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Perspective

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Advancing mechanobiology from single molecules to complex cellular systems

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Krishna Chaitanya Kasuba[1,2,16], Gotthold Fläschner[3,4,16], Akanksha Jain[1,16], Michael Krieg[5,16], Upnishad Sharma[1], Valentin Gensbittel[1], Michele M. Nava[1], Miguel Camacho Rufino[6], Barbara Treutlein[1], Prisca Liberali[1,7], Xavier Trepat[3,4,8], Frank Jülicher[9,10], Matthieu Piel[11], Dagmar Iber[1,12], Matthias P. Lutolf[6,13], Botond Roska[14], Massimo Vassalli[15] & Daniel J. Müller[1]

Cells operate as networks of proteins, membranes, condensates and compartments, each sensing and displaying distinct intracellular mechanical properties. However, cells also sense, adapt and respond to manifold mechanical properties of the environment, including adhesion, tension, stiffness, shear, viscoelasticity, plasticity, pressure and confinement. By gauging these properties at various timescales and across nano to macro length scales, cellular systems alter their collective responses. The field of mechanobiology aims to elucidate how cellular systems such as tissues, organoids or organs perceive, respond to and influence mechanical cues, and how these impact physiological processes including homeostasis, growth, division, differentiation, movement, development, adaptation and apoptosis. This Perspective highlights challenges within mechanobiology that must be systematically tackled to advance exploration and deepen our understanding of the mechanical attributes of intricate multicellular organisms. Such understanding necessitates the engineering of multicellular models as reference systems, the development of new tools to rigorously quantify and manipulate mechanical properties from the nanoscale to macroscale and theoretical frameworks to decode mechanobiological complexities. Ultimately, addressing these challenges will improve the analysis, monitoring and prediction of mechanobiological processes across molecular, multicellular and organismal scales, thus advancing mechanodiagnostics and mechanomedicine.

Within complex molecular networks, interactions govern mechanical phenomena such as cell state, size, shape, volume, adhesion, migration and proliferation that are crucial for the physiology and pathology of cellular systems[1,2]. Collectively, these interactions guide the assembly of cells into tissues, organs and organisms. Cellular systems also sense mechanical cues and respond by applying cues to their environments[3,4]. For example, mammalian cells typically round up and stiffen during mitosis to create sufficient space for cell division[5], exert pressure to facilitate locomotion through processes such as blebbing[6] and sense the mechanical properties of neuronal systems[7] and during brain development[8,9]. Mammalian cells also sense the structure and stiffness of their surroundings and adapt growth, homeostasis, differentiation, apoptosis or stem cell lineage in response[10–12]. This interplay of applying, sensing and responding to mechanical cues is at the heart of mechanobiology[1,3,13,14]. As cells distinguish between mechanical cues, such as pressure, deformation, tension, stiffness, space or shape,

A full list of affiliations appears at the end of the paper. e-mail: daniel.mueller@bsse.ethz.ch

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BOX 1

Emerging challenges and opportunities in mechanobiology

- **Quantify and morphologically map mechanical cues from molecular to cellular resolution**
  New tools to quantify various mechanical cues from molecular, cellular, tissue and organ(oid) scales across wide mechanical and spatiotemporal ranges are needed.
- **Development of nanotechnological tools to sense, localize and apply mechanical cues**
  The toolbox to achieve this goal consists of quantum dots, fluorescence sensors and actuators, photoswitchable polymers and molecular machines, DNA origami and nano tools exemplified in Fig. 1.
- **Reference systems to calibrate the various tools used to characterize mechanical cues**
  Reference samples of cellular systems (including molecular, organelle, condensate, cell, organoid, tissue, organ and embryo) that are suitable for calibrating tools that measure mechanical cues and relating them meaningfully must be obtained.
- **Decipher and correlate mechanical cues such as shape, volume, pressure, tension, stiffness, force, viscoelasticity, adhesion and flow**
  The complementarity of these parameters will pave the way to understanding how complex cellular systems sense, respond and apply mechanical cues.
- **Control and apply mechanical cues across length scales and timescales**
  Understanding of how cellular systems respond to mechanical cues requires tools to apply them at defined magnitudes, locations, times and rates.
- **Multiplex mechanical cues to cell states, signalling pathways, development, physiology and malfunction**
  Multiplexing of mechanical cues with biological, physiological and clinical parameters of cells is required for a holistic mechanobiological understanding.
- **Establish mechanobiological models of complex cellular systems**
  The development of detailed, dynamic and experimentally validated theoretical and computational models that capture the nonlinear, emergent and adaptive behaviours of complex biological systems is crucial.

which are distributed heterogeneously within complex cellular systems (including extracellular matrix (ECM), tissues, organoids and organs), the challenge is to understand which cues cells transduce to direct system-wide responses[2,12,15,16].

The quantification and description of mechanical properties of complex cellular systems is challenging (Box 1). It was believed that deconstructing these systems into molecular or macromolecular components would clarify their function as a whole, and much has been learnt by studying reductionistic systems. Removing cells from the native environment has allowed us to understand key mechanisms, but it also precludes us from accurately assessing their physiological behaviours. For example, isolation distorts vital molecular interactions and ignores essential environmental factors present in living organisms. This extraction of components from cellular systems and characterization in artificial settings simplifies complexities but also strips away crucial elements, such as growth factors, ECM, cell–tissue contacts and mechanical cues[15]. We have learned that understanding molecular and cellular processes requires observation within their most natural context[17,18]. Thus, to genuinely grasp the mechanobiology of cells and their higher-order systems, we must examine them in complex, realistic environments such as tissues, organoids, organs and organisms. However, this approach poses considerable challenges: many existing nanotools for quantifying mechanical properties are not well suited to complex cellular systems, and they often yield inconsistent results, fail to provide the necessary mechanical data or cannot deliver the mechanical stimuli required to elicit cellular responses.

