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Opportunities and challenges in biological soft matter research

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Soft matter, a relatively new scientific field, encompasses the study of materials between traditional liquids and solids. Familiar examples include complex fluids, liquid crystals, colloidal suspensions, emulsions of immiscible fluids, polymeric networks in both aqueous and non-aqueous media, and gels that are often soft and permeable, just to name a few.

One diverse subset of soft matter covers biological matter. Since most, if not all, biological entities consist of water and organic compounds, they are often soft and compliant. In essence, most biomaterials, including biological entities such as cells, tissues, and organs, may be viewed as biological soft matter. Therefore, Biological Soft Matter as a section of the new journal, *Frontiers in Soft Matter*, will naturally be both broad and interdisciplinary. It seeks to inspire dissemination of new findings made by physical and life scientists, as well as bioengineers and biomedical scientists who share a broader perspective rather than staying within the confines of traditional specialties.

Biological soft matter deals with biological materials and systems. Thus, the work to be published in this new section naturally shall fall within a focused sub-field of materials science. *Frontiers in Soft Matter* encourages the publication of studies that focus on the physical and emergent properties of biomaterials ranging from the microscopic to the macroscopic scales. Examples of microscopic biomaterials may include DNA/RNA/proteins, subcellular components (e.g. molecular motors, pumps, channels, membranes, cytoskeletons, granules, centrosomes, nucleolus, etc.), live cells as small as viruses and bacteria or as large as macrophages and neurons, and even tissues and organs of animals and plants. The physical properties include, but are not limited to, single molecule dynamics, self-assembly, phase transitions, viscoelasticity, complex fluids, liquids and gels, and all forms of active matter phenomena and processes. Our goal for the Biological Soft Matter section of *Frontiers in Soft Matter* is to serve as a nexus connecting physical and life scientists who share the interdisciplinary perspective of understanding physical properties of life and, more broadly, for the new journal to serve as a global hub for soft matter scientists to share original findings with unrestricted access to all. Although it goes beyond the goal of the journal to publish the development of future drugs, the basic research that this new specialty area seeks to publish will provide an interdisciplinary knowledge base to foster future advances in the life sciences and in medicine that are rooted in the principles of fundamental physics and materials science.

Recent advances in selected areas of study

An interdisciplinary approach to the study of biological materials from the vantage point of soft matter physics has led to significant advances in biological science. Liquid-like droplets or membrane-less granules formed by intrinsically disordered proteins and/or RNA may be the most contemporary example among soft materials of biological origin. These subcellular granules, termed bio-condensates, typically form by liquid-liquid phase separation (LLPS), a prototypical mechanism of soft matter physics (Hyman et al., 2014; Shin and Brangwynne, 2017). Despite their abundance in cellular systems, they have only recently caught the attention of the broader community of life scientists. Applying the principles and technical tools developed in soft matter physics has led to major advances towards understanding issues as essential as germline development (Brangwynne et al., 2009), causes of neurodegenerative diseases such as ALS and Alzheimer's (Patel et al., 2015; Alberti and Dormann, 2019), and cellular aging (Alberti and Hyman, 2016). In particular, by simply adopting (or borrowing) key concepts in phase transition physics, many intriguing phenomena that occur in bio-condensates become readily understandable (Hyman et al., 2014; Shin and Brangwynne, 2017; Berry et al., 2018). This is at the present an active field of study with profound implications for cellular biology and medicine.

