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INVITED REVIEW

An historical perspective on cell mechanics

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Abstract The physical properties of the protoplasm have long been of interest, and today, several intricate methods, including atomic force microscopy, have been employed in studies of cellular mechanics. However, many current concepts and experimental approaches actually have their beginnings over 300 years ago. Unfortunately, these pioneering studies have been all but forgotten. In this paper, we have reviewed some of the early literature on cellular mechanics to place modern work within an historical framework. It is clear that with current nanoscience approaches, modern experiments employing cell indentation, manipulation, particle rheology and micro- or nano-needle poking are now quantifying mechanical properties which were only qualitatively described 100 years ago. Aside from the variety of approaches our predecessors have employed to understand cellular mechanics, we feel an understanding of the past will help to propel nanoscience into the future. As nanophysiology and nanomedicine are developing, we as a community should take time to consider the early roots of these fields.

Keywords Protoplasm · Cell mechanics · Elasticity · Viscoelasticity · Viscosity · Atomic force microscopy

Introduction

> "Much excellent research has been done with a test tube and a Bunsen burner, but certain problems cannot be successfully attacked without the aid of intricate apparatus. It is the latter type of research, in so far as it applies to studies on the physical properties of protoplasm with which this report deals." (Seifriz, 1937 [1]).

In the late seventeenth century, the likes of Robert Hooke and Antony van Leeuwenhoek were using simple optical microscopes to peer down into a tiny living universe in which fluid and cellular motion appeared to be extreme. In a letter [2] written on Christmas Day, 1702, van Leeuwenhoek describes what may be the first observations of the ciliate *Vorticella*, "In structure these little animals were fashioned like a bell, and at the round opening they made such a stir, that the particles in the water thereabout were set in motion thereby…which sight I found mightily diverting." The appearance of motion in this tiny world was not lost on these early observers. Brownian motion of particles and organelles inside living cells have been commonly reported [3, 4]. It was also conjectured that it may be possible to estimate viscosity by measuring these quantities. Although the tools were not available in the seventeenth century to perform accurate micro-rheology and nano-indentation experiments, many of the philosophical ideas and concepts we deal with today had their beginnings over 300 years ago. Moreover, the technological basis and understanding of cell and tissue mechanics has its foundation in the rapid industrialisation of the nineteenth century—the need for a thorough understanding of mechanical and structural testing and theory (indentation, beam bending, the Hertz model) of macroscale materials such as engines, boats and bridges [5]. This in turn reflected an earlier silvan economy—indeed, understanding the adaptation, structure and material properties of different woods (oak versus pine) preceded and defined our concept of tissue adaptation (for example, Wolff's law as applied to the skeleton) [5]. At the end of the nineteenth century, the mechanical properties of

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living cells were experimentally examined and analyzed using a variety of techniques based upon these macroscale engineering mechanics. Today, over a century later, our current nanoscale testing and modelling of biological materials is still fundamentally based on nineteenth-century practices [6–8].

The living cell is a universe unto itself. It was quickly recognized that the cellular universe is vastly complex and always experiencing turbulent forces and dynamics within the protoplasm which were somehow related to function. In this historical review, we will present work from very early studies involving the mechanical motion and properties of living cells. We will attempt to describe these studies in relation to modern approaches including, but not limited to, atomic force microscopy (AFM) [9]. Although this review hardly covers the entire wealth of scientific literature on the subject, we have attempted to revisit discoveries and philosophical concepts over the past 300 years to fit current work on cellular mechanics into an historical perspective. We hope such perspective will reveal that although we are asking similar questions as early scientists, modern nanoscale approaches are finally providing robust quantitative descriptions of cellular mechanics. These modern approaches are becoming of great importance as the role of nanoscience in physiology and medicine is now emerging.

