimal input from the designers. The input required is often the size and shape of the space in which the design ought to fit and the quantitative specifications of what that component should do. Topology optimization, in this sense, is simply the problem of distributing a limited amount of material into a larger domain for given quantitative specifications [30,31].

Material distribution within a domain can be seen as a binary optimization problem of having material at a point or not. Since such a problem is not amenable for efficient computation, gradient-based optimizations methods are used by transforming it into a continuous problem. For this, the 0–1 nature of the material distribution becomes a continuous function \(\rho(x)\), which is defined at every point \(x\) of the domain and is constrained to be between 0 and 1. \(\rho(x)\) can be thought of as a fictitious density and it works well for problems with mechanical loads. But the mechanics does get complicated when we consider coupled problems. For example, in coupled electrostatic-elastic problem, we have forces acting on the boundaries. But we do not know boundaries within the domain \textit{a priori}. Rather the regions with zero value of \(\rho(x)\) become holes and boundaries get determined. Here, we need a way of transforming the boundary force into a body force such that the force acts everywhere with varying magnitude depending on the material state (0 or 1) of that point. Keeping this in mind, we had mentioned using the concept of Maxwell’s stress tensor [15] in section 2.1. This ensures that the force acts everywhere and the material is everywhere, although it is negligibly small within the holes and bulky interiors and is present only at the boundaries, as it should be. Similar situations arise in the case of piezoelectric and thermal actuation problems and in each case they are dealt with differently so that suitable modifications are made to the mechanics problems [32,33].
Imagine the problem of modeling convection in a thermally actuated microsystems component. If the topology is not known, that is, the number, size, and shape of the holes are not known, how would one model convection, which is essentially a surface phenomenon? Here too, one has to smoothen the problem to have convection everywhere – even in the bulky inside – but with negligibly small magnitude so that gradients can be taken [33].

While topology optimization can give geometric forms for given specifications, the obtained topology may not always be manufacturable. This is because microfabrication techniques are not adequately versatile to give any shape to a component. Incorporating the manufacturing considerations into the topology optimization is a need of the hour at present. Some efforts are underway in this direction. In some cases, the manufacturing restrictions are included explicitly as constraints [34] while in others, they are taken into account in defining the design variables for topology optimization [35,36]. The aim of these methods is to automate the synthesis of microsystems. An alternative to reduce the computational burden on a designer is to use reduced-order models.

3.2 Reduced-order modeling

The behaviour of microsystems is mostly governed by partial differential equations that couple with each other. A discretized partial differential equation involves many degrees of freedom (dof), which easily runs into a few thousands even in a moderately complex problem. The accuracy is also proportional to the number of dof: usually, the more the number of dof, the better the accuracy. The essence of reduced-order modeling is to use as few dof as possible without overly compromising on the accuracy.

One simple but effective technique used often in microsystems is the lumped-modeling [2]. Here, an energetically correct model is used with as few variables as possible. For example, a mass attached to a spring can capture the elastic kinetic and potential energies stored in a large deformable structure. Likewise, a simple parallel-plate capacitor for electrostatic energy, and an inductor for magnetic energy, and so on. This concept is commonly used in microsystem design and is well articulated in [2]. But determining the values of the lumped parameters (the spring constant, capacitance, inductance, etc.) is far from trivial and it can be done easily only for linearized (small displacement) equations. Even then, it is useful because the lumped models indicate how the response of a component depends on material properties and geometry.

While lumped models are constructed analytically with an understanding of the physics of the phenomena involved, numerical methods can also be used for generating reduced-order models. The main idea here is to obtain a reasonably accurate system of equations in as few degrees of freedom as possible. The data used here can come from extensive finite element solutions of partial and ordinary differential equations or from real experiments. The task then is to reduce the large dof of a finite element model to only a few. A natural thing to do here is to use eigenmodes [37] and it is common in mechanics. Since in any system, the response would have large contributions from only a few modes, the method of superposition of a few selected eigenmodes works and it is amenable for increasing the accuracy by taking more and more modes into account. However, the eigenmode method works for only small displacements of the structure. Furthermore, in a coupled system of equations, computing the forces acting on the mechanical structures cannot easily be done in the reduced system of equations. Coupled electrostatic-elastic problem is a good example. Here, in order to avoid the computation of the capacitance in those few degrees of freedom special attention is required. One method is to use Padé-type approximations in which the capacitance is fit to a rational polynomial based on the full-computation of the entire system of equations done a priori [38]. The other, more efficient, method is to use Karhunen–Loeve series [39]. A recent monograph contains a succinct description of the model order reduction methods applied to electrothermal-elastic micromechanical structures [40]. Some of these methods, which are applicable for other types of structures also, include: control theory methods wherein non-observable and non-controllable freedoms are suppressed; Krylov subspace methods where reduced models can be constructed using Lanczos or Arnoldi processes; and Guan reduction methods where the internal freedoms are expressed in terms of the freedoms of the external physical nodes of the finite element mesh. Micromechanical simulation software allows today automatic reduced-order model extraction but the accuracy of these processes needs further improvement.

We have discussed the role of mechanics in simulation and design in the previous and current sections. We next discuss how mechanics is affected by or affects materials and microfabrication.

4. Materials, microfabrication and micromechanics

Microsystems behaviour is largely determined by their mechanical properties even though they
operate in multiple physical energy domains. The properties are intrinsically related to the fabrication techniques used to make them. Thus, materials, microfabrication, and mechanics are dependent on each other and influence the feasibility of miniaturization and the performance of the miniaturized system.

4.1 Material properties issues

In 1987, Senturia wrote a paper with the title, ‘Can we design microrobotic devices without knowing their mechanical material properties?’ [41]. Provocative as the title may be, it indeed captures the essence of the problem: knowing the properties is all too important in simulation and design. Materials aspects in microsystems were comprehensively reviewed by Spearing in 2000 [42] and again revisited in 2007 [3]. The basic scaling law of having, at the microscale, increased surface area as compared with volume has many consequences for mechanics of solids. Friction forces have a much larger effect on the mechanical behaviour to the extent that microsystem designers avoid as much as possible the use of parts that rub against each other. Instead, compliant (i.e., elastically flexible) structures are used [43].

Mechanical strength is enhanced at the microscale because plastic flow that occurs because of dislocation motion is restricted as the layers become very thin. Increased strength also means that materials can sustain large residual stresses as compared with macro-mechanical structures. Interfacial strength becomes a bottleneck in microsystems, which are mostly heterogeneous layered structures. Fatigue failure is also of potential concern in microsystems devices because they undergo cyclic stresses a large number of times (note that one of the implications of the scaling law is that the natural frequencies are extremely high at the microscale). For example, micro-mirrors used in projection displays – successful commercial products today – undergo trillions of cycles in their lifetime. Yet, fatigue is not deemed to be a major cause for concern in them. Indeed, there is a debate as to whether cyclic fatigue really occurs at that scale. Because of the high purity of the microfabricated materials, crack initiation and growth tend not to be very high. However, strength considerations remain important in the design of microsystems components where residual stresses, bond strength between layers, friction and wear, etc., play a significant role.

