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Non-Bilaterians as Model Systems for Tissue Mechanics

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Synopsis   In animals, epithelial tissues are barriers against the external environment, providing protection against biological, chemical, and physical damage. Depending on the organism's physiology and behavior, these tissues encounter different types of mechanical forces and need to provide a suitable adaptive response to ensure success. Therefore, understanding tissue mechanics in different contexts is an important research area. Here, we review recent tissue mechanics discoveries in three early divergent non-bilaterian systems—*Trichoplax adhaerens*, *Hydra vulgaris*, and *Aurelia aurita*. We highlight each animal's simple body plan and biology and unique, rapid tissue remodeling phenomena that play a crucial role in its physiology. We also discuss the emergent large-scale mechanics in these systems that arise from small-scale phenomena. Finally, we emphasize the potential of these non-bilaterian animals to be model systems in a bottom-up approach for further investigation in tissue mechanics.

Introduction

Epithelial tissues in animals are subjected to different types of mechanical forces during their entire life cycle. In order to foster the animal's survival and success, these tissues must respond, adapt, and withstand external forces. Thus, an important goal of tissue mechanics research is to apply the principles of mechanics to characterize and quantify the mechanical properties and understand the response of biological tissues (Fung 1990). This can lead to further insights about how the properties of individual cells and their collective interactions give rise to emergent mechanical properties of the tissue.

Tissue mechanics also play an important role in biological processes such as development and physiology (Fung 1990; Guillot and Lecuit 2013). Important advances have already been made in tissue mechanics research focused on human biomedical applications (Fung 1990; Park et al. 2015); as well as developmental processes in model animals such as the fruit fly, *Drosophila melanogaster*, and zebrafish, *Danio rerio*

(Blankenship et al. 2006; Lecuit and Lenne 2007; Guillot and Lecuit 2013; He et al. 2014; Mongera et al. 2018). *In vitro* cell-culture systems have also been a popular model for tissue mechanics studies (Harris et al. 2012; Latorre et al. 2018; Xi et al. 2019; Bonfanti et al. 2022). However, little is known regarding the tissue mechanics of early divergent, non-bilaterian organisms. Here, we highlight recent tissue mechanics discoveries in non-bilaterian systems and their potential in opening up new questions and research directions (Abrams et al. 2015; Carter et al. 2016; Prakash et al. 2021).

Non-bilaterians are some of the first multi-cellular species to evolve from unicellular organisms, making them the earliest diverging organisms to not have a bilateral axis of symmetry. The non-bilaterian phyla include Porifera, Placozoa, Ctenophora, and Cnidaria (Dunn et al. 2014). These non-bilaterians have been the focus of several recent biological studies (Srivastava et al. 2008; 2010; Moroz et al. 2014; Leclère et al. 2019), but have received little attention from a biophysical perspective. The objective of this review is to inspire and

motivate biomechanicians and biophysicists to work on these interesting and understudied systems.

Here, we will focus on three non-bilaterians: *Trichoplax adhaerens* of phylum Placozoa, and *Hydra vulgaris* and *Aurelia aurita* of phylum Cnidaria (Fig. 1). These non-bilaterians provide several key advantages as model organisms for tissue mechanics research—they have all been successfully maintained in the lab, are soft and experimentally tractable, have simple body plans, and their tissues are suitable for live imaging. Compared to bilaterians, the organs and organ systems in non-bilaterians do not arise from as many germ layers and do not exhibit as many classes of cellular specialization, allowing organization on the tissue level to play a prominent role in physiology and behavior. Here, our focus is on fast timescale (minutes to hours) tissue remodeling events that are mainly driven by mechanical forces, as opposed to tissue morphogenesis in model systems that usually occur over much longer timescales, and are mainly determined by genetic/molecular programs or cellular processes (Blankenship et al. 2006; Lecuit and Lenne 2007; Guillot and Lecuit 2013; He et al. 2014; Mongera et al. 2018). We will focus on tissue remodeling phenomena, including local cellular rearrangements, tissue fractures, and healing, in the context of physiological processes such as feeding, locomotion, reproduction, and repair. Important aspects such as growth and regeneration that take place over longer timescales (days to weeks) are neglected.