To deepen our mechanobiological understanding of living systems, from molecular to multicellular structures, we must refine experimental approaches to accurately measure and manipulate their mechanical properties with precise spatial and temporal resolution and combine these with physiological parameters (Fig. 1). Ideally, these measurements would span spatial dimensions from subnanometre to centimetre ranges and cover timescales that allow us to describe the heterogeneity and dynamics of biological processes. For example, when applying mechanical stimuli to complex cellular systems, we must be able to address how various mechanical cues are distributed and transduced. Given that mechanical properties depend on the timescale at which they are probed, we need to expand basic mechanical assessments to include rheological measurements. It is also crucial to develop methods for measuring mechanical parameters and applying mechanical stimuli with molecular precision in increasingly complex systems. Despite the wealth of mechanical information that can be measured (including force, adhesion, tension, contraction, friction, stiffness, deformation, pressure, flow, viscosity, volume or shape), a comprehensive understanding of complex systems requires knowledge of the relationships between these measurements. Finally, to understand how cellular processes perceive, react to and influence mechanical properties, we must integrate mechanical data with morphological, genomic and proteomic analyses. The complexity of systems and data requires the incorporation of theoretical models that provide a holistic, rather than reductionistic, understanding. Therefore, in this Perspective, we discuss five key challenges that must be addressed to advance mechanobiology. As this ambitious goal will probably expand as we explore specific issues and details, we hope that these challenges will serve to explore and uncover opportunities in engineering complex biological systems[15], translational mechanobiology or mechanomedicine[19].

Quantifying and comparing mechanical properties across scales

Cell biologists often describe the mechanical properties of cellular systems qualitatively. For example, stiffer cellular systems are interpreted mainly through the accumulation of actin and myosin or other cytoskeletal components (Box 2). This limitation arises due to the lack of easily applicable and translatable methodological approaches suitable for quantifying mechanical properties within complex cellular systems. Although single-molecule and single-cell methods can provide quantitative mechanical data on cellular systems (Fig. 1 and Box 1)[4,7,17,20], these data are often difficult to compare because they measure different mechanical properties. For example, micropipette aspiration measures pressure, a scalar quantity without direction, and other techniques, such as optical and magnetic tweezers or atomic force microscopy measure force[20–22], a vector with both magnitude and direction. Yet the conversion of pressure into force and vice versa can be challenging, because the exact parameters needed (in this case, contact area) are inaccessible or imprecise[23]. Other methods, such as monolayer stress microscopy, measure surface tension and stress, which are tensors represented by matrices[24]. Inside living cells, mechanical measurements are often taken using fluorescence-based sensors, which can be

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Fig. 1 | Conceptual embodiment of mechanobiology across biological processes, structures and properties and available micro- and nanotools. Mechanobiology integrates dynamic biological processes, structural organization, physical properties and analytical tools. The framework highlights how structural components span spatial scales from organ-level to molecular assemblies and the micro- and nanotools that can be used to parameterize cellular systems at bulk, single-cell and single-molecule resolutions. Biological processes, structures and properties define how mechanical signals are generated, propagated and interpreted across cellular systems. Methods and tools enable the measurement, visualization and manipulation of parameters that are directly or indirectly related to mechanical properties. Advances in mechanobiology will require these interconnected layers (wheels) to be related to uncover causal links between mechanical and biological functions. AFM, atomic force microscopy; ChIP, chromatin immunoprecipitation; FCS, fluorescence correlation spectroscopy; FRAP, fluorescence recovery after photopbleaching; FRET, fluorescence resonance energy transfer; MS, mass spectroscopy; TEM, transmission electron microscopy; TFM, traction force microscopy; TIRF, total internal reflection.

genetically encoded and linked to cellular structures but detect limited force ranges. It can also be difficult to relate the mechanical properties of cellular systems to the contributions of their constituents. For example, mechanical indentation of the soft cell membrane largely measures the properties of the directly underlying (and much stiffer) actomyosin cortex[20].

Another source of data variability is the reliance on theoretical models for the extraction of mechanical parameters from experimental data (Box 3)[20]. However, these models tend to oversimplify complex biological phenomena, leading to discrepancies in interpreting the measurements obtained through different methodologies. A prime example, the Hertz model, describes how the contact force between two idealized objects relates to deformation[20]. However, cells and cellular systems are far from linearly elastic, isotropic, smooth or non-adherent. Several models attempt to refine this problem by accounting for shape, contact area and adhesion[25]. Another critical factor that is often oversimplified in models is the assumption of constant cell volume. Recent studies indicate that cell volumes and pressures change in response to environmental conditions and mechanical stress[26–28]. This variability alters mechanical parameters, such as stiffness and viscosity. Each

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BOX 2

Key biological terms and concepts

Actin/myosin. Structural proteins that form the cytoskeleton and drive cellular movements and shape changes.

Blebbing. A process in which the cell membrane detaches locally from the underlying cortex, forming bulges or blebs that are involved in cell migration and death.

CRISPR–Cas9. Gene-editing system that allows targeted modifications of DNA sequences within living cells.