Another area of biological soft matter deals with the dynamical and rheological properties of composite materials formed by biological macromolecules such as proteins, DNA/RNA, and polysaccharides. Specifically, the cytoskeletal protein filaments such as F-actin, microtubules, and intermediate filaments endow animal and plant cells with their structural integrity. Thus, there has been extensive study on their mechanical properties (Janmey, 1991). Other proteins such as collagen, fibronectin, laminin. and mucin are major contributors to the structural and mechanical properties of extracellular matrices (ECMs) in animal tissues (Hynes, 2009). Equally complex materials, known as extracellular polymeric substances (EPS), encapsulate dense populations of bacteria into large aggregates, known as biofilms (Flemming and Wingender, 2010; Flemming et al., 2016). A myriad of constituent biomolecules-be they lipids, polysaccharides, or proteins-are produced inside the cells but then secreted and assembled extracellularly, forming ECMs, EPS, and adhesion sites that connect cells with their surroundings. The importance and sheer complexity of these biological systems offer many opportunities for interdisciplinary studies, particularly those utilizing soft matter perspectives and research techniques.

Most biological systems are powered by the intrinsic energy of the constituent entities (Marchetti et al., 2013; Needleman and Dogic, 2017). Thus, there is a natural overlap between studies of biological soft matter and those of active matter. The cytoskeletal proteins actin and tubulin, for example, are tightly bound with the biological energy carriers ATP and GTP, respectively. Therefore, the composite F-actin and microtubule networks manifest dynamical processes, including large scale patterns and collective motion (Liu et al., 2006; Murrell and Gardel, 2012). Such pattern dynamics can be enhanced by the addition of motor proteins such as myosin, dynein, or kinesin, all capable of harnessing energy by catalyzing ATP hydrolysis to generate active flow and directional material transport at the microscopic, mesoscopic, or even macroscopic scale (Sanchez et al., 2011; Sanchez et al., 2012).

Large suspensions of motile bacteria driven by flagella or other mechanisms represent particularly exciting systems for the study of biological active matter (Zhang et al., 2010; Dunkel et al., 2013). Spreading over a moist surface or confined in a thin layer of fluid, large swarms of bacteria can form a plethora of collective patterns such as bio-nematic (Zhou et al., 2014), turbulent phases (Wensink et al., 2012; Dunkel et al., 2013), jets and vortices (Dombrowski et al., 2004), dynamic clusters and motile rafts (Zhang et al., 2010; Chen et al., 2012), large-scale oscillations generating a traveling wave (Chen et al., 2017), etc. There are even experiments in which motile bacteria are released into nematic liquid crystals so that as these tiny creatures of nature find their way around by navigating along director fields they effectively probe the topological defects present in the liquid crystalline state (Peng et al., 2016). These are only a few examples where live bacteria render the systems they reside in as dynamic and active.

Theoretical and modeling studies of soft matter are as varied as experimental phenomena, yet nearly all existing work is rooted in statistical mechanics. The models and simulations often proceed with some simplified equations of motion. Vicsek *et al.* (Vicsek et al., 1995), for instance, developed a model to treat constituent particles as weakly aligning with their neighbors while individually moving at a constant speed. Despite its simplicity, the model has proven successful in accounting for collective motion in bacterial swarms, including dynamic clusters. In addition, by considering both the polar alignment and angular velocity between neighboring bacteria, a modified Vicsek-type model has been shown to successfully account for weak synchronization and large-scale collective oscillations observed in dense bacterial suspensions (Chen et al., 2017). Another simple treatment, introducing competing alignment and anti-alignment of tunable strength and range, can also account for large-scale pattern dynamics (Grossmann et al., 2014; Grossmann et al., 2015). In a purely viscous fluid matrix, inclusion of hydrodynamic coupling among motile ellipsoid-shaped particles at moderately high concentrations has been shown to break clusters into rafts, and cause counter-rotating layers of bacteria confined in circular disks (Lushi et al., 2014). An approach incorporating viscoelasticity has also been developed to account for slow oscillations in the flow direction of an entire swarm of bacteria observed over a system size of many centimeters (Liu et al., 2021). By combining both experimental studies and theoretical modeling, the approaches rooted in soft matter physics have proven to be highly successful and will likely bear more fruit in the foreseeable future.