We begin this review with a brief overview of the physical properties of biological tissues. We dedicate the next three subsections for each organismal system: *T. adhaerens*, *H. vulgaris*, and *A. aurita*. For each organism, we begin by introducing the organism's biology and body plan organization. We describe the tissue organization and the subsequent role of tissue organization important for each organism. Then, we highlight specific cases of how tissue mechanics play an important role in various form-function relationships in each of these systems. Specifically, we look at tissue mechanics through the lens of reproduction and shape change in *Trichoplax*, feeding and locomotion in *Hydra*, and shape change in *Aurelia*. Finally, we conclude by highlighting how non-bilaterians, including those featured here, are excellent model systems to investigate the biophysics of tissues.

Tissues as materials

Understanding the mechanics of cells coming together to form tissues takes center stage in tissue mechanics. The following sections introduce some important con-

cepts in tissue mechanics to provide a better understanding of the examples discussed in this review.

Individual cells must come in contact with each other to form tissues. Cell junctions serve as contact points between neighboring cells. The difference in types of cell junctions is based on how they connect cells. Cell junctions serve one of three functions in their connection: occluding junctions, anchoring junctions, and communication junctions (Alberts et al. 2002). Occluding junctions seal two cells together, forming an impermeable barrier between adjacent cells so that leakage of materials into the negative space between cells is prevented. Tight junctions and septate junctions are two types of occluding junctions that differ based on how and where they connect cells (Alberts et al. 2002; Jonusaite et al. 2016). Anchoring junctions mechanically connect cells either to other cells or to the extracellular matrix through the cytoskeleton and distribute mechanical stress across a membrane (Alberts et al. 2002). There are four different types of anchoring junctions, which differ based on the cellular structure used to connect the cells and the types of proteins they used to connect the cells: adherens junctions, focal adhesions, desmosomes, and hemidesmosomes (Alberts et al. 2002). Communicating junctions allow for passage of chemical or electrical signals from one cell to its neighbor (Alberts et al. 2002). Gap junctions are a common type of communicating junction that allow for transfer of ions and other small molecules between cells (Unwin and Zampighi 1980; Goodenough and Paul 2009). The most common example of gap junctions is the electrical synapses between neurons (Goodenough and Paul 2009).

Cell junctions, serving as connection sites between cells, are directly affected physically and chemically when tissues fracture and repair. Here we focus on the physical effects on cell junctions due to fracture and repair but do not discuss the chemical effects. Recent technical advances allow for characterizing mechanical forces between cell–cell junctions in terms of strength and tensile stress limit, i.e., how much a material resists until being torn (Charras and Yap 2018; Esfahani et al. 2021; Lenne et al. 2021). Materials deform in one of three ways in the presence of external mechanical forces such as tension and shear. Elastic deformation is a completely reversible process where the material returns to its original shape in the absence of an external force. Ductile and brittle deformations are both plastic or irreversible processes. A brittle deformation results in fracture, faulting, or breaking of material, whereas a ductile transformation results in a permanent shape change with decrease (or thinning) in cross sec-

Fig. I Non-bilaterian animals are excellent model systems to study tissue mechanics. (A) *Trichoplax adhaerens* of phylum Placozoa, Image courtesy of Oliver Voigt/Wikimedia Commons/CC-BY-SA-3.0. (B) *Hydra vulgaris* of phylum Cnidaria, Image courtesy of Stephanie Guertin/Wikimedia Commons/CC-BY-SA-3.0. (C) *Aurelia aurita* (Moon jellyfish) of phylum Cnidaria, Image courtesy of Alexander Vasenin/Wikimedia Commons/CC-BY-SA-3.0.

tion but does not necessarily lead to breaking or fracture.