Extracellular matrix (ECM). Complex three-dimensional network of proteins and other molecules outside cells that provides a biochemical and structural framework and regulates the behaviour of cells.

Genomics. Large-scale study of the genome (the complete set of DNA of an organism), including all genes and their structures, functions and interactions.

Membrane potential. The voltage difference across the cell membrane, which is crucial for processes such as energy conversion, molecular transport, signalling and mechanical sensing.

Organoids. Miniaturized, simplified model systems of organs grown in vitro from stem cells or fibroblasts. Organoids are used for studying development, disease and regeneration.

Proteomics. Large-scale study of all proteins (the proteome) expressed by cells or organisms.

Transcriptomics. Large-scale study of all or selected RNA content (the transcriptome) expressed by cells or organisms.

Transduction. Process by which cells convert mechanical or chemical signals into cellular responses.

BOX 3

Key materials terms and concepts

Hertz model. Classical model describing the contact mechanics of elastic bodies, often used to approximate mechanical properties.

Tensorial quantities. Quantities such as stress or strain that describe not just how much force or deformation is present, but also in which directions and how they vary across a surface or volume.

Strain. Relative deformation of a material under stress.

Stress. Force per unit area of a material resisting deformation.

Viscoelasticity. Material property describing behaviour that combines both fluid-like (viscous) and solid-like (elastic) responses.

Rheology. The study of how materials deform and flow in response to mechanical forces over a wide range of conditions. It encompasses the measurement and analysis of properties such as viscosity, elasticity and viscoelasticity.

applied model has inherent assumptions and limitations that may not fully capture the complexity of biological systems. Therefore, the development of more sophisticated models that incorporate biological changes, like those observed in cell volume, pressure or morphology, is crucial to advance our understanding of mechanical properties in tissues. Recent advances infer three-dimensional forces directly from cell shapes in tissues[26,28]. Combined with advanced imaging technologies and image processing algorithms, this enables the approximation of mechanical parameters in an otherwise undisturbed tissue context. Complementary high-resolution cell-based simulation frameworks can incorporate diverse biophysical models—including the ECM, nucleus and organelles—and infer mechanical properties by adjusting parameters to match observed three-dimensional shapes[29].

As the mechanical data depend on the experimental technique used and theoretical models, these data must be interpreted with great care[17]. The biophysical information provided by each technique and model must be well understood and limitations considered. However, the field of mechanobiology would benefit from reference samples that allow different techniques to be calibrated[20,21,30], the models to be tested and the mechanical properties to be correlated meaningfully. The establishment of such reference samples and a better understanding of the limitations and applicability of each approach would offer the potential to combine them to gain more holistic information on the multiple mechanical properties of complex cellular systems. For example, the field could agree on one cell type or cellular system (condensate, organelle, organoid, tissue, organ, organism) whose state and morphology are very well described and can be precisely controlled to systematically quantify manifold mechanical properties. Such model-specific reference samples can serve to evaluate the complementarity and intrinsic limitations of mechanobiological techniques[20,21], which would help users to decide which assay to apply to their particular biological question. Finally, such an ideal scenario could guide the development of novel technologies and refined models that provide complementary insight into the mechanical properties of cellular systems.

Recording timescales of mechanical sensing, regulation and application

An important limitation of mechanical measurements is that the biophysical properties of living systems depend on the biological process per se and on the timescale at which they are measured[31]. The timescale of a mechanical cue, whether described as a strain rate (for example, the rate at which a material is deformed) or a frequency (for example, particularly for periodic forces), can drastically alter cellular sensing and response. Mechanosensory modalities like touch and hearing strongly depend on the timescale at which the force is applied. Such frequency selectivity may be realized because mechanical properties depend nonlinearly on the timescale of the mechanical deformation or stress applied[32,33]. This is because complex and adaptive cellular structures and compartments comprise elastic components that act as springs and viscous components that dissipate energy like dampers. Moreover, unlike inert materials, cells display active stress generated by out-of-equilibrium structural elements such as the actomyosin cytoskeleton. Depending on the deformation rate, different structural components and processes within the cell become involved or dominant. For instance, slower deformations allow more time for molecular rearrangements and viscous fluid flows within cells[34–36]. Similarly, cellular sensing of mechanical cues depends on their timescales, as (for example) mechanoreceptive neurons are more sensitive to strain rates than strain[37–39].

At present, the mechanical properties of cellular systems are characterized mainly at one or a few timescales. Different techniques measure mechanical properties at different timescales, so measurements should be compared with care (Box 4). In materials science, researchers address this problem by measuring mechanical properties over broad timescales, providing insight into the full rheological

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BOX 4

Nano- and microtools for measuring mechanical properties

Atomic force microscopy. High-resolution imaging and manipulation technique that uses a microcantilever to image and measure mechanical properties of cells and molecules.

Optical and magnetic tweezers. Precision tools that use focused laser beams or magnetic fields to trap and manipulate microscopic particles or molecules, enabling the study of mechanical properties and interactions.

Micropipette aspiration. In this method, a fine glass pipette is used to apply suction and measure the mechanical properties of cells or vesicles.

Traction force microscopy. Infers the forces that cellular systems exert on a deformable substrate by tracking the displacement of embedded markers.

Brillouin microscopy. Imaging technique that measures frequency shifts in scattered light caused by acoustic vibrations within materials, from which mechanical properties are approximated.

Droplets. Deformable probes for studying mechanical properties of materials or cells by observing how their shape changes in response to external forces or environmental conditions.