Reliable and consistent measurement of mechanical properties of microsystems components remains a challenge. A common and the most essential property such as the Young’s modulus, as recently as a decade ago, showed considerable variability of up to 30% between different methods used to measure it. Making tensile test specimens and measuring their elongation using optical methods [44], nano-indentation methods [45], Raman spectroscopy [46], etc., are used. But preferred method seems to be on-chip test structures that can be co-located with the devices being made [47]. This helps one to know the properties that take into account process variabilities across a batch and even across the wafer. One of the popular methods is to measure the electrostatic pull-in voltage of cantilever and fixed-fixed beams and thereby estimate the Young’s modulus. By using beams of varying widths, Poisson’s ratio can also be estimated in this manner [47]. Measurement of shear moduli and thermal expansion coefficient are less understood [3]. New measurement techniques and standardized techniques for them are necessary. This is especially needed because not only silicon but also polymers and ceramics are increasingly being used in microsystems today. Next, we move on to the issue of limitations of microfabrication techniques and how they affect the geometry of fabricated structures from the mechanical behaviour viewpoint.

4.2 Geometry and microfabrication

Relative tolerance in microfabricated features is not very good; when one wants a beam of 1 micron wide, the variability in it can be significant [48]. Undercutting in etching, mask misalignment, unintended anisotropic or isotropic etching, etc., lead to complex geometrical features that are not generally considered in the design process. Furthermore, since all lithography-based processes can anchor a structure only at the substrate on the bottom side, boundary conditions are not always very clear. A cantilever beam is not really a straight one as assumed at the macroscale; it is often a bent compliant support. Because of the conformal nature of the deposition processes, the geometry of the curved portion of the beams is often unclear. But small variations in this geometry can have a significant influence on the mechanical behaviour. Today’s microsystem simulation software includes a module to generate the solid model for analysis by graphically emulating the microfabrication processes. But their abilities are far from perfect. Hence, a design based on such modeling tends not to be completely accurate. Ironically, the emulated geometry can only be done after the design is completed rather than before. This problem needs to be addressed in the design stage by properly accounting for the microfabrication considerations. Some work is underway in this direction in an automated procedure called topology optimization.
Figure 2. Optimal structural topology optimization for surface-micromachined structures that illustrates the importance of taking the micromachined geometry in design. (a) Problem specification for a stiff structure constrained on the left edge and with a point load, (b) optimal design without any manufacturing considerations, (c) optimal design for a chosen micromachining process, (d) the layered geometry of (c) with sacrificial layers also shown, (e) optimal design for another chosen micromachining process, (f) the layered geometry of (e) with sacrificial layers also shown. Compromise in the strain energy (SE), the measure of stiffness, can be noticed in the figure for obeying the manufacturing consideration.

[30,49]. Here, as shown in figure 2, the mask layouts themselves are used as the design variables so that the actual geometry is taken to build a model which is optimized [36,50]. Even here, the lack of predictability of exact geometry remains a concern and needs to be investigated further.

As we have discussed so far, dealing with solids has considerable challenges in microsystems even though the scaling effects on solids is largely unchanged up to micron scale. It is not so in the case of microfluidics, as discussed next.

5. Traditional vs. microfluid mechanics: general consequences in internal flows

In traditional systems on macroscopic scales, fluids are typically handled in large vessels and ducts (pipes). Although in many ways the fundamental equations describing the physics and chemistry of such larger-scale processes are still similar as in microfluidics, some effects being important on a macroscopic scale become unimportant on smaller scales, whereas other effects that can largely be neglected macroscopically turn out to be dominant in microfluidics. We may briefly delineate this issue by referring to a simple instance from traditional thermo-fluid sciences. Let us consider an engineer who is designing a macroscopic fluidic transport system. For a vast majority of systems, the task will boil down eventually to the design of a turbulent flow network, keeping in mind that large Reynolds numbers are common to the traditional engineering conduits in most practical applications. On the other hand, the flow in microfluidic devices is commonly laminar (because of low Reynolds number effects), which implies certain advantageous and disadvantageous features simultaneously acting in tandem. Apparent advantages are the facts that for inexperienced analysts the laminar flow analysis may appear to be deceptively simpler than turbulent flows, whereas a well-known disadvantage is that rapid mixing is difficult to achieve over diffusion dominated laminar regimes. Not only that, many aspects of a classical fluidic actuation in the laminar regime may appear to be prohibitive towards their implementations and extensions in the micro-systems, such as the unfavorable scaling of the frictional energy dissipation in inverse proportion of the fourth power of the hydraulic diameter, for a given flow rate. Furthermore, several other critical features predominate in a small scale, for example the capillary effects. While the capillary pressure (difference in pressure across the meniscus demarcating a two-fluid system in a capillary) scales inversely with the capillary diameter and hence may be insignificant for larger diameter pipes, those may indeed
bear significant consequences with regard to the control of fluidic transport in smaller scale systems. Neglecting the surface tension effects, thus, may give rise to significant errors in the analysis of a microfluidic system, whereas similar effects might not be so dominant over systems of larger extents.

Surface tension force by itself may give rise to several other interesting phenomena in microscale internal flows, which may not otherwise be important in their macroscale counterparts. From classical fluid dynamics, it is well known that internal flows are typically associated with an entrance region followed by a fully developed regime. In microscale liquid flows, a third regime (known as meniscus traction regime) also comes into play, so as to match the velocity profiles with those obtained in the vicinity of the capillary meniscus. The latter regime is attributed with a dynamically evolving interplay of adhesion and cohesion forces, consistent with the meniscus topography [51]. Fluid dynamic influences of the meniscus traction regime may be further complicated by the fact that the velocity of liquid meniscus itself may be related to its surface energy. In simplistic terms, immediately after a layer of fluid molecules is adsorbed onto the microchannel surface, the next set of fluid molecules may sail more easily over the same, giving rise to a dynamic evolution of the contact angle. Physically, since the points on the interfacial lines arrive at the contact line within a finite time span, an effective slip law needs to be posed for relieving a force singularity condition by ensuring that a finite force is necessary to move the contact lines of a fluid. This effectively imposes a dynamical constraint on the contact angle \( \theta \), as a function of velocity of the contact line. From fluid dynamics perspective, this departure of contact angle from its static equilibrium value is mainly due to viscous bending of the interface near the contact lines, in local equilibrium with the dynamically evolving cohesive and adhesive forces, and need to be aptly considered for modeling the pertinent capillary dynamics [52].

6. Surface tension gradients as flow actuators

Fundamental principles associated with surface tension driven flows rely on the motion induced by the variation of surface tension from point to point on a mobile phase boundary, giving rise to tangential strains on the same. Such tangential strains at the interface are inevitably accompanied by a fluid motion, so as to maintain the balance of surface tension and viscous forces. Fluid motion induced by the tangential gradients of surface tension is classically known as the Marangoni effect. Similar to the thermocapillarity (where temperature gradient creates the driving surface tension force), one can also exploit the effects of electrocapillarity or electrowetting, in which electric potentials can be employed to alter the surface tension and thereby cause a fluid motion. The first comprehensive investigations on electrocapillary phenomena were performed by Lippman, way back in 1875 [53]. In Lippman’s experimental apparatus, the interfacial tension modulation due to electrical effects was observed through a capillary rise phenomenon, and hence, was later termed as electrocapillarity [54]. A decisive advantage of electrocapillary actuation, in comparison to its thermal counterpart is the speed with which electrical potentials can be applied and regulated, with possible characteristic timescales of less than a few milliseconds. Furthermore, electrocapillary based microactuators consume much less power as compared to the typical thermocapillary microdevices. Thus, compared to the thermocapillary flows, electrocapillary flows are much more energy efficient, with a much faster speed of operation (speeds more than 100 mm/s have been successfully achieved by electrowetting action, in contrast to a typical speed of only about 1 mm/s in thermocapillary flows).