The role of mechanical forces in biology is certainly not a new idea but is currently gaining wider acceptance. However, this has not always been the case. In 1850, Carpenter wrote "the degree to which the phenomena of Life are dependent upon Physical agencies has been the subject of inquiry and speculation among scientific investigators of almost every school. That many actions taking place in the living body are conformable to the laws of mechanics, has been hastily assumed as justifying the conclusion that all its actions are mechanical…" In 1917, Thompson discussed the apparent mechanical nature of cellular processes in his classic *On Growth and Form* [5], writing that "…though they resemble known physical phenomena, their nature is still the subject of much dubiety and discussion, and neither the forms produced nor the forces at work can yet be satisfactorily and simply explained." At about this time, many reports were emerging which began to quantify mechanical properties in cells which, until this point, had largely been supported by qualitative, empirical observations. Moreover, early debates about the appropriate theoretical picture one should have about the cell were also emerging [3, 4, 10, 11]. Cells were initially thought to be of homogeneous gels, sols, viscoelastic and plastic fluids. These lines of thought continue today; however, many models have been developed which describe cellular mechanics in several ways, including a viscoelastic continuum, a combination of discrete mechanical elements, or a combination of viscoelastic fluid within a dense meshwork [6–8, 12–18]. However, for the number of models which exist today, there seem to be just as many experimental proofs which either support or refute each proposed model (for example, recent work on the soft glass rheology phenomenon [19, 20]). Through experimental refinement over the past century, highly accurate measurements of viscosity, elasticity, plasticity and motion have been carried out by several techniques. However, this has not led to a complete theoretical description of cell mechanics that is both time-dependent and predictive.

Importantly, it is not fully understood whether these mechanical phenomena and properties are merely side products of biological processes or if they are intimately controlled at the genetic and physiological level through feedback loops, actuation and/or response pathways. In the past several years, some reports have begun to answer this highly complex question [21–25]. Here, we will generally limit our discussion towards AFM-based contributions, given the scope and contributors to this special issue on nanophysiology in the *Pflügers Archiv European Journal of Physiology*. However, contributions from many fields and techniques have been fundamental in the development of our current understanding of cellular mechanics [6–8]. Clearly, the field of cell mechanics and especially its relation to cell physiology or nanophysiology is vital and growing as many avenues exist to explore the micro- and nano-scopic cellular world. In this review, we will attempt to place modern AFM work side-by-side with studies from the seventeenth century onward to fit our understanding within a fascinating and sometimes surprising historical framework.

The architecture of the protoplasm In the late nineteenth century, cell doctrine was being generalized and the term protoplasm was used widely as a description of the contents of a cell [3, 26–30]. Early on, the protoplasm was viewed almost spiritually, as it had the ability to self-replicate, and many at the time accepted the idea of so-called vital and physical forces existing within the cell. Vitalists believed that vital forces emanated directly from the "Will of the Omnipotent and Ominpresent Creator" [31], and physical forces were a result or the modi operandi of Vital forces. Over time, there emerged a great debate between the "Vitalists" and "Mechanists" about the structure, function and purpose of the protoplasm, where mechanists believed that all processes within the cell could be explained by physical or chemical mechanics [32, 33]. Many of these arguments actually continued well into the twentieth century, often arising from the inability of scientists to determine the exact chemical structure of the protoplasm or to explain certain mechanical phenomena [34–37].

The main elements of cellular architecture within the protoplasm were determined in the mid to late 1800s, and

up until that point, cells were considered as small compartments containing homogeneous fluids [38]. With the development of modern microscopic techniques during the eighteenth and nineteenth centuries [1], including darkfield illumination, oil immersion lenses and high-quality glass optics free from aberrations, together with advances in sample preparation and staining methods (developed by the great European histologists such as Golgi, 1906 Nobel Laureate), the nucleus, nucleoli, chromatin, nuclear membranes, vacuoles, cytoplasmic streaming, filamentous structures (cytoskeleton, reticulum, the mitotic spindle, and actin–myosin striations in muscle) were observed [28–30, 38–40] (Fig. 1). The granular nature of the protoplasm led to the belief that it was accurately described as a colloidal suspension, giving rise to the early discussions and measurements of viscosity [4, 30]. As with the development of the optical microscope, the AFM, a new paradigm in microscopy, was utilized early on to visualize some of these cellular structures.

Early AFM imaging of live cells quickly revealed the ability to image elements of the cytoskeleton as well as monitoring its dynamics [41–45]. Nuclei were often observed as large structures and contributing significantly to the apparent height of the cells. Due to the nature of AFM imaging, mechanical information was readily inferred and later quantified using various imaging mechanisms [41, 46, 47]. High-resolution AFM imaging has provided detailed information on the structure, function and mechanics of nucleic acids [48–55], several types of membrane proteins [56–61], nuclear pore complexes [62–67], biological filaments [68–77], molecular motors [78–83] and cell wall surfaces [84–92] which was not accessible with optical microscopy in the 1800s. Although there are many technological differences between both optical and scanning probe microscopy techniques, separated by well over a century, both have intriguingly pointed towards the mechanical nature of the cell.