Deformation cytometry. Rapidly measures the mechanical properties of individual cells by analysing how they deform while flowing through microfluidic channels.

Nanosensors. Characterize mechanical cues in cellular systems by, for example, changing fluorescence in response to mechanical forces or deformations at the nanoscopic level.

spectrum. In biology, the active regulation of mechanical properties lies within ≪100 Hz, whereas probing the mechanics at >1,000 Hz provides snapshots of the passive properties of cellular structures and compartments. Functions including cell migration or division operate on ultraslow timescales (minutes to hours) at which active components become dominant and inaccessible to current rheology techniques[14,20]. Therefore, developing rheological approaches, ideally ranging from ≤0.01 to ≥10,000 Hz (refs. 32,33), will allow the comparison of mechanical measurements taken from different approaches and, importantly, characterization of the full spectrum of how complex biological systems sense, regulate and apply mechanical cues[40].

Mimicking realistic biological systems

Organoids are transformative tools that provide insight into cellular self-organization during development and morphogenesis, and show the capacity to replicate human-specific aspects of (patho)physiologies (Fig. 2a). However, unguided organoid development is often stochastic, producing highly variable morphologies[41]. Mechanical cues, including the stiffness and (nano)topography of the surroundings, apply mechanical stress and spatial constraints that influence how cells organize, differentiate and function[2,42]. The stiffness and viscoelasticity of the ECM can determine the fate of stem cells to form bone, muscle or neural tissues[10,43,44]. Replicating such cues in vitro through bioengineering approaches, including microfluidic systems, organ-on-a-chip or functionalized scaffolds, can direct the spatial arrangement of cells, which is essential for organoids to mimic the architecture and function of primary tissue[15]. Organoids that experience mechanical constraints and cues similar to those encountered in vivo can show enhanced functionality[45,46]. For example, controlling the initial organoid geometry guides intestinal organoids into defined shapes, sizes and cell distributions[45–47]. Mechanical cues also improve the maturation of cardiac organoids[48], control the patterning and morphogenesis of intestinal organoids[42,49,50] and guide brain development and function[13,51]. The appropriate mechanical environment in organoids is necessary to replicate (patho)physiological functions[46], such as those that operate during fibrosis or cancer[52,53]. Organoids that replicate the appropriate mechanophysiological aspects are more suitable systems to model in vivo tissue responses to medical treatments in real-world scenarios[44,54].

Understanding the mechanical properties of biological tissues is critical for the development of in vitro cellular systems that reflect the properties of tissues. However, biophysical tools that allow high throughput, multiscale quantification of mechanical properties at resolutions that approach that of diffraction-limited light microscopy are not commonly accessible, and new tools that can quantify tissue biomechanics and their microenvironments, mechanically constrain selected regions or apply controlled mechanical stimuli to trigger specific cellular responses are needed (Fig. 2b). Cell and tissue properties have been inferred by combining image-based measurements of cell geometries with theory and laser ablation to estimate (un)jamming transitions and fluidization in tissues[12,55,56]. Many techniques can apply mechanical cues from the outside of cellular systems, such as micro/nano-needles, micropipettes, microcantilevers, parallel plates or confiners, whereas other approaches embed nanometre- or micrometre-sized beads or oil droplets in the tissue to measure mechanical properties[20,45,57]. However, beads and droplets also bring along limitations, including the need to detect the full rheological properties of the undistorted tissue or apply mechanical cues across wide time, force or pressure ranges[21,22]. Similarly, fluorophores can indicate forces acting in molecules, membranes, cells or tissues but have limited force ranges and cannot apply mechanical cues[58–60]. Moreover, the morphological details of how applied mechanical cues distribute in complex tissues and where and how they trigger cellular responses are needed to better understand their mechanobiology. Nanoscale mechanosensors show promise for extending this portfolio to gauge the mechanical properties of complex systems across time and length scales[61,62]. Brillouin microscopy has also emerged as a non-invasive label- and contact-free technique to visualize viscoelastic properties of biological samples at diffraction-limited resolution, but the quantitative interpretation of the elastographic data requires further validation[63]. There is an unmet need to develop new methods or refine existing ones to apply various types of mechanical cues and to decipher the subsequent mechanical responses of tissues. It would be even better if tools could measure and apply several mechanical cues simultaneously. Combining existing techniques to apply larger mechanical constraints to cellular systems (such as organoids or animals) and visualize mechanical force distributions and multifunctional readouts would be ideal to describe how and where mechanical cues trigger cellular responses that influence organoid and animal physiology.

Multiplexing complementary data

The intricate nature of multicellular systems necessitates the incorporation of numerous parameters to fully comprehend their mechanobiological properties, sensing capabilities and responses to specific mechanical inputs. In its simplest form, this can involve morphological parameters such as cell shape, alignment and assembly in tissues[2,15,28]. However, the dynamics inherent to cellular systems extend beyond mere structure, encompassing a network of regulatory pathways that include signal transduction, cell state transitions, and gene and protein expression[12,64]. To unravel this multi-tier complexity, biological parameters must be integrated with mechanical data acquired from the same system (Fig. 3). Consequently, such an approach could provide