The electrocapillary principles are all based on the fact that the surface tension occurs to be a strong function of the electrical potential acting across an interface. As a consequence, the apparent contact angle, \( \theta \), gets modified from its value at zero voltage, \( \theta_0 \), in the following form: \( \cos \theta = \cos \theta_0 + \Delta \theta \), where \( \theta \) is the capacitance of the interface per unit area and \( V \) is the interface potential. A physical interpretation to the voltage-dependent contact angle modification term can be provided as follows. Upon connecting the initially uncharged droplet to the power source (battery), a charge \( \delta Q \) flows from the battery to the droplet and to the electrode. The resultant work done on the droplet-electrode capacitor (of total capacitance \( C \)) is given by \( \delta W_{\text{droplet}} = V_Q \delta Q \), where \( V_Q \) is the potential of the capacitor on being energized with an instantaneous charge of \( Q \). Since \( V_Q = Q/C \), the total work done is given by \( \int \delta W_{\text{droplet}} = \frac{1}{2} CV_Q^2 \), where \( V_Q \) is the potential of the power source (battery). The incremental work done on the battery, on the other hand, is given by \( \delta W_B = V_B \delta Q_B = V_B(-\delta Q) \). Since the battery voltage is a constant, we have, \( \int \delta W_B = -V_B \int \delta Q_B = -CV_Q^2 \). Thus, the net work done on the battery-electrode system is given by \( \int \delta W_{\text{droplet}} + \int \delta W_B = -\frac{1}{2} CV_B^2 \). In a physical sense, electrowetting decreases the effective contact angle, which is driven by the energy gain upon redistributing the charge from the battery to the droplet. This reduction of apparent contact angle is fundamentally related to the fact that a minimization of the free energy requires a maximization
of the capacitance. Applying a potential between the droplet and the electrode, therefore, would tend to spread the droplet as much as possible, in an effort to increase the capacitance. In even more simple terms, because of the applied electric field, opposite charge densities are induced at the fluid-solid interface and in the substrate electrode. The electrostatic attraction between the aqueous solution and the electrode enhances the coverage of the surface by the aqueous solution, thereby inducing an enhanced wetting effect.

Researchers have attempted in altering the surface tension forces in small scale systems by optical means as well, unveiling a promising and fascinating area of opto-microfluidics. One way of achieving the same has been demonstrated through a coating of the microfluidic substrate with photosensitive surface films (such as TiO$_2$), and shining the resultant surface with a light irradiation of matching wavelength (for instance, UV light for TiO$_2$ that has a band gap energy of 3.2 eV), as a result of which electron-hole pairs are formed [55]. These pairs can then reduce and oxidize the species that are adsorbed on the surface. Recombination of the electron and hole is a competing reaction. Based on the relative rates of oxidation and reduction, an excess or depletion of charge can be generated at the surface. The consequent change in surface energy due to the direct absorption of phonic energy by the optically tunable semiconductor film may create local gradients in the surface tension forces (altering the state from a hydrophobic to a hydrophilic one, for example), and hence may actuate a fluidic motion on the microchannel substrate. It also needs to be noted in this context that the micro-flow velocities may change only on the part of the surface of TiO$_2$ that is irradiated with UV light. Therefore, a desired spatial resolution of fluidic control may be obtained since various patterns of TiO$_2$ can be designed on the channel surfaces being exposed to the fluid. This would allow a local control of the flow velocities, without any fringing effects. Not only that, the light can be strategically switched on or off, allowing the effects to be temporally controlled as well.

In order to modulate the bulk flow features with light actuation, photosensitive nanoparticles (such as gold nanocrescent particles) may also be dispersed in the fluid [56]. Without any photo-actuation, the liquid on a hydrophobic surface remains stationary. Because of the ‘coffee-ring’ effect, the local concentration of the nanoparticles near the liquid–air interface is higher than that of the interior. When a focused light illuminates the nanoparticles near the liquid–air interface, heat is almost instantaneously (within a few nanoseconds) generated and transferred from the nanoparticles to the surrounding liquid. This significantly accelerates the vaporization process at the liquid–air interface forming the meniscus. Simultaneously, the original liquid contact line is pinned and the liquid lost in evaporation is replenished from the interior region. The vapour in the colder air adjacent to the substrate-liquid interface condenses almost immediately after the evaporation. As a consequence, droplets form very close to the liquid–air interface. These droplets then coalesce with each other and grow into the larger ones. These larger droplets eventually merge with the original liquid body and extend its contact line (see figure 3a for a schematic illustration). The nanoparticles are drawn to the modified contact line, by a combined advective-diffusive transport. A continuous flow augmentation through this mechanism may be expected, if the optics is also translated in tune with the dynamic evolution of the liquid–vapour interface. Previous observational studies have demonstrated that the droplet coalescence can facilitate flow significantly, and holds the potential of altering the contact line dynamics to a significant extent, leading to a micro-capillary motion.

Using optofluidics, various micro-devices have recently been designed, tested, and demonstrated. For example, we may refer to the schematic of an optofluidic valve developed by our group, as depicted in figure 3b. This device operates on the basis that the upper inner surface of a T-junction is coated with a hydrophobic metal oxide semiconductor film. Depending on the side to which we may want to direct a droplet waiting at the junction of the T, we may shed UV light on the inner surface of either the left or the right branch. The exposed side becomes hydrophilic because of opto-capillary actuation, so that the droplet moves preferentially towards that direction. This movement, in terms of speed and directionality may be controlled at will, by selectively switching the light source on and off and by translating the optical system.

7. Interfacial boundary condition: Slip vs. no-slip

7.1 General considerations

It is at an interface between solid and fluid where microfluidics turns truly complex: near the contact, the physical properties of the fluid are not the same as in the bulk and the influence of molecular scale interactions tend to become predominant. The celebrated no-slip boundary condition, implying zero relative velocity between the fluid and the solid, may tend to get severely
challenged at many instances involving interesting microflows. The no-slip assumption at the interface is an idealized paradigm, assuming moderately strong attractive forces between fluid and wall. At the micro and nanoscale, new phenomena arise because surface forces, and all types of micro effects, ignored at the macroscale, become important, these include: surface tension, air bubbles, liquid evaporation, porosity, osmotic effects, van der Waals forces, electrostatic forces, etc., resulting in possible true or apparent slips. In the case of slip, a slip length, $L_s$, must be introduced. Slip length is defined as the distance behind the interface at which the liquid velocity extrapolates to zero (see figure 4).

### 7.2 Gas flows

The primary distinction between fluid flows in the micro-scale and the conventional devices originates from the pertinent surface area to volume ratios. For traditional devices, this may be of the order of $1 \text{ m}^{-1}$, as compared to as low as $10^6 \text{ m}^{-1}$ for typical microdevices with characteristic length scales of the order of $1 \mu \text{m}$ [57]. This profoundly affects the mass, momentum and energy transport; and leads to additional effects like slip flow, rarefaction, compressibility, etc. The later effects are particularly more perceptible and prominent in gases than in liquids, primarily attributable to the significant characteristic alterations in the density of gases with changes in pressure as compared to liquids.