Trichoplax

The early divergent marine species *T. adhaerens* (Fig. 1A) is the most well-studied member of the basal animal phylum of Placozoa (Srivastava et al. 2008; Smith et al. 2014; Armon et al. 2018; Schierwater and DeSalle 2018). This is because Placozoa is comprised of only three species, with *T. adhaerens* as the earliest documented, and the other two species only recently discovered (Eitel et al. 2018; Osigus et al. 2019). *Trichoplax adhaerens* has been found in many parts of tropical oceans around the world (Pearse and Voigt 2007; Eitel et al. 2013). It is considered to be the simplest free-living animal since it consists of less than ten cell types (Smith et al. 2014; Romanova et al. 2021) and lacks neurons, muscles, extracellular matrix, and a basement membrane (Srivastava et al. 2008; Schierwater and DeSalle 2018). *Trichoplax adhaerens* has a simple and flat body plan, with a thickness of only 25 μm, but individuals exhibit a large variation in width, ranging from $\sim$50 μm to 10 mm (Prakash et al. 2021, Fig. 2).

The role of tissue layers in *Trichoplax* physiology

In *T. adhaerens*, the flat body plan consists of three tissue layers: an upper dorsal epithelium, a central layer of fiber cells, and a lower ventral epithelium (Smith et al. 2014). The dorsal epithelial cells have a thin and flat architecture, while the ventral epithelial cells have a columnar structure, and the two tissue layers are coupled at the edge of the organism (Smith et al. 2014). The epithelial cells are connected together only by adherens junctions - no tight junctions have been found (Smith and Reese 2016). Although both tissue layers have monociliated cells, the cilia of ventral epithelial

cells are unique since they can adhere to the bottom substrate, providing the organism sufficient traction forces to walk and generate push/pull forces (Bull et al. 2021a). *Trichoplax adhaerens* does not have a fixed shape like other animals (Prakash et al. 2021). Instead, the organism is constantly changing shape in an amorphous manner driven by ciliary traction with the bottom substrate (Prakash et al. 2021; Bull et al. 2021a). Individuals exhibit an extreme range of shape morphologies ranging from circular disks and rings to long elongated threads (Prakash et al. 2021). *Trichoplax adhaerens* reproduces by vegetative fission or asexual reproduction, resulting in two or more daughter animals (Srivastava et al. 2008; Eitel et al. 2011; Prakash et al. 2021; Fig. 2B). In these organisms, epithelial tissue remodeling processes can play an important role in determining the organismal shape change dynamics and asexual reproduction (Prakash et al. 2021).