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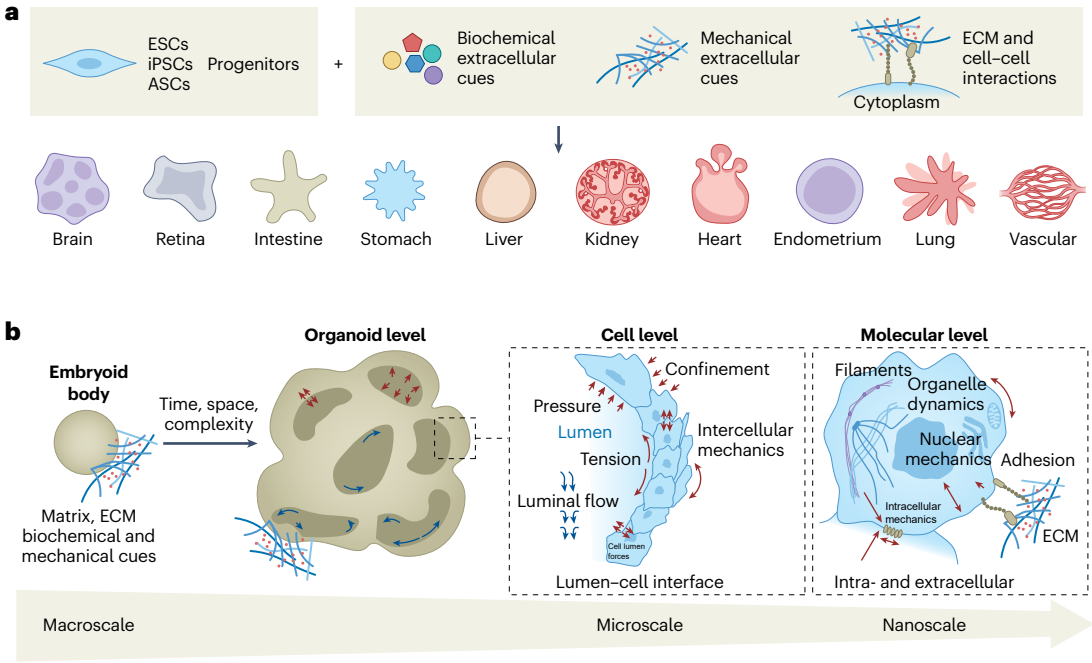

Fig. 2 | The mechanobiology of complex cellular systems is tightly linked to the physiological environment and requires appropriate tools to quantify and apply mechanical cues across dimensions and timescales. a, Engineered in vitro human tissue models, or organoids, involve integrating key components: (1) embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), progenitors or adult stem cells (ASCs); (2) biochemical extracellular cues, including soluble factors or morphogens; (3) mechanical extracellular cues, including (visco)elastic properties and confinement; and (4) ECM components and cells. Put into the corresponding context, stem cells can develop different organoids that represent key cell types and tissue architectures of primary tissues. **b**, To understand how mechanical cues contribute to guiding the development of cells from the embryoid body to organoids, and how such cues contribute to organoid function, we will need to quantify various molecular and cell mechanical parameters (exemplified in Fig. 1) and apply mechanical cues across timescales and length scales. The schematics outline some of the mechanical cues that may be applied and measured at organoid, cellular and molecular scales. Together, this comprehensive information across length and timescales can advance our understanding of how mechanical cues distribute heterogeneously and how they are sensed within complex cellular model systems. Blue and red arrows indicate mechanical cues of various origins.

insight into mechanisms that regulate cellular behaviour beyond gene expression changes, thus offering potential avenues for therapeutic intervention and the design of novel biomimetic materials[1,13,45,65].

The integration of mechanobiological parameters of cellular systems requires interdisciplinary collaboration spanning life sciences, medicine and (nano)technology[66,67]. Multiscale datasets that combine spatial, morphological, transcriptomic and mechanical parameters could reveal how architecture, protein localization, signalling, and electrophysiological and mechanical cues jointly determine the action and state of cellular systems. However, a major challenge lies in capturing the temporal dynamics of cellular systems, the properties of which are transient, heterogeneous and context-dependent. While we have highlighted the necessity of characterizing various mechanical properties over different timescales and length scales, multiplexing approaches will require similar scales for the recording of the cellular parameters that can complement the mechanical data. Technological breakthroughs will thus be essential in many fields.

Successful multiplexing relies on many techniques being expanded and integrated. The tissue architecture can be visualized with live imaging, histological staining, and optical and electron microscopy, while organs at work can be observed using magnetic resonance imaging or ultrasound elastography[2,68]. At the single-cell scale, quantitative measurements may focus on the cell type, state, morphology, migration, division and apoptosis visualized through bright-field, fluorescence, fluorescence resonance energy transfer, total internal reflection or super-resolution microscopy[67,69]. Light-sheet microscopy enables the quantitative profiling of both tissue-scale and single-cell dynamics over weeks, including lineage tracing and in toto multiview imaging of developing embryos[70]. To connect mechanical input with biological output, functional readouts such as single-cell and spatial genomics, real-time PCR or mass spectrometry can resolve gene regulatory, metabolic and proteomic responses[66,71]. Techniques such as Live-seq allow transcriptomic profiling of cells along developmental or mechanically induced trajectories[72]. Complementary single-molecule and single-cell force spectroscopy methods can quantify mechanical properties across broad spatial and temporal scales, including atomic force microscopy[20], optical and magnetic tweezers[21,22], micropipette aspiration, deformability cytometry[73], droplets[57] and traction force microscopy[74]. The identification of mechanosensitive molecules including YAP, talin and LIM domains and CRISPR–Cas9-based labelling strategies accelerated the engineering of genetically encoded endogenous fluorescence reporters to monitor mechanotransduction in cellular systems[75–77]. Morphological phenotyping should be complemented with biomechanical testing and manipulation devices[78,79], while the integration of western blotting, enzyme-linked immunosorbent assays or RNA sequencing can link mechanical stress to downstream molecular biological responses. Such advanced multiplexed molecular information could also be provided through iterative immunohistochemistry[67].