Protoplasmic mechanics In a series of three lectures given by Stuart [93] in 1737 and 1738, it was shown that blood, blood vessels and nerves, dissected from a corpse, could all be tested mechanically. Early concepts of hydrostatics, elasticity and viscoelastic fluids were discussed and, apparently, it was observed that nerves were inelastic. In the living organism, mechanical oscillations were studied at length. In his lecture in 1857, Paget [94] discusses the spontaneous contractions of the heart after being removed from a living organism. The mechanical contractions were observed to continue without the need for a functioning nervous system, a property of heart and muscle cells which have been exploited recently in the AFM literature [95–98]. Other mechanical oscillations were discussed such as observations on ~3 μm diameter vacuoles in several organisms, cell-wall oscillations in plants and the movement of cilia [94]. In each of these cases, no known muscle structure or nervous system was present. It was not understood how such mechanical oscillations provided an advantage to these organisms. However, the concept of biological mechanics was clearly under development.

Early studies on the mechanical properties of the protoplasm were mainly concerned with viscosity. This was partly due to experimental limitations as microscopic methods of observation were not yet well developed (Fig. 2). Cytoplasmic streaming (the circular flow of cytoplasm in eukaryotic cells) was observed very early [4, 99] and used as a qualitative measure of the protoplasmic viscosity. It was also clear that the motion of internal

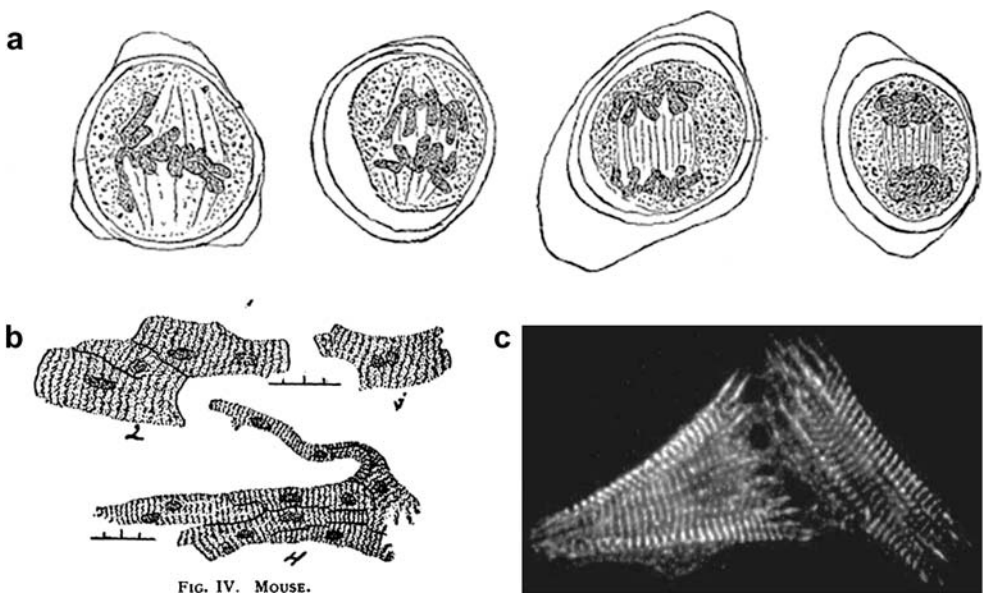

Fig. 1 Images of living cells from the late nineteenth century. **a** Detailed studies of mitosis were completed by Campbell in 1890 (image reproduced with permission from the Torrey Botanical Society [172]). **b** Striated structures were observed in cardiomyocytes of many species including humans in 1887 (image reproduced with permission from the American Society of Microscopists [173]). **c** Modern immunofluorescence staining of actin with rhodamine-phalloidin, over a century later, also reveals striated structures in rat cardiomyocytes