The recent spurt in the development of MEMS and NEMS has raised several interesting questions with regard to the suitability of the traditionally accepted thermo-fluidic modeling considerations for microscale gas flows. Central to these considerations, the applicability of the classical continuum hypothesis has often been seriously debated, which is based on the following two important postulates:
Increasingly more significant as to a free molecular one may occur, which becomes of even the bulk flow paradigm from a continuum exceeds the order of $10^{-7}$ ratio of these two, known as the Knudsen number. The contribution of the stream-wise temperature gradients associated with the thermal creep phenomenon was subsequently added to the Maxwell-slip conditions, with a consideration that the slip velocity is simultaneously caused by the velocity gradient normal to the wall and a temperature gradient tangential to the wall. Identical considerations were also invoked by Smoluchowski for modeling the temperature jump boundary conditions at the walls [59].

Several slip-based models have been proposed in the literature for modeling microscale gas flows, following up the seminal contributions from Maxwell. However, the very fact that the standard continuum considerations may still succeed to work at all regions except at the solid boundary started giving rise to several interesting questions. It could eventually be inferred that the concerned discrepancies may not originate from the fact that the fundamental conservation principles cease to work for microscale gas flows. Rather, these may be attributable to an apparent abstraction from the seemingly non-trivial dependences of the fluid flow characteristics on the pertinent molecular level interaction mechanisms with characteristic sharp gradients adjacent to the confining boundaries. A common consensus is that it is not necessarily that the continuum conservation equations tend to get invalid in these cases, but the gradient terms in these equations might become incapable of capturing strong local gradients of fluid properties adjacent to the solid substrate.

Recently, it has been suggested by several researchers [60,61] that the constitutive assumption in-built with the standard forms of the Navier–Stokes–Fourier (NSF) equations need to be extended, to render them applicable for fluid flows with strong local gradients of density and temperature. These modifications have originally been motivated from a thoughtful continuum-based re-interpretation of experimentally-observed thermophoretic motion, the hierarchical re-ordering of the Burnett terms in the Chapman–Enskog expansion of the viscous stress tensor, and the velocity/thermal creep coefficients introduced by Maxwell in an effort to account for non-zero slip velocities and temperature jumps at the fluid–solid interface (irrespective of the fact that the continuum hypothesis might otherwise be satisfied in the bulk). Brenner [60] first pointed out that the Navier–Stokes equations, in their traditional forms, are incomplete and provided extensions based on the concept of volume diffusion. In a strict sense, the concept of continuum is an abstraction that does not exist in reality, because of the presence of discrete material entities (such as molecules) that have empty spaces separating them. Such empty
spaces are heavily interlinked with the extent of rarefaction or compression in the system. As a consequence, the presence of strong gradients of density may pose certain ambiguities in mathematically defining the ‘velocity’ of the continuum at a point. In an effort to avoid such ambiguities, one may refer to fluxes, instead of velocities. In that interpretation, the term ‘velocity’ that is commonly employed to describe the conservation of fluid mass (continuity equation) essentially describes a normalized flux density of a system of particles with a fixed mass and identity. With respect to an Eulerian control volume, the same can be interpreted as an advective flux density of mass across an element of the pertinent control surface. Superimposed on this advective flux, one may also have a phoretic or diffusive transport of mass across the control surface, which may be spontaneously actuated by local gradients of density and/or temperature. Physically, this diffusive flux can be manifested by the Lagrangian velocity of a passive and neutrally-buoyant non-Brownian tracer particle introduced into the flow, relative to the advective fluid motion. Because of such diffusive transport of fluid particles, one may have a net diffusive transport of mass across the control surface, without violating the constraining requirements of the conservation of mass from a continuum perspective, in a sense that individual molecules are free to enter and leave a material space with an invariant mass.

Based on the local gradient-driven diffusive transport considerations, researchers have developed modified constitutive relationships based on the velocity of a material frame that advects with the fluid flow, and therefore, is a representative of the advective flux density of the local flow. This ‘velocity’ invariably features in the calculations of the material or total derivatives appearing in the pertinent continuum conservation equations. In a strict sense, however, this is not the true physical velocity of fluid flow, but merely a description of a normalized flux density that advectively transports mass, momentum or energy within the fluid envisaged as a continuum. Superimposed on this advective flux, one can also have a phoretic or diffusive transport of mass across the control surface, which may be actuated by local gradients of density and/or temperature, independent of action of any equivalent macroscopically-resolvable imposed pressure gradient. A classical example of phoretic transport is the phenomenon of thermophoresis, in which heat-conducting, force-free and torque-free tracer particles (typically, spherical) move from hotter to colder regions in the fluid (usually, a gas), against an externally imposed temperature gradient, without necessitating the aid of any externally imposed pressure gradient. Physically, this diffusive flux can be manifested by the Lagrangian velocity of a passive and neutrally-buoyant non-Brownian tracer particle introduced into the flow, relative to the advective fluid motion. Accordingly, the net ‘velocity’ may be considered as a summation of the advective and the diffusive components, to yield [60,61] \( U^T_i = U_i + u^D_i \), where \( U^T_i \) is the total velocity, \( U_i \) is the advective component of velocity and \( u^D_i \) is the diffusion velocity. The explanation of the mass diffusion phenomenon by kinetic theory is immediately obvious: a net flow may result in the direction in which gradients of the thermodynamic properties are present, in consequence of difference in the thermal velocity of molecules at different locations [62].

### 7.3 Slip boundary condition for liquids?

Because of sufficient intermolecular forces of attraction between the molecules of the solid surface and a dense medium such as the liquid, it is expected that the liquid molecules would remain stationary relative to the solid boundary at their points of contact. Only at very high shear rates (typically realizable only in extremely narrow confinements of size roughly a few molecular diameters), the straining may be sufficient in moving the fluid molecules adhering to the solid by overcoming the van der Waals forces of attraction. Another theory argues that the no-slip boundary condition arises due to microscopic boundary roughness, since fluid elements may get locally trapped within the surface asperities. If the fluid is a liquid then it may not be possible for the molecules to escape from that trapping, because of an otherwise compact molecular packing. Following this argument, it may be conjectured that a molecularly smooth boundary would allow the liquid to slip, because of the non-existence of the surface asperity barriers.

One of the important consequences of the interfacial phenomenon in the context of liquid flows in microchannels may be appreciated by referring to the apparently anomalous predictions from simple pressure drop – flow rate characterizing experiments. Numerous experimental investigations [63] have been executed by the researchers in this regard to pinpoint several significant (though, not necessarily systematic and repetitive) deviations in the frictional behaviour of pressure-driven liquid flows through microchannels, in perspective of the classical theory that has been emphasized over the years as an inevitable ritual. These studies have almost routinely exhibited an increase of friction factor with increase in effective surface roughness, characterized through suitable parameters. Researchers have also proposed semi-empirical models based on the concept of the so-called...
‘roughness viscosity’ [64], ‘porous medium layer’ [65], etc., in an effort to fit the theoretical predictions with the observed experimental data. On the other hand, in sharp contrast, a number of research studies have revealed reductions [66] in friction for pressure-driven liquid microflows, in comparison to the classical theory of Poiseuillian flows, despite encountering rough microchannel-walls. Such apparently contradictory observations tended to threaten the amazing acceptability of the paradigm of the celebrated ‘no-slip’ boundary condition, which, for decades, had marked the saga of innumerable successes in reproducing the essential features of fluid flow within the continuum regime. However, because of the lack of precise understanding of the relative competing influences of friction enhancing and friction reducing effects, the fundamentals of frictional characteristics in pressure-driven liquid microflows remained to be poorly understood for a long time.