Ultimately, recent advances in machine learning offer new possibilities for integrating such mechanical, molecular and imaging data and enabling the discovery of hidden patterns across these many modalities[80]. Future breakthroughs in machine learning and computational approaches are likely to be instrumental in overcoming this data multiplexing challenge.

Establishing models of complex cellular systems

Integrating datasets across spatial and temporal scales transforms mere descriptive information into stringent constraints for model construction. Increasing the number of constraints enhances the robustness of

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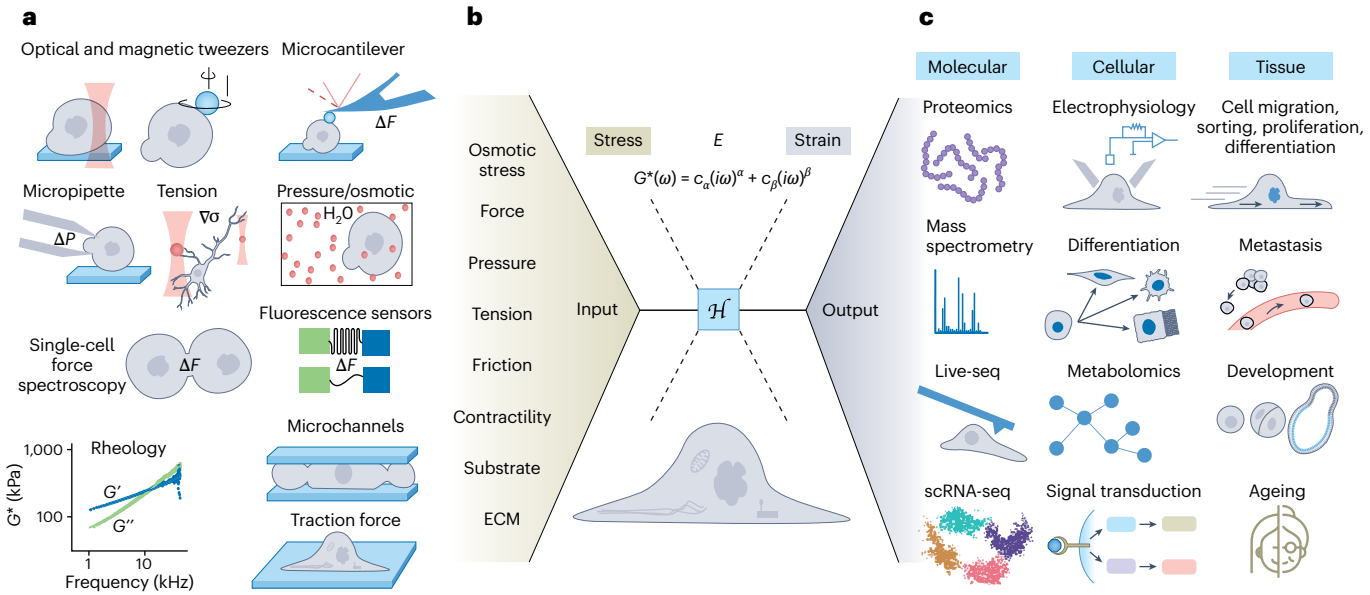

Fig. 3 | Mechanobiology of living cellular systems requires characterizing and multiplexing mechanical, morphological and functional parameters across length and timescales. a, Techniques that measure the various mechanical properties and mechanically manipulate molecular and cellular systems allow the selective characterization and stimulation of mechanotransduction pathways. *F*, force; *P*, pressure; *σ*, tension; *G**, complex shear modulus; *G′*, storage modulus; *G″*, loss modulus. **b**, Cellular systems, including individual cells and their components, act as multimechanical sensors, whose response transfer function *H* converts the mechanical information into a biological response. In ordinary, homogeneous, isotropic elastic materials, the Young's modulus *E* relates stress and strain (mechanical deformation). For the viscoelastic cytoplasm, *E* is not a constant but depends on the frequency ω itself and is best described by the complex shear modulus $G^*(\omega)$ of the fractional Kelvin Voigt model, with c_α and c_β representing prefactors and α and β power-law exponents of the model. However, the responses of many cellular systems are more complex. **c**, As mechanical properties and externally applied mechanical cues can have a plethora of consequences for organismal physiology, a multiscale toolbox must be employed to measure responses on molecular, cellular and tissue levels. In an ideal scenario, this input would be used to establish models that can describe the complexity of mechanical sensing and responses of cellular systems.

models, making them less arbitrary and more predictive. The key challenge lies in incorporating these constraints into models that can capture nonlinear, multiscale, collective behaviours while quantifying uncertainty and generalizing across conditions (Fig. 4). While oversimplified models of biological systems can provide important conceptual insights, they often collapse under experimental scrutiny when nonlinearity, feedback, heterogeneity and history effects govern the cellular dynamics. It is therefore crucial to develop models with sufficient detail to enable experimental validation and to elucidate basic mechanobiological principles, which typically requires powerful computational algorithms. Crucially, multicellular systems are driven, dissipative, non-equilibrium systems, rather than near-equilibrium materials. Nonlinear interactions between cells, genes, proteins, metabolites, other biomolecules and ECM often form complex networks that can only be understood by models that accurately represent their dynamic and interdependent nature. Models should therefore accommodate active stress generation and remodelling, not just passive responses. Such interactions can exhibit considerable temporal and spatial dependencies, ranging from the nanoscale to the microscale[81]. Beyond means, the fluctuations and their timescales are mechanistic signals that can reveal helpful details about the underlying system. Furthermore, many behaviours and properties of cellular systems emerge from collective interactions[14].