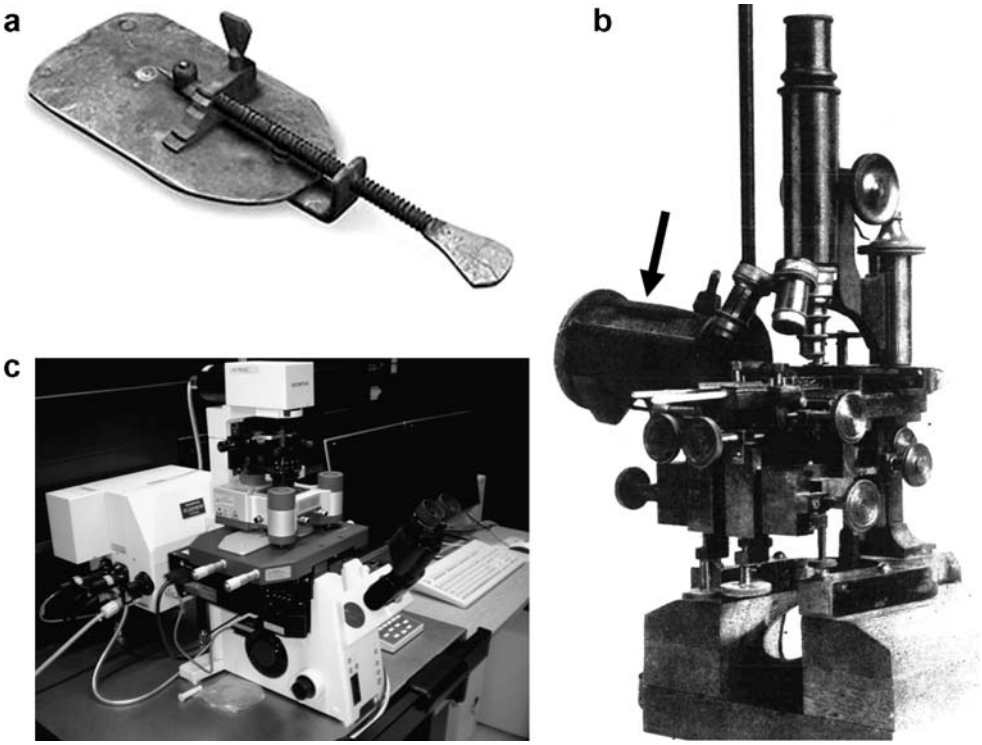

Fig. 2 Early microscopes used in the study of cellular mechanics. **a** The Leeuwenhoek microscope from the early 1600s was one of the first utilized in early microscopy (image reproduced with permission from Molecular Expressions images). **b** The magnetic microscope from the 1920s used in studies which were the predecessors of modern particle microrheology. The microscope incorporated an electromagnet (*arrow*) into the design to oscillate magnetic microparticles inserted into living cells (image reproduced with permission from The Company of Biologists [103]). **c** The modern AFM, integrated with an inverted laser scanning confocal microscope to allow simultaneous mechanical perturbations and measurements to be performed while imaging cellular structures in three dimensions

granules could also be used as markers for viscosity measurements [3, 4]. This represents some of the earliest uses of particle tracking in cell mechanics and is essentially a predecessor of modern-particle tracking and microrheology measurements [100, 101]. Although this early work was carried out in the 1920s and suffers from an obvious lack of appropriate experimental and theoretical considerations, some of the same issues were being discussed as they are today, such as the influence of the size of the granule, the mesh size of the protoplasm, damage to the cell and the influence of temperature [3, 4, 102]. Similarly, an early magnetic microscope developed in 1923 [103] was used to oscillate nickel particles (~16 μm in diameter) inserted into living cells. Aside from the similarities to modern particle micro-rheology [19, 20, 100, 101], this approach is similar in concept to magnetic bead-twisting cytometry [104–106]. An early example of magnetic manipulation also involved injecting iron particles into bacteria and observing how fast they were attracted to an electromagnet [4]. A distinct but very common approach to viscosity measurements at the time involved the centrifugation of cells. Granules would be "thrown to one end of the cell" and slowly migrate back to their original position", a qualitative estimate of protoplasm viscosity at the time [4].

Changes in viscosity were measured during sea urchin egg mitosis and fertilization, sometimes by as much as two orders of magnitude [4]. Interestingly, it was also observed that preventing changes in viscosity could halt mitosis [107, 108]. Furthermore, changes in protoplasmic viscosity in response to the action of temperature, radiation, electric currents and several chemicals (anaesthetics, salt, organic solvents, and even the early chemotherapy agents being developed in the 1940s) have all been measured [3, 4, 29, 107, 109–124]. Although the major observable in AFM studies is the Young's modulus or elasticity (which is a related but fundamentally different parameter from viscosity), similar measurements have been performed in cells over the last two decades with AFM. These include the effects of anti-cytoskeletal drugs [41, 125, 126], chemotherapy reagents [114, 127] and electrical stimulation [27, 128].