A series of recent investigations by our research group have attempted to resolve the apparent anomaly of ‘reduced’ fluid friction while confronting with ‘rough’ solid surfaces in narrow confinements, by appealing to the thermo-fluidics over experimentally-resolvable spatio-temporal scales. In simple terms, it has thus been recently established that we may design rough surfaces to make them behave in the smoothest possible way in terms of fluid friction. We discovered from our studies that specially designed tiny water-transport channels (or pores) may achieve this apparently impossible task by a simple mechanism [67]. Confining rough surfaces made of hydrophobic (water-disliking) materials may trigger the formation of nano-scale bubbles adhering to the walls in tiny channels (see figure 5a). This incipient vapour layer acts as an effective smoothening blanket, by disallowing the liquid on the top of it to be directly exposed to the rough surface asperities. In such cases, the liquid is not likely to feel the presence of the wall directly and may smoothly sail over the intervening vapour layer shield. Thus, instead of ‘sticking’ to a rough channel surface, the liquid may effectively ‘slip’ on the same (see figure 5b). While the microscopic roughness of the solid surface impede the motion of the adhering fluid promoting the stick-flow, the incipient vapour layers formed on the solid surface tend to augment the level of slippage. Thus, deliberately designed rough surfaces may lead to an apparently frictionless flow behaviour. This may essentially not be due to an explicit effect of the surface roughness, but an implicit effect of the same that leads the inception of tiny vapour bubbles of few nanometer sizes close to the channel walls [67]. Nanobubbles may be nucleated when the driving force required to minimize the area of liquid–vapour interface is smaller than the forces that pin the contact line of the substrate. In such cases, the hydrophobic surface itself acts like a nucleation site. Hydrophobic units are not thermodynamically favored to form hydrogen bonds with water molecules. Hence, these give rise to excluded volume regions encompassing the locations characterized with sharply diminishing number density of water molecules. Close to small hydrophobic units, water molecules can structurally change and reorganize without sacrificing their hydrogen bonds.
However, close to larger hydrophobic units, persistence of a hydrogen bond network is virtually impossible. The loss of hydrogen bonds near the hydrophobic surfaces effectively expels liquid water to move away, thereby forming thin vapour layers. Such interfacial fluctuations may destabilize the liquid further away from the solid walls, leading to a pressure imbalance. This effectively gives rise to an attractive potential between the two surfaces [67]. Further, loss of hydrogen bonds close to any such hydrophobic surface effectively repels liquid molecules, thereby favoring the formation of thin vapour layers. In confined fluids, long-ranged interactions may also trigger separation-induced phase transitions. Such separation-induced cavitation physically originates from an increase in the local molecular field due to the replacement of polarizable fluids by solid walls.

Conditions in which liquid layers sail smoothly over thin vapour layers covering the solid boundaries may be termed as ‘apparent slip’, since the no-slip boundary condition still remains a valid proposition at the walls (see figure 5a). It is only the apparent inability to capture and resolve the steep velocity gradients within the ultra-thin vapour layers that prompts an analyzer to extrapolate the velocity profiles obtained in the liquid layer above the vapour blanket, to mark an apparent deviation from the no-slip boundary condition at the wall. Interestingly and counter-intuitively, spontaneous roughening effects on liquid flows occurring over smooth bubble layers have also been recently observed, thereby raising serious doubts on the universality of the above-mentioned physical conjecture. Influences of stochasticities on this amazing physical behaviour have also been seriously questioned, although they have by no means been well-resolved.

Keeping in view of the disparate physical manners in which a pressure-driven liquid microflow could be influenced by the intrinsic surface conditions, the above considerations have been further extended by us to develop a generalized model of fluid friction for pressure driven liquid flows through microchannels. This theory has been based on a broad consensus that has been achieved regarding the patterns of influence of the surface conditions on the resultant magnitude of friction factor (which, effectively, is a non-dimensional pressure drop). Considering the stochastic nature of many input model parameters, as attributed to the uncertainties in prevailing surface conditions, numerous random experiments have been performed with chosen ranges of these data, to come up with a generalized formulation of friction factor for pressure-driven liquid microflows through parallel plate channels [68], replacing the use of the celebrated Poiseuillian formalisms, instead.

Intensified research investigations on confinement induced hydrophobic interactions and the consequent smoothening or roughening effects have apparently redefined the physical understanding of the underlying complex thermo-physical systems, raising further unresolved issues in understanding the science of fluid-solid interactions at small scales. Utilizing some of the recent advances in this regard and addressing some of the concerned ‘open’ questions in the near future, researchers may potentially develop engineered rough surfaces with triggered hydrophobic interactions and consequent inception of friction-reducing vapour phases [69] so as to achieve a super-fluidic transport over small scales. Narrow confinements capable of mimicking the selective and rapid fluidic transport attainable in biological cellular channels but designed on the basis of such newly-discovered surface roughness-hydrophobicity coupling would open up a wide range of new applications, such as transdermal rapid drug delivery systems, selective chemical sensing and mixing in nano-scales and several other lab-on-a-chip based applications.

8. Electrokinetics in microfluidics

A majority of microfluidic functions required in various lab-on-a-chip devices includes pumping, mixing, thermal cycling, dispensing and separating. Many of these processes are executed electrokinetically, implying that electrical fields are employed in manipulating the relative movements between the various particles, solid, and fluid phases.

Length scale matching is important for efficient momentum and energy transfer for controlling the motion of desired fluids and molecules. Most of the biological objects of interest, such as DNA, proteins, and cells, have a characteristic length from nanometer to micrometer. Electrokinetics is especially effective in this domain by taking advantage of the small length scales. With the development of MEMS fabrication technology, integration of micro or nanoscale electrodes in fluidic device is a relatively simple procedure. Therefore, electrokinetic forces are ideal for manipulating biological objects and performing fluidic operations. By utilizing electrokinetic effects, fluid flow can be manipulated, in general, using the following methodologies. In this context, it is important to keep in mind that a general expression for electrokinetic body force on a continuum, per unit volume, may be written as

\[ F = \nabla \rho_{\varepsilon} \cdot E - \frac{1}{2} E \cdot \nabla \varepsilon + \nabla \left( \frac{1}{2} E \cdot \epsilon \frac{\partial \varepsilon}{\partial \rho} \right), \]
where $E$ is the local electric field, $\varepsilon$ is the local permittivity of the medium, and $\rho$ is the fluid density. In the foregoing discussions, we will consider two fundamental examples concerning electrophoretic effects, namely, electroosmosis and streaming potential.

8.1 Electroosmosis

When a solid is in contact with an electrolyte, the chemical state of the surface is generally altered, for example, by ionization of covalently bound surface groups or by ion adsorption. As a result, the surface inherits a charge while counterions are released into the liquid. For instance, common glass, SiOH, in the presence of $\text{H}_2\text{O}$, ionizes to produce charged surface groups $\text{SiO}^-$ and release of a proton. At equilibrium, a balance between electrostatic interactions and thermal agitation generates a charge density profile. The liquid is electrically neutral, but for a charged layer adjacent to the boundary, which bears a charge locally equal in amplitude and opposite in sign to the bound charge on the surface. This charged layer is commonly known as the electric double layer (EDL) [70].