Tissue remodeling via cellular rearrangements

The vegetative (asexual) reproduction process in *T. adhaerens* begins when an individual forms two coherent regions that start pulling away from each other (Fig. 2B). The tissues between the two pulling regions are subject to mechanical forces (tension), and respond by undergoing a rapid thinning deformation to form a thin narrow thread, taking <1 hour. From a materials science viewpoint, this rapid thinning process resembles a "ductile" material transformation process, where "ductility" refers to the ability of a material to be drawn into thin wires. This rapid thinning process involves local tissue remodeling via fast-time-scale cellular rearrangement mechanisms (Prakash et al. 2021). If the two opposing parts of the organism generate sufficient traction forces, eventually the thread will break at the length-scale of a single cell, forming two or more daughter organisms and completing the
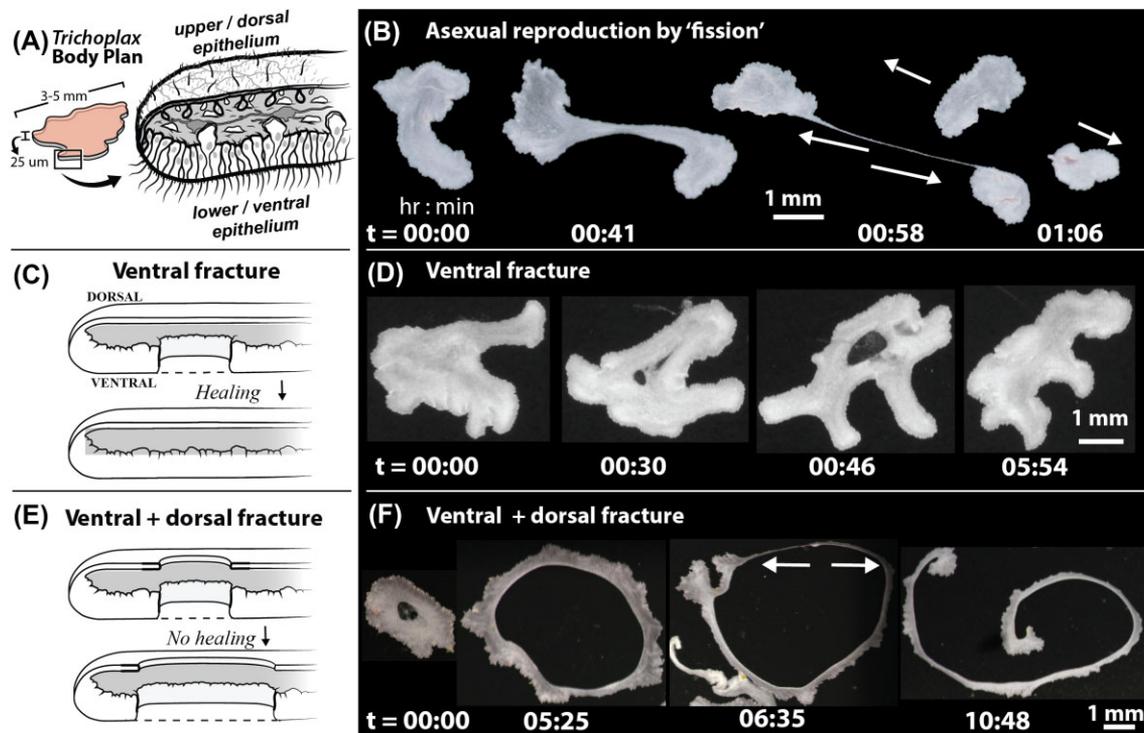
Fig. 2 Tissue mechanics in *T. adhaerens*: (A) Cartoon shows the flat body plan, and cross-section shows the upper/dorsal and lower/ventral epithelial tissue layers. (B) Time-lapse image sequence of asexual/vegetative reproduction process; in the central region, tissues deform rapidly to become a narrow thread that eventually breaks. (C), (D) Cartoon and time-lapse image sequence of fracture hole formation in the ventral epithelium and subsequent healing. (E), (F) Cartoon and time-lapse image sequence of fracture hole formation in both ventral and dorsal epithelium. This type of fracture hole does not heal, but instead, enlarges to form a thin edge that eventually breaks, giving rise to a string-like animal. Images in this figure are adapted and reproduced from Prakash et al. (2021).

reproduction process (Srivastava et al. 2008; Eitel et al. 2011; Prakash et al. 2021). The smaller daughter organisms will grow in size and again undergo fission when their size reaches >2–3 mm (Prakash et al. 2021).

Tissue remodeling via fractures

Trichoplax adhaerens can grow to large sizes (>2–3 mm), and larger individuals are capable of executing extreme shape changes, making them an interesting model organism for tissue mechanics (Prakash et al. 2021). Larger individuals generate larger traction forces than smaller individuals due to their motility. This leads to surprising shape morphologies, such as fracture holes and their healing dynamics, and long string-like organisms (Prakash et al. 2021; Fig. 2C–F). Fracture holes can be rapidly induced in the bulk of their ventral tissues solely due to motility-induced tensile or shear mechanical forces at the organismal scale (Prakash et al. 2021; Fig. 2C). They begin at small scales as microfractures and coalesce in ∼30 min to form large, stable, ventral holes visible at the organismal scale (Fig. 2D). From a materials science viewpoint, this fracture for-

mation and growth process resembles a "brittle" material transformation process, where "brittleness" refers to the tendency of a material to break. In many cases, ventral holes can also rapidly heal themselves, taking ∼30 min, if the hole edges come into contact as the organism moves (Fig. 2D).