Grand challenges

Challenges abound in the biological soft matter field as an emerging discipline. Chief among these are the complexity of biological systems, a lack of precise accounting of all molecular-level interactions, and limitations of both experimental techniques and theoretical tools. With genetic tools more and more commonly deployed, cascades of genes upregulated or downregulated can readily be manipulated and assessed. It is often much harder, however, to precisely pinpoint the functions of downstream products. Thus, the genotype-phenotype-morphotype chain of events often requires extensive characterization. Powerful techniques such as X-ray, NMR, and mass spectroscopy are available to determine molecular structures. Additional tools such as microscopy and rheological studies must also be performed to assess the molecular and intercellular interactions. Most of these studies must be performed in environments crowded by various components, including those not directly participating in interactions. However, by affecting physical properties of the matrix, such as osmolarity, permeability, viscoelasticity, hydration, etc., even inert macromolecules can profoundly affect the behavior of living soft matter, leading to varied experimental outcome.

The complexity of macromolecules of biological origin and of intermolecular interactions poses serious challenges to modeling efforts, as well as the validity of various approaches, particularly those requiring simplifications to keep the techniques either mathematically solvable or computationally tractable. There are numerous examples of models developed that successfully account for experimental discoveries, including key features observed and certain parameters measured. The plurality of models developed for the common phenomenon of bacterial swarming motility, for instance, points to the challenges facing both theorists and experimentalists. The theorists must properly capture and account for dominant interactions and make stringent predictions in experimentally accessible regimes. On the other hand, the experimentalists must come up with critically informative designs, choose the most suitable measurement tools, and accurately determine parameters to validate modeling predictions.

Acceptance of an interdisciplinary perspective is another challenge in the emerging field of biological soft matter. To be impactful, researchers must overcome scientific language barriers including terminological ambiguity. A good example of this is the evolving definition of a common form of bacterial collective motility called swarming (Henrichsen, 1972; Harshey, 2003; Kearns, 2010)]. Microbiologists have sought to narrow the scope of bacterial swarming motility to the collective motion of flagellated bacteria over surfaces (Harshey, 2003; Kearns, 2010). As numerous species and various genetically altered strains have been studied, more and more exceptions have been encountered, leading to confusion. For instance, there is no general consensus as to whether or not certain surface spreading behaviors ought to be referred to as swarming, such as in the spread of Myxobacteria (Kaiser, 2007; Kearns, 2010) or in a mutant strain of *Pseudomonas aeruginosa* lacking flagella (Murray and Kazmierczak, 2008). Additional names have been assigned to similar yet different forms of bacterial motility, such as gliding (Harshey, 2003; Kearns, 2010), sliding (Murray and Kazmierczak, 2008), and surfing motilities (Yeung et al., 2012; Hennes et al., 2017a; Hennes et al., 2017b; Kovács et al., 2017; Sun et al., 2018). Physicists who choose to study bacteria as active matter systems often find it challenging to contend with variable and sometimes inconsistent terms and interpretations found in the microbiology literature. Over time, the definition of terms may be codified with a broadened perspective and newly revealed connections.

Outlook

Opportunities present themselves as the community of soft matter scientists rises to meet some of these grand challenges. Cross-disciplinary thinking and communication frequently offer low hanging fruit. One historical advance in prenatal medicine was a simple injection of surfactants to expectant mothers ahead of a premature birth. A common and effective prevention of heart attack or stroke turns out to be thinning the patient's blood to maintain a safely low blood viscosity in order to increase the blood circulation. Additionally, many bioengineering studies naturally overlap with soft matter research. Among those well-known examples are hydrogels used for food processing, tissue engineering, corrective lenses used to aid human vision, and targeted drug delivery. As elaborated above, the physical concept of the liquid-liquid phase transition that results in biomolecular condensates has brought out key insights on some essential biological functions. A deeper understanding of the role that extracellular matrix materials play in cellular interactions will likely lead to medical applications as varied as drug delivery, surgical suture, tissue repair, etc. In conclusion, biological soft matter research will surely thrive on its interdisciplinary nature, as well as its relevance to a broad range of applications.

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

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Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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