Models must also be designed to consider the systems biology view of biological networks within cellular systems, and to capture their emergent properties. Cellular models may incorporate feedback loops, in which the output of a process influences its own input or that of another process[2,82]. Together with nonlinear reaction kinetics, such feedback loops can drive bifurcations and multistability, which models must represent explicitly. The constant influence of the environment on cells and tissues includes numerous physical and mechanical parameters, as well as factors such as nutrient availability, signalling molecules, ECM or other cells. Thus, we need sophisticated models that integrate these environmental variables to more realistically simulate cellular behaviour in tissues[29]. Cellular systems also exhibit considerable degrees of variability and randomness, both in terms of individual cell behaviour and in responses to cellular populations[83]. Advanced models should incorporate stochastic elements and account for the heterogeneity of molecules, cells and tissues.

Establishing such models, which requires the integration of multimodal datasets at large scales, poses significant challenges and requires the capability to handle the inherent data complexity and heterogeneity. Traditional mechanistic models, while interpretable and grounded in biological theory, often fail to capture the richness of such data. Conversely, purely data-driven approaches, such as deep learning, excel at fitting high-dimensional datasets but typically lack interpretability and mechanistic insight. This has led to a growing interest in hybrid modelling strategies that combine the strengths of both paradigms[84,85]. Physics-informed neural networks embed physical laws into the architecture of neural networks, offering ways to maintain mechanistic fidelity while sidestepping the computational burden of numerically solving partial differential equations and allowing the simultaneous learning of model parameters[86,87]. The ultimate goal of characterizing cellular systems is often to delineate fundamental principles and predict how tissues will behave under various (patho)physiological conditions and in response to drugs or mechanical stimuli. The aim is not merely fitting existing data, but predicting behaviour under new perturbations and recovering governing relations in active, non-equilibrium systems with nonlinearity, feedback and memory. Practically speaking, models should state which parameters the data can determine and attach calibrated uncertainty, take protocols and history as inputs, remain valid when moving (for example) between tissue stiffness/viscoelasticity, cell density and cell state, and actively propose the next informative perturbations to guide mechanotransduction and microenvironment design.

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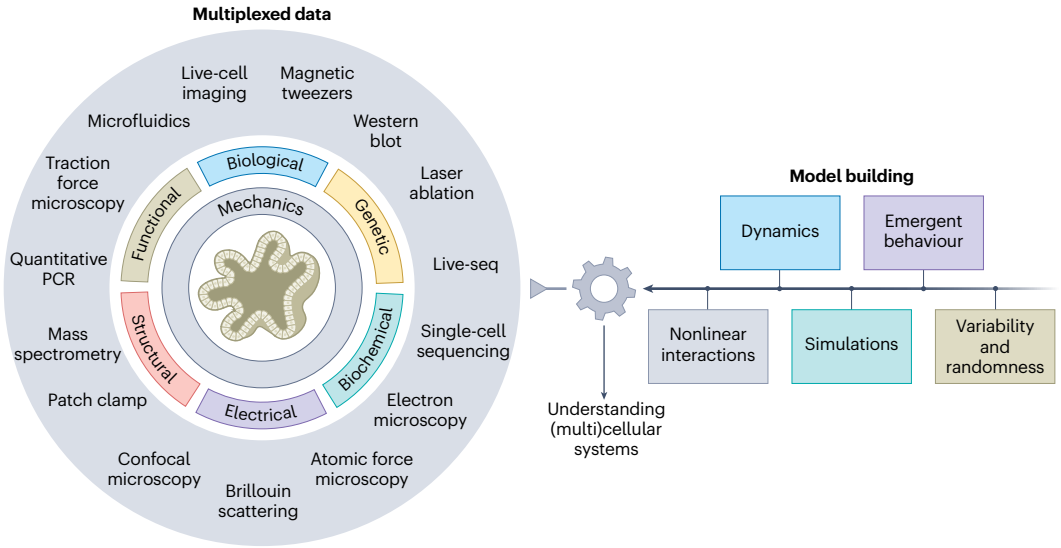

Fig. 4 | Building models that connect multiplexed data with biological complexity. Robust theoretical models are needed to describe the mechanical properties, sensing and responses of complex biological systems, requiring consideration of various morphological, functional, genetic, biochemical and electrophysiological parameters. Simplifying approximations, such as linearity assumptions, must be critically evaluated with such data to test the models. The inherent dynamic nature of mechanobiological processes and their non-equilibrium states must be recognized. Randomness and variability should be explicitly accounted for, rather than focusing only on mean behaviour. This might necessitate the use of simulations over analytically solvable models. Recognizing and incorporating emergent behaviours in these modelling frameworks is essential to advance our understanding of (multi)cellular systems.