Sometimes, ventral holes do not heal, and the dorsal epithelium located above the ventral hole (Fig. 2E, F) also sustains a fracture hole. The organism is now left with a through-hole inside it, and the two tissue layers seal themselves to form a permanent edge inside the organism (preventing any further healing). This individual will now have the donut-shaped geometry of a toroid. Over a time-scale of ∼10 hours, the inside hole diameter continues to increase until one edge becomes thin and breaks, changing the organism's original shape to now be a long, thin string (Fig. 2F). From a morphological perspective, fractures enable faster topological transformations from a circular shape to a long string-like shape than shape change mechanisms, which rely on cellular rearrangements (Prakash et al. 2021).

Tissue remodeling processes in *T. adhaerens* were further investigated using in-silico tissue models (Prakash et al. 2021). For example, a simplified, heuris-

tic, two-dimensional, sheet model of ventral epithelium consisting of soft balls representing cells, connected by springs simulating adhesion bonds, was subjected to pulling forces to simulate tensile loading. This model represents tissue remodeling processes at fast time-scales (minutes) and neglects long-term effects of growth (several hours). Results of this model show that both the pulling force and the length at which the springs break govern tissue response. Simulations exploring a wide range of these two parameters resulted in a phase diagram that reveal an elastic–ductile–brittle transition in the material properties. This model reproduces experimental observations, supporting the hypotheses that elastic–ductile tissue transitions occur during the local cellular rearrangement process when *T. adhaerens* divide by vegetative fission (Fig. 2B) and that elastic–brittle transitions occur when *T. adhaerens* sustain tissue fractures during organismal shape change (Fig. 2D, F). Hence, *T. adhaerens* is an excellent model system for further investigations in tissue mechanics, as it has been demonstrated that solely mechanical forces can give rise to the tissue remodeling processes that play a critical role in their life cycle (Prakash et al. 2021).

In *T. adhaerens*, we have discussed the key role of tissue mechanics in its physiological activities, such as reproduction by vegetative fission and continuous organism-scale shape change. Tissue remodeling mechanisms such as ductile transformations for vegetative reproduction, and brittle deformations for extreme morphological shape changes, are unique adaptations found only in this animal thus far. Hence, these ductile–brittle tissue transitions seem to be effective for their specific flat body plan. Tissue mechanics therefore acts as an important link between the biological form (flat body plan) and function (reproduction and shape change).

Hydra

Hydra vulgaris is a freshwater, invertebrate polyp of the Cnidaria phylum, which exhibits the characteristic radial symmetry, cnidocytes, and a body plan derived from two germ layers (McLaughlin 2017). *Hydra*'s body plan consists of a two-layered tube body and a mouth composed of a ring of tentacles and dome-shaped hypostome (Fig. 3A, D). Its body plan is composed of two epithelial layers, the endoderm and ectoderm, separated by an extracellular mesoglea. Cells in the tissues of the body column cycle continuously with those of the head and foot regions, maintaining the equilibrium between cell production and loss (Galliot et al. 2006; Wang et al. 2023).

The role of tissue layers in *Hydra* physiology

In addition to the dynamic nature of its tissues, the existence of a differential thickness between the thinner ectodermal layer and the thicker endodermal layer is of particular importance (Bode 2003). This difference in thickness is most pertinent when examining the *Hydra* mouth. When closed, the mouth is a continuous epithelial sheet sealed with septate junctions, similar to the model organism *Drosophila*, and appears as a ladder-like junction between two cells (Banerjee et al. 2006; Izumi and Furuse 2014). These septate junctions act as intercellular connectors, merging adjacent epidermal cells with inner, luminal cell edges (Hand and Gobel 1972; Carter et al. 2016).