A schematic depicting the charge and the potential distribution within an EDL is depicted in figure 6. Immediately next to the charged surface, a layer of immobilized counterions is present, which is known as the compact layer or the Stern layer or the Helmholtz layer. This layer is about a few Angstroms in thickness, and hence the potential distribution within the same can be taken as almost linear. The charge and the potential distributions within this layer are strong functions of the geometrical characteristics of the ions and the short-range interaction forces between the ions, wall and the adjacent dipoles. From the compact layer to the electrically neutral bulk liquid, the net charge density gradually reduces to zero. The layer of mobile ions beyond the Stern layer is called the Guoy–Chapman layer, or the diffused layer of the EDL. These two layers are separated by a shear plane. The potential at this shear plane is known as the zeta potential ($\zeta$). The thickness of the EDL is known as the Debye length ($\lambda$), which is the length from the shear plane over which the EDL potential reduces to $(1/e)$ of $\zeta$. The Debye length solely depends on the properties of the liquid and not on any properties of the surface. For example, for a 1:1 electrolyte of concentration $C$, $1/\kappa = 0.304/\sqrt{C}$ nm (where $C$ is in molar units). This is estimated by taking $T = 298 \text{ K, } \varepsilon = 78.5 \times 8.85 \times 10^{-12} \text{ C}^2/\text{N.m}^2$, $e = 1.602 \times 10^{-19} \text{ C, } k_\text{B} = 1.38 \times 10^{-23} \text{ J/K}$ and $n^\infty = 1000 \text{ N}$, where $N$ is the Avogadro number. Thus, for a $10^{-4} \text{ M NaCl}$ solution, $1/\kappa \approx 30 \text{ nm}$ and for 1 M of the same solution $1/\kappa \approx 30 \text{ nm}$. Physically, as the bulk ionic concentration increases, more counterions are attracted to the region close to the charged surface to neutralize the surface charge. As a result, the EDL thickness is reduced and the EDL appears to be somewhat ‘compressed’. If a potential is applied along the channel, the diffuse electrical double layer will move due to the electrostatic force. Due to the cohesive nature of the hydrogen bonding of water molecules, the entire aqueous solution is effectively pulled. Since this pull depends on the local charge density, it effectively becomes zero outside the EDL. Thus, there is no effective velocity gradient outside the EDL, and the velocity profile remains virtually uniform across the remaining part of the microchannel cross-section, typically reminiscent of a plug like flow.

8.2 Streaming potential

It is interesting to note that even in a pure pressure-driven flow occurring through a narrow fluidic confinement, the ions in the mobile part of the EDL are transported towards the down-stream end with the liquid motion. This causes an electrical current, known as the streaming current, to flow in the direction of the imposed fluid motion. However, the resultant accumulation of ions in the downstream section of the channel sets up its own induced electrical field, known as the streaming potential [71]. This field, in turn, generates a current to flow back against the direction of the pressure-driven flow. This so-called conduction current balances the streaming current at steady state, so that the net electrical current becomes zero, consistent with a pure pressure-driven flow condition.
Researchers have utilized the generation of streaming potential to convert hydrostatic pressure differences into useful electrical energy, to characterize interfacial charge of organic thin films, to measure wall charge inversion in presence of multivalent ions in a nanochannel, to analyze ion transport through nanoporous membranes, to design efficient nanofluidic batteries, etc. as some of the technologically relevant applications.

The streaming current and streaming potential in a pressure-driven flow can drive an external load and therefore may represent a means of directly converting hydraulic energy into electrical power through exploitation of micro/nanoscale flow physics. The results are more favourably scalable for nanochannels than microchannels, primarily because of the fact that the extent of zone in which a net volumetric charge density exists in a nanochannel is much more than that in a microchannel, when normalized with respect to their respective hydraulic radii. The notion of employing such electrokinetic effects in an energy conversion device is not new, but implementation of this concept towards making practical engineering devices have not been far from being elusive, except for isolated test cases. Even in such cases, the energy conversion efficiency has been found to be quite poor (about 5%), primarily attributable to a huge flow-pumping power necessary to overcome strong frictional resistances against pressure-driven microflows and nanoflows. Indeed, high energy-conversion efficiency and high output power are the fundamental requirements for such devices to be practical and capable of solving some burning global problems in the field of energy science and engineering. Exploration of this nascent and novel technology for generating electrical energy directly from a hydraulic form (instead of going through other mechanical/coupling losses) in miniaturized devices without necessitating any fuels, thus, appears to be very much pertinent and appealing in the global energy crisis scenario, and indeed a very attractive proposition. Efforts, however, need to be directed to make the scheme energy efficient and viable through exploration of some additional facets of interfacial phenomena over small scales.

Based on our recent discovery that one may cleverly design deliberate rough hydrophobic surfaces (which are common artifacts of the micro/nano-fabrication processes) to make them behave in the smoothest possible way in terms of resulting in ultra-low flow resistances, one may realize a significant rate of ‘apparently slipping’ flow on utilizing only a meager applied pressure gradient, by exploiting the surface roughness as a blessing in disguise. The spontaneous formation of an electrically charged layer (EDL) adhering to the channel surface, very much typical to such tiny pores, may in turn amplify this tendency of slippage to a large extent, by pumping the layer of fluid even more effectively along with the movable charges [72]. Based on this novel conjecture, we may design miniaturized super-fluidic systems with an unimaginably high rate of liquid pumping, with the employment of very low flow-pumping pressure-gradient.

The engineered microsystems of solids and fluids are complex enough as discussed until now in this paper. However, this complexity pales in comparison when we consider biological microsystems – the cells. We will briefly consider them next.

9. Mechanical models of cells

Cells are soft and wet. So are tissues, which are collections of cells and inanimate extracellular matrix secreted by cells. The behaviour of cells and tissues cannot be understood only from the deterministic approaches of classical mechanics. Just as engineered microsystems have coupled energy domains, biological microsystems have even stronger coupling with other domains, which is not fully understood yet. This is a field that is still in its nascent stage of development with a lot of challenges ahead but with many promising approaches that are pursued today. The description that follows is neither exhaustive nor is it universally agreed upon; it is an emerging field of study.

9.1 Biophysical approaches

Just like engineered microsystems do, cells also attach themselves to their environment and to each other, move about, and deform. This is only one side of the coin. The flip side is that cells also grow, re-organize themselves, sense their environment, transduce the mechanical signals they receive into chemical signals, and induce a variety of biochemical processes. No engineered material, active or smart as they are called, are capable of this complex behaviour in such a deceptively simple system like a cell. The crucial fact that cells are living entities brings in another dimension that their properties continuously change due to their interactions with their environment. This is a rather unusual feature when we compare it with engineered systems. Another equally important feature is that thermal fluctuations have significant effect on cells. Hence, statistical mechanics plays an important role in addition to classical mechanics.