Outlook

The complexity inherent in cellular systems necessitates the use of complex experimental, theoretical and computational approaches to understand their mechanobiology. This combination of multiple tools allows scientists to comprehensively characterize, accurately model, understand and manipulate these systems, potentially leading to breakthroughs in our understanding of health and disease. Here we have outlined the need to quantify the various mechanical properties of complex systems across the nanoscale to the macroscale. In ideal scenarios, nanotools would allow measurements of mechanical properties at high force sensitivity and across dynamic ranges, thus detecting molecular and cellular interactions at sufficient morphological resolution and at timescales spanning from microseconds to days (Box 1). Tools are now being advanced to meet such needs (Box 4). As the field of mechanobiology receives tremendous attention, with the expectation that many more fundamental discoveries will be made, we are aware that it seems impossible to address all challenges at once to advance the field. However, considering a few experimental methodologies to mechanically phenotype cellular systems in combination with advanced multiplexing and model system building is likely to bring unexpected discoveries.

For example, by measuring tension, viscosity and pressure while imaging the morphology of cellular systems, one could also monitor the cell membrane potential and ion fluxes using electrophysiology. Such multiparametric approaches could elucidate how cellular control of osmotic pressure and volume affects cell state and mechanics, and vice versa. Beyond multiplexing the parameters needed to describe cellular complexity, there is a great need to further develop conceptual frameworks and more refined physical models to establish meaningful relationships among these parameters. These include multiscale computational approaches that integrate discrete cell-based modelling with continuum mechanics to represent cellular effects in tissues. This may also yield a better understanding of how the biophysical properties and behaviour of single cells affect tissue mechanics. In addition, models that integrate mechanical properties with chemical signalling, electrical activity and other molecular and cellular parameters are needed to capture the full complexity of cellular and tissue behaviour.

Another critical aspect of mechanobiology is the plasticity of mechanical deformation, including the rupture and repair of cellular compartments, cytoskeleton, larger protein assemblies or membranes. Moreover, the way that cellular systems can modulate mechanical responses in low-frequency active and high-frequency passive domains is a rich area of discovery. Here, tools could measure the mechanical frequencies at which cellular systems change from conservative to dissipative responses[88]. Translational aspects of mechanobiology include medical applications. Mechanosensitive ion channels and engineered bionanopores can be expressed in specific cell types, making them sensitive to mechanical stimulation with ultrasound, which, unlike light, can reach deep within tissue. Such ultrasound-based stimulation of cell types equipped with mechanosensitive channels ('sonogenetics') has recently been introduced to restore vision in the brain of animals[89]. Other approaches use electromagnetic nanomanipulation technologies, such as magnetogenetics[90] or magnetoelectrics[91] for the neuromodulation of the brain.

Finally, organoid models may be subjected to various mechanical cues (such as space, stretching, compression, shear stress and movement) that influence organ development, function, and healing processes in the body. For example, studying the interplay between mechanical cues and cellular behaviour in organoids provides insights that are as crucial as those gained through traditional studies focusing on biochemical and genetic pathways[50,92]. By testing how organoids or embryos sense and respond to mechanical cues, scientists may be able to direct stem cell differentiation at spatial precision within organ development, providing better in vitro tissue models with controlled architecture and cellular diversity that could lead to more effective organ control, repair or replacement. Ultimately, advanced theoretical models that analyse, describe and predict how complex (multi)cellular systems employ mechanical pathways will improve our understanding of disease mechanisms and diagnostics. They can aid medical interventions through mechanosignalling modulators, mechanosensitive drugs or mechanotherapies, open new doors for tissue engineering through scaffold designs or advance regenerative medicine by supporting wound healing and tissue repair. Such translational potential of mechanical

characterization and modelling will significantly improve biotechnological and medical applications.

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Competing interests

M.C.R. and M.P.L. are employees of F. Hoffmann-La Roche. The other authors declare no competing interests.

Additional information

Correspondence should be addressed to Daniel J. Müller.

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[1]Department of Biosystems Science and Engineering, Eidgenössische Technische Hochschule (ETH) Zürich, Basel, Switzerland. [2]Department of Bioengineering, University of California, Berkeley, Berkeley, CA, USA. [3]Institute for Bioengineering of Catalonia (IBEC), The Barcelona Institute of Science and Technology (BIST), Barcelona, Spain. [4]Institució Catalana de Recerca i Estudis Avançats (ICREA), Barcelona, Spain. [5]ICFO–Institut de Ciencies Fotoniques, The Barcelona Institute of Science and Technology, Castelldefels, Spain. [6]Institute of Human Biology (IHB), Roche Pharma Research and Early Development (pRED) Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd, Basel, Switzerland. [7]Friedrich Miescher Institute for Biomedical Research (FMI), Basel, Switzerland. [8]Centro de Investigación Biomédica en Red en Bioingeniería Biomateriales y Nanomedicina (CIBER-BBN), Barcelona, Spain. [9]Max-Planck-Institute for the Physics of Complex Systems, Dresden, Germany. [10]Center for Systems Biology Dresden, Dresden, Germany. [11]Institut Curie UMR144, CNRS, PSL University, Paris, France. [12]Swiss Institute of Bioinformatics, Basel, Switzerland. [13]Institute of Bioengineering, School of Life Sciences and School of Engineering, École Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland. [14]Institute of Molecular and Clinical Ophthalmology Basel (IOB), University of Basel, Basel, Switzerland. [15]James Watt School of Engineering, University of Glasgow, Glasgow, UK. [16]These authors contributed equally: Krishna Chaitanya Kasuba, Gotthold Fläschner, Akanksha Jain, Michael Krieg. ✉e-mail: daniel.mueller@bsse.ethz.ch