Mouth opening dynamics

When the *Hydra* opens its mouth, it must tear a hole through the epithelial tissues at each instance of opening the mouth (Carter et al. 2016). Mouth opening is an exclusively viscoelastic process, meaning that while undergoing deformation, cells exhibit both viscous and elastic traits (Carter et al. 2016). This was confirmed via cell shape analysis and by tracking individual cells during mouth openings (Carter et al. 2016). It was observed that cells were not rearranging and instead were conserving existing cellular contacts (Carter et al. 2016). The *Hydra* must overcome the mouth-opening force that exists while the endoderm and ectoderm are sealed. When the mouth is closed, septate junctions connect the cells in both epithelial sheets (Campbell 1987; Banerjee et al. 2006; Carter et al. 2016). In the ectoderm, the sealing force to be overcome is solely that of the septate junctions, while the endoderm needs to additionally overcome the forces from the myonemes, circularly oriented contractile structures (Campbell 1987; Banerjee et al. 2006; Carter et al. 2016; Fig. 3B, E). Both of these closing forces must be exceeded by the opening force to lead to successful mouth opening. These sealing forces have been estimated to be in the range of 1–3 nN on the basis of the force required to separate tight junctions sealing two cells together (Vedula et al. 2009; Carter et al. 2016).

Although the opening force required must be estimated, the kinematics of the mouth opening can be fully characterized by a logistic equation (Carter et al. 2016). The mouth opening area is normalized to the maximum opening area of that instance of *Hydra* opening its mouth then plotted against time to resemble a logistic curve. This curve can then be time-shifted and applied individually to the ectoderm and endoderm mouth opening area (Carter et al. 2016). This results in a modified logistic equation that accounts for the normalized area of the mouth as a function of time and various
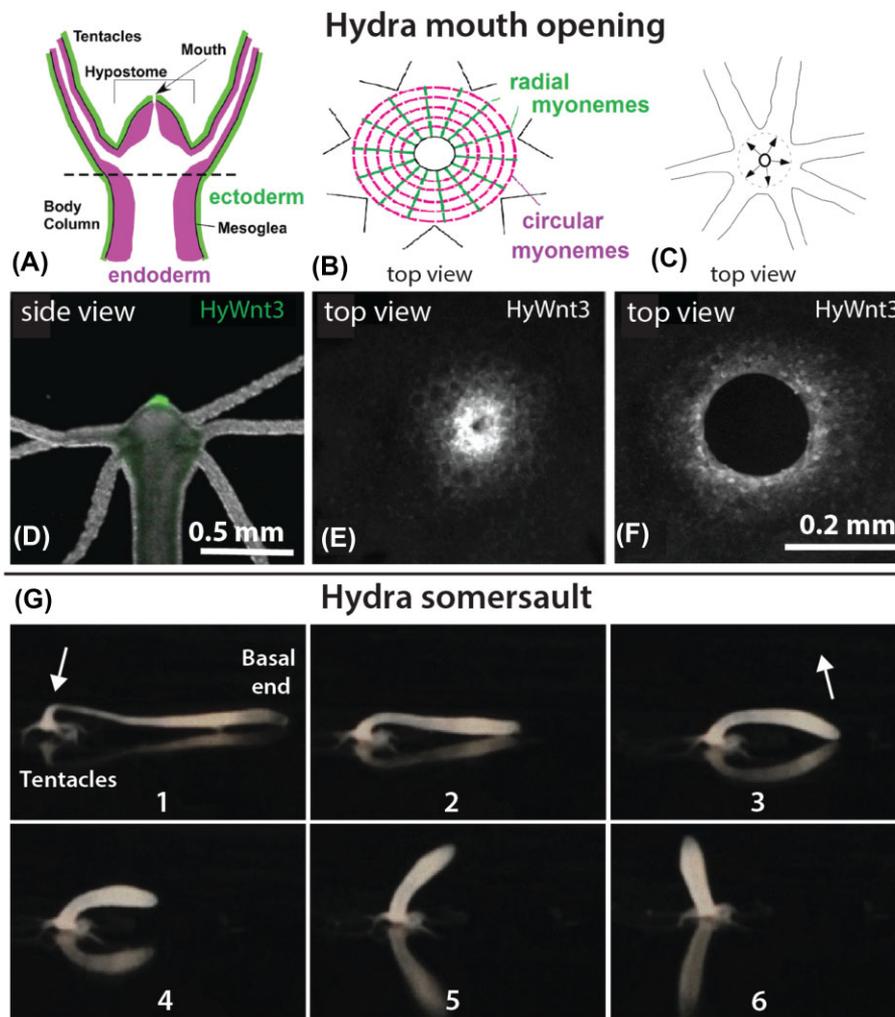
Fig. 3 Tissue mechanics in *H. vulgaris*: (A), (D) Cartoon and brightfield/fluorescence image show the side view of *Hydra*; the body plan consists of two tissue layers: a thinner ectoderm (green outline) and a thicker endoderm (purple outline). The mouth lies in the center of a ring of tentacles and together they compose the *Hydra*'s "shoulder", i.e., the region above the dotted line (Carter et al. 2016). (B), (E) When closed, *Hydra*'s mouth is composed of radial and circular contractile units called myonemes (Carter et al. 2016). (C), (F) When mouth opening occurs, the contractile myonemes assist in providing the opening force necessary to tear the ectodermal and endodermal tissue layers, before sealing them once again (Carter et al. 2016). (G) The *Hydra* somersault, driven by differential tissue stiffness, is composed of three general stages. In Stage I (panels 1–2), the *Hydra* body column extends while tentacles anchor to the substrate. In Stage II (panels 3–4), it disconnects the basal end from substrate and raises the body column. In Stage III (panels 5–6), the body column is completely raised (Naik et al. 2020; Wang et al. 2023). Images in this figure are adapted and reproduced, with permission, from Carter et al. (2016), Naik et al. (2020).