The majority of AFM mechanical measurements on living cells rely on nano-indentation approaches and extracting mechanical parameters from measured force–displacement curves. Although the main mechanical indicator is taken to be elasticity, rheological parameters have also been extracted from living cells using various approaches [129–131]. Indentation approaches have been used in conjunction with scanning to produce force maps [41–44, 132] or in single spots on living cells to measure time dependence [125, 127]. Early indentation experiments on living cells almost a century ago employed the use of glass microneedles which were slowly inserted into many cell types to estimate viscosity [39, 133–135]. Although very qualitative, this method and variants of "microdissection" became a very common way to estimate the mechanical properties of the protoplasm. In 1931, a "microoperation" with a microneedle was described in which

needles were used to push and penetrate into organelles of living cells [135]. Interestingly, in 2005, a "nanoscale operation" was described in which an AFM tip, modified with a nanoneedle, was employed to push and penetrate into the nucleus of living cells [136]. Although separated by about three quarters of a century, both reports describe the penetration and deformation of the cell nucleus using very similar approaches (Fig. 3). Granted, the AFM measurement provided a quantitative measure of force which was not possible with the early report. Furthermore, simultaneous laser scanning confocal imaging (Fig. 2) provides much more detailed three-dimensional information which was also not possible in 1931.

Just prior to the development of the AFM in 1986, "cell poking" with calibrated microneedles was developed [137–139]. Unlike the early methods which pushed the needle straight through the cell, the needle was indented into the cell membrane to measure cellular deformations and elasticity. Complementary to much older work from the late 1920s, the effect of anti-cytoskeletal drugs were also measured [137]. Some early examples of whole-cell elasticity were demonstrated using plant cells [140]. Plant tissue was clamped on either end and stretched using

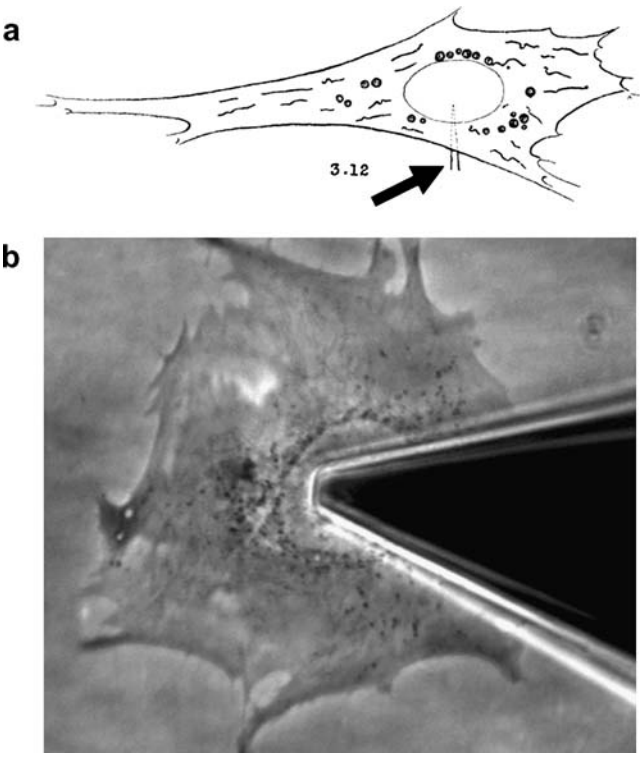

Fig. 3 Cell indentation as a means of measuring mechanical properties was developed as in the early 1900s. **a** In 1931, glass microneedles (*arrow*) were used to "operate" on living cells by indenting and eventually entering the nucleus (image reproduced with permission from the Royal Society [135]). **b** Much later, modern techniques using AFM as seen in the phase-contrast micrograph. These similar methods of "nano-indentation" have also been described as "nano-operations" [136]

known weights to produce stress–strain curves. Conceptually, this work is related to modern directions towards investigating multi-cellular assemblies, monolayers and tissues [16, 24, 25, 141]. Micropipette aspiration [142–145] has also come into use to study whole-cell mechanics by examining cellular and nuclear deformations in response to suction [146–149]. Microplates [150, 151] have been employed to measure cellular deformation and elasticity in response to force. Cells have been either literally "ploughed" from a surface using a cantilever to measure adhesion forces which aid in attachment and motility [152]. There is an extensive literature, dating back to the late 1800s, on wound healing and migration which are also highly mechanical in nature [153]. Recently, AFM has been used to measure the protrusive forces [44, 154] at the edge of migrating cells in complement to traction force assays [155, 156], micropipette and laser trap studies [157]. Migration is a key element in cancer metastasis, and in recent years, cells have been optically trapped and stretched in electromagnetic fields to measure mechanical properties in relation to metastatic potential [158–161] (complementary to early deformability assays [162]). In addition, magnetic traps have been utilized to perform rheological measurements with magnetic beads [20, 163–165]. Measurements of mechanical parameters, organelle deformations and force transmission have all been performed with magnetic bead-twisting cytometry [163, 166]. These studies are similar in concept to the early studies by Seifriz [103] and his magnetic microscope as well as early organelle tracking in response to indentations with micropipettes [135].