There is no agreement among different models suggested for cells’ mechanical behaviour. The reasons for this may be that there are a number of cell
types, the experimental data is usually obtained \textit{in vitro} rather than \textit{in vivo}, cells reorganize themselves over spatial and temporal scales comparable to that of the time-resolution of the experimental techniques used, and cells consist of several vastly different entities within them. The cell membrane, made up of lipid molecules arranged in a bilayer due to hydrophobic-hydrophilic effects, is embedded with bulky transmembrane proteins. The cell membrane behaves both as a solid and a fluid. It not only provides protection or demarcation boundary to enclose the cell but also helps in mechano-sensing through ion channels and other mechanisms. Cytoskeleton that provides the shape and size to the cells is a complex structure in itself as it is made hierarchically with actin filaments, intermediate filaments, and microtubules. Many theories are proposed to understand cytoskeleton’s mechanical behaviour. The study of mechanical behaviour of cell nucleus has only begun now. There are a large number of other molecules within the cytoplasm that makes up the interior of the cell apart from the nucleus. A comment made by Crick and Hughes in their seminal paper of 1950 (wherein they studied, reportedly for the first time, the physical properties of cytoplasm of chick fibroblasts) is recalled today by researchers in this field: “...If we were compelled to suggest a model, we would propose Mother’s Work Basket — a jumble of beads and buttons of all shapes and sizes, with pins and threads for good measure, all jostling about and held together by ‘colloidal forces’.” A quick glance at the modeling attempts to understand such a system is pertinent at this point to appreciate the level of difficulty in proposing mechanical models for cells.

Based on the experimental measurements of different types of cells using different techniques, Fredberg and Babry [73] propose Sollich’s [74] model of soft glassy material for cytoskeletons of cells. In this theory, the constituents of the interior of the cells remain in deep energy wells unless disturbed by large fluctuating forces. The fluctuation depends on the temperature. Thus, the behaviour can vary from flow-like response to stiff solids.

The mechanical behaviour of the cells is also explained using the concept of tensegrity structures. Tensegrity structures, proposed by Buckminster Fuller, are stabilized assemblies of cable-like elements that are in tension and tube-like elements in compression. Thus, unlike brick and masonry structures that carry mostly compression, tension gives the structural integrity to tensegrity structures. Ingber [75] argued that actin filaments in the cytoskeleton are in tension while microtubules are in compression. This is shown to be true in experiments because actin filaments are curved when left alone whereas microtubules are straight. But the reverse is true inside the cell: the actin filaments are taut and tubules (because of compression-induced buckling) are curved. There is also other circumstantial evidence to the tensegrity theory. The membrane tension and the effects of extra cellular matrix as well as the dynamic behaviour can also be explained with the tensegrity model. Conveyance of mechanical and chemical signals through the tensegrity structure of the cytoskeleton remains to be explored further.

There are also arguments against treating cytoplasm as an aqueous medium. It is argued that when a membrane ruptured accidentally in the normal wear and tear of the cells or intentionally during experiments, the cells should not survive [76]. Therefore, the cytoplasm is to be treated as a gel. The gel can undergo a phase transition to a solid state. The phase transition can explain the motility and various ways in which cells sense and respond. This view leaves it open for application of the sol-gel theories developed by engineers for non-living matters of that kind.
A bottom-up approach to modeling cells is also pursued. Here, the behaviour of single filaments is studied and using that the behaviour of a network of filaments is deduced. Figure 7 shows approximate values of forces acting on biomolecules. Covalent forces keep the molecules intact and uncut as they change their shapes. Long molecules undergo a little stretching, some twisting, and mostly bending. These are often modeled using the simple theories of strength of materials although the forces acting on them are vastly different from that of the macroscale flexible beams. As can be seen in figure 7, viscous, thermal, electrostatic and van der Waals forces dominate. Analysis of the deformation of individual molecules requires statistical mechanics treatment known as freely jointed chain, worm-like chain, etc., [77]. Bending and twisting stiffness of the single molecules are estimated using entropic theories. Two and three dimensional networks are also considered in a similar spirit to deduce equivalent elastic moduli [77].

Some others have used continuum models for understanding the experimental observations. Continuum models are applicable only when the observed displacements are much larger than the smallest features of the constituent parts. Given its occasional fluid-like behaviour, viscoelastic models are often used. Indeed, finite element simulations have been attempted for understanding the deformation behaviour of erythrocytes (red blood cell) [79]. Such simulations and models have a number of limitations in that they only qualitatively capture the behaviour and that too with debatable fidelity [80]. This is because, as noted above, cells behave both like solids and liquids and hence the continuum treatment should take that into account. In this line of thought, some multi-phasic continuum theories are also put forward [80]. Here, the solid and fluid behaviours are simultaneously considered with appropriate momentum balance terms added to the equilibrium equations. In addition to any body force that may be present (which is often negligibly small in cells) in the equilibrium equation, the momentum of the fluid flowing past the solid phase is added to the divergence of the solid state stress; similarly, the momentum term is subtracted from the stress in the fluid phase. Constitutive relations are to be written for both the solid and fluid phases. The basis for this type of modeling of cells comes from the continuum theories developed for hydrated soft tissues [81]. Indeed, two phases are not enough when the ionic phase is also considered. Hence, triphasic and multi-phasic models are also considered [82]. The challenges in this approach are in estimating the constitutive properties that reflect reality and the complexity in the numerical solution of the coupled multi-phasic equations.

9.2 Continuum biomechanics

Understanding the behaviour of the soft matter of cells and tissues warrants substantial extension of classical mechanics that is primarily developed for engineering materials. Just as mechanics is based on fundamental postulates based on which predictive theories can be deduced, biomechanics too aims to elucidate the responses of the biological matter using analytical deduction. However, that level of an understanding is not yet available for biological matter at different size scales. Hence, sometimes an alternate term ‘mechanobiology’ is used to describe an inductive approach wherein particular observations are used to formulate theories for underlying mechanisms [83,84]. In spite of the fact that biological matter behaves significantly differently under different conditions, the classical theories of continuum mechanics have helped, with some extensions, in understanding some aspects of biomechanics of tissues, bone, etc. The tools employed in these studies are finite elasticity, membrane mechanics, viscoelasticity, mixture theory, growth and remodeling, and thermomechanics. The latter highlight the fact that the elasticity of soft matter is primarily entropic rather than energetic [85,86].

Recent thinking in continuum mechanics appreciates the ability of biomaterials to grow and remodel their internal constitution in response to subtle changes in their surroundings due to disease, injury, etc. [83]. Interesting questions have been raised as to whether stress, strain, strain rate or a similar mathematical measure of continuum mechanics can explain complex ways in which cells can sense subtle mechanical stimuli. How cells sense these mathematically defined quantities is unclear and warrants further studies at the molecular level. The issue here is to relate conformational changes in the biomolecules to changes in bulk mechanical behaviour. The continuum mechanics of development of tissue, growth, and remodeling, damage and healing, also need substantial extensions. The role of experimentation is equally important [87] in paving the way for these studies. Overall, continuum biomechanics is an interdisciplinary field that requires close collaboration among biologists, biochemists, biophysicists, engineers, mathematicians, and clinicians.

10. Experimental tools for bio-micromechanics

Measuring displacements and forces acting on the cells or exerted by them in their native aqueous
medium are important in biomechanical studies. As discussed above, cells are small, soft, and wet. This is in contrast to the macroscale objects and hard (mostly silicon, its compounds, and metals) objects at the microscale. So, an entirely new set of measurement techniques are needed. Many are developed and are continually improved. We consider some of them below.

10.1 Metrology for biomechanics

It is estimated that a typical cell experiences forces in the range of 1 pN to 10 nN from its environment. The displacements caused due to the forces are of the order of a few nm to a few μm. Today, there are tools that can probe groups of cells or isolated single cells in these ranges of forces and displacements. Figure 8 shows a large subset of such techniques. Most of these can measure elastic and viscoelastic properties while some can only measure viscous properties.

For groups of cells, the most common technique is culturing them on a membrane and stretching the membrane. The cells adhering to the membrane stretch, which is measured optically. The strain induced in this way can be uni-axial or bi-axial and is up to 30% [88]. Sedimentation is a technique wherein sufficiently small granules are diffused through a cell to measure the viscosity of cytoplasm [89]. Hydrostatic pressure is applied on the cells using compressed air or cells are grown on a porous surface to apply pressure to measure the effect of mechanical stress on the cell response. In order to study the effect of shear stress on cells, a fluid is passed over the cells. While the cell aggregates indicate the average effect of mechanical stimuli, single cell studies help understand the biomechanics of the cells more specifically for fundamental insights.

The most common technique of inducing force/displacement on a cell is using micropipettes, which are simply sharp glass needles of diameters as small as a fraction of a micron. Singles cells can be sucked inside the pipettes by applying vacuum at the other end. The range of forces that can be applied by varying suction pressures is from tens of pN to tens of μN. This technique helps deduce the mechanical properties of the cell membrane rather than the cytoplasm because it is the membrane that gets stretched.

Attaching particles, usually beads coated with antibodies or other biomolecules for inducing adhesion to cells, is another technique for applying forces on cells. If the particles are magnetic, external magnetic field is varied to stretch or twist the cells. These are known as magnetic tweezers [90] or magnetic twist cytometry [91]. Electric fields can also be used by choosing particles of appropriate dielectric constant. If the particles have appropriate refractive index, lasers are used to apply radiation pressure and thereby stretch or move the cells. This is known as laser tweezers technique [92]. Lasers can also be used without attaching particles. One such technique is an optical stretcher where two de-focused lasers create statically balanced stretching on a cell [93].

Atomic force microscope (AFM) is a widely used technique. It contains a sharp (10–50 nm diameter), usually silicon-made, tip mounted on a cantilever beam. An AFM, which is usually used to imaging, can also be used to apply forces on cells. Resolution of the forces that can be applied on a cell depends on the stiffness of the cantilever, which typically ranges from few hundredths to tens of N/m. This is usually of the order of pN. Spatial resolution, which is determined from the lateral deformation of the cells, is of the order of 100 nm. An AFM measures the local mechanical properties rather than the bulk stiffness of the cells or the stiffness distribution inside them. Flowing a fluid over to apply shear stress can also be done on single cells. This is useful to endothelial cells. Many other techniques are reported for mechanical probing of cells. Good overviews of these can be found in [6,12,88]. Apart from these, there is another perspective called bio-micromanipulation. We discuss this next.
10.2 Bio-micromanipulation

Manipulation in robotics and mechanisms literature means changing the pose of an object or changing the shape of an object. While micromanipulation retains this connotation, it also implies certain kinds of ‘cell surgery’. That is, injecting into a cell, pronuclei formation by exchanging nucleus between two cells, in vitro fertilization, etc. [94].

Interestingly, using microgrippers for mechanical characterization of cells has not received much attention. Holding a cell between two plates to push, pull, or roll it, is reported [95]. Complete characterization, bulk and intrinsic property distribution inside the cells, might be possible if a microgripper is used to grasp and manipulate a cell. Figure 9 shows a biomanipulation setup using which a cell can be grasped and manipulated using a compliant gripper [50]. Compliant gripper is a special type of deformable structure known as compliant mechanism. These can be designed for any prescribed manipulation task, for different materials and sizes, and for requisite stiffness. The polydimethylsiloxane (PDMS) grippers shown in figure 9b have stiffness as low as 1 N/m and can in fact be designed for lower stiffness than this. The gripper can be immersed in aqueous medium because specific points in it are moved mechanically using a probe attached to a micropositioner. The forces applied on the gripper during manipulation are measured using vision-based force-sensing technique [50,96]. Here, suitable number of points on the compliant gripper are monitored visually to measure their displacements and from those, the forces are computed by solving an inverse problem in elasticity [97]. Thus, this technique enables us to compute the bulk stiffness of a single cell because the displacement is known because of visual measurement and the force is known because of the computation.

The mechanical characterization using microgrippers has an advantage over all other techniques: it enables us to estimate the material property distribution inside the cells. This is possible by solving a second inverse problem wherein the boundary forces and displacements are used to estimate the stiffness distribution of the interior of a body presumed to be elastic [98]. This requires several sets of boundary force-displacement data [99]. For this, it is necessary to manipulate the cell by rolling, twisting, and re-grasping differently. This is possible with compliant grippers. This work in progress by our group [98] and will be reported in the future.

11. Closure

An overview of mechanics of microsystems, microfluidics, and biological cells is presented in this paper. We will give a summary of each of them below.

Microsystems: Microsystems (or MEMS as it is popularly known) is a mature field today. Its main emphasis is on using solids and deforming them using a variety of force fields to conceive novel sensors, actuators, and systems. Many of them are available commercially today. In this paper, we
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highlighted the role of mechanics in simulation and design of Microsystems. Even though the behaviour of solids at the micron scale does not deviate much from the assumptions made by continuum mechanics, modeling of Microsystems remains challenging. This is due to the coupling, often strong and nonlinear, among various energy domains involved. This leads to the challenging problem of solving coupled partial differential equations involving a large number of degrees of freedom. We explained this using the examples of electrostatic-elastic and electro-thermal-elastic Microsystems. We also noted that dissipation is an important and as-yet incompletely understood issue in Microsystems. We then considered two important aspects: synthesis and reduced-order modeling of Microsystems. Both of these sophisticated numerical techniques should scale well to be effective. Finally, we considered materials and microfabrication aspects briefly to discuss how mechanics is related to both. Many of the issues we have discussed here is integrated into commercial microsystem simulation software. But there is a need for further development to make it all reach the level of maturity and versatility found in macroscale mechanics or VLSI design.

Microfluidics: Many microfluidic devices have been developed in the past few years, based on the ability to pattern substrates, implement the lab-on-a-chip concept, control and enhance chemical reactions and heat transfer, manipulate particle position, orientation and transport rates, and develop mixing and separation processes. These systems are progressively being applied in the biomedical, pharmaceutical, printing and chip-cooling applications, to name just a few. It is natural to think that these systems will be integrated with smart materials and fully automated devices for more efficient operations, offering both research and engineering opportunities for the future. The importance of scaling down these devices, as well as characterizing and understanding the interplay of fluid flow, surface forces, and potentially statistical and molecular interactions, are among the research questions that will need to be addressed in more detail in the years to come, so that micro and nanosystems technology sheds its dogma from a research hype into useful products that are simple, compact, affordable, multi-functional, and evolutionary in all respects. Understanding the underlying science, more than hitting the technology through trial and error processes, will perhaps hold the key in maturing the research on microfluidics towards achieving this important objective.

Cellular biomechanics: In the last two sections of the paper, we took glimpse at the issues involved in mechanical modeling of biological cells. The viewpoints discussed in these two sections are considerably different from those of the traditional mechanics. They call for statistical mechanics and more fundamental physical biophysical approaches vis-à-vis classical mechanics and continuum mechanics. The modeling work in this nascent field of cellular biomechanics is going in tandem with the experimental techniques. Hence, we took a quick look at that aspect too in this paper.

In summary, this paper provides a broad-brush summary of the state of the three topics as they stand today while identifying gaps and challenges that lie ahead. It is by no means exhaustive.

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