Obviously, there have been a wide variety of approaches demonstrated over the past 150 years to measure the mechanical properties of living cells. Although the mechanical properties of living cells and organisms was initially very conceptual, we have witnessed a significant growth in the methodologies employed to measure such properties [6–8]. Many laboratories worldwide have become expert at measuring mechanical properties of cells; however, it is clear from the above literature review that many of the same questions are being asked today that were posed and explored over the past century. Clearly, biological cells and tissues possess mechanical properties, and these properties do appear to change during physiological processes and in disease. Mechanical detection of these states may indeed be a key development important for the future of 'nanomedicine' and 'nanophysiology'. However, these concepts have existed for some time, and it begs the question—Is there more we can do aside from developing very accurate tools to mechanically detect biological processes?

Outlook on cell mechanics and "nanophysiology" In 1737, Stuart [93] originally discussed the idea of being able to

control the heart by stimulating it correctly. Although the measurement of accurate mechanical parameters is of extreme importance, the idea of controlling and altering biological pathways is equally enticing. Previously, it has been shown that mechanical force delivered by the AFM tip can induce various chemo-mechanical responses [167–169]. In recent work, it has also been shown that the mechanical environment of many cell types (including cancer and stem cells) can be used to control and alter gene expression and differentiation pathways [21–25, 164, 170, 171]. We now have the tools to measure mechanical properties, and we have the tools to alter the mechanical environment of a cell or even deliver well-defined forces to a cell. Therefore, can we now move towards initiating and controlling biological pathways in cell cultures and perhaps, one day, in vivo? Perhaps, the emerging field of nanophysiology will include a branch dedicated to the nanomechanical control of biological pathways. This poorly understood area of pursuit, in concert with ultra-sensitive detection technologies and modern pharmaceutical treatments, may have a significant role to play in the development of nanomedicine and the diagnosis and treatment of diseases.

Complementary to the many applications one may envision for nanotechnology in medicine and physiology, it is also becoming clear that the governing physical principles of cell mechanics remain poorly understood and the subject of intense debate. Specifically, the concept of elasticity is ill-defined for a living cell. The cell is heterogeneous, dynamic, undergoes continuous cytoskeletal remodelling and likely highly anisotropic. Therefore, the Hertz model, commonly used in AFM nanoindentation experiments, does not ideally apply. Furthermore, the cellular Poisson ratio is equally ill-defined and has conventionally been taken to be constant, although this may not actually be the case. There is no evidence to show that the Poisson ratio does not itself change during physiological processes, and this may or may not be correlated to changes in Young's modulus. Therefore, as mentioned above, our theoretical descriptions of cell mechanics still require much further development. However, there is no doubt this will occur as future debates and empirical observations take place.

Conclusions regarding cellular mechanics are often drawn from studies carried out on one cell type, under a limited set of conditions, and generalized towards a broad range of cells, if not all cells. However, we suggest that mechanical responses and the biochemical/structural basis for mechanical parameters are likely dependent on the type, physiological and mechanical environment of the cell. Although many cell types contain the same structural components (that is, the cytoplasm, cytoskeleton, nucleus, membranes, etc.), it may be unlikely to utilize them along identical pathways during biological processes. Therefore, rather than searching for a unified theory of cell mechanics, we, as a community, might try to identify heterogeneity in phenotypic mechanical responses and transduction pathways in living cells. Classification might be according to the mechanical model(s) (or combination of models) which describes the cell most appropriately, along the lines of which signalling pathway(s) are activated upon mechanical stimulation, which internal structures are important for mechanotransduction, or the mechanical changes which take place during physiological processes.

Regardless of this speculation, the field of cell mechanics is alive and well. The trend towards interdisciplinary research among so-called nanoscientists is an encouraging one and represents one of the major advances in the field of cell mechanics. In the early studies of the protoplasm, there was significant antagonism and territorial fighting between biologists and chemists [37]. Today, we see that scientists are becoming ever more able and willing to cross diverse disciplinary lines. As we look back on the history of cell mechanics, we realize that it was only about 100 years ago that a raging debate was taking place about the components of the protoplasm. Certainly, the field today is full of speculation, inconsistencies and disagreement, but this is what drives science forward.

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