fit parameters to allow for the full capture of the kinematics of mouth opening for both ectoderm and endoderm separately (Fig. 3C, F; Carter et al. 2016).

The somersaulting *Hydra*

Tissue mechanics also play an important role in *Hydra* locomotion. A differential stiffness within its body enables it to perform the "*Hydra* somersault" (Mackie 1974; Han et al. 2018). The *Hydra* somersault occurs in three general stages: in stage 1, the body column is stretched, and the tentacles hold on to the substrate

(Fig. 3G:1, 2). In stage 2, the basal end is released (Fig. 3G:3, 4). In stage 3, the body column contracts and is lifted, transporting the base to a new location in the direction of the *Hydra*'s motion (Fig. 3G:5, 6).

This type of movement is only possible due to the difference in the local mechanical properties of the *Hydra*'s body column, specifically that of a 3:1 ratio in the Young's modulus between the shoulder region and the body column (Naik et al. 2020). The Young's modulus is the ratio between tensile stress and tensile strain in a material, which represents how easily a material stretches and deforms. Thus, when the
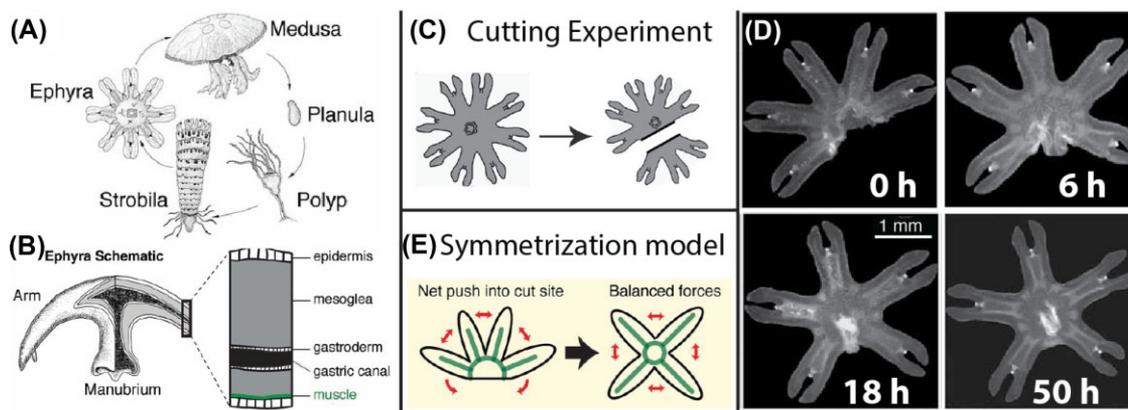
Fig. 4 Tissue mechanics in the Moon Jellyfish *A. aurita* (Abrams et al. 2015). (A) Cartoon of *A. aurita* life cycle: fertilized eggs develop into planulae (larval stage), which then develop into a non-motile polyp form. Next, the polyps transform into strobilae and release free-swimming ephyrae (juvenile stage), which later develop into medusae (adult stage). (B) Cross-section of ephyra: The epithelium consists of an epidermis, gastric layer, and mesoglea—a viscoelastic substance that fills the volume between the epidermis and gastric lining. (C) Schematic of experimental amputation of arms in ephyra. (D) Time series images of shape symmetrization (without regeneration) of the five-armed amputated ephyra. (E) Schematic of the symmetrization model, where arms relocate to a new position until the forces are rebalanced and symmetry is regained. Images in this figure are adapted and reproduced from Abrams et al. (2015)/Creative Commons/CC BY-NC-ND.

Hydra moves from one place to another, it utilizes the differential stiffness of the body column to enable efficient transfer of mechanical energy stored in stretching to bending (Naik et al. 2020; Wang et al. 2023).

In *H. vulgaris*, we described how important physiological activities, such as feeding and locomotion, are largely impacted by tissue mechanics. The tissue remodeling phenomena involved in mouth opening for feeding, and body column bending for movements, are unique phenomena found only in this organism thus far. These tissue remodeling phenomena further illuminate the relationship between the *Hydra's* particular body plan, the tissue mechanics discussed, and the *Hydra's* behaviors of feeding and locomotion.

Aurelia

A jellyfish's muscular and neuronal systems characterize them as more morphologically complex invertebrates when compared to *T. adhaerens* and *H. vulgaris*. Scyphozoan jellyfish, including the moon jellyfish *A. aurita*, have a life cycle with two adult forms, with one being the sexually reproducing fully motile medusae and the other form being the asexually reproducing sessile polyp (Fig. 4A; Lucas 2001). Despite lacking a functional brain, *A. aurita,* possess complex radially distributed neural and sensory systems that help the organism detect light and odor, enabling quick responses to stimuli (Satterlie 2011). The cross-sectional view of juvenile ephyra-stage *A. aurita,* reveals three layers: the epidermis, mesoglea, and gastrodermis (Mayer 1910). The outer epidermis contains the neural net (Mayer

1910). The inner gastrodermis, a specialized endodermis, lines the gastric cavity (Mayer 1910). The region between the ectoderm and the endoderm is filled by mesoglea, a viscoelastic substance (Fig. 4B) (Mayer 1910).

Aurelia aurita's habitat is versatile, ranging across varying temperatures and depths (Schroth et al. 2002). Though *A. aurita* can be considered top predators in their ecosystems, many predators, including other jellyfish, attack them opportunistically, resulting in lost appendages (Thiebot et al. 2017). *Aurelia aurita*, and other jellyfish, can recover from amputation events through one of two processes; reorganization or regeneration. Jellyfish have been widely studied for their regenerative abilities and symmetrization, specifically the medusae and ephyrae (Hargitt 1897; Schmid and Alder 1984; Sinigaglia et al. 2020). The focus in this review will be on the fast time-scale process of tissue symmetrization in *A. aurita*.

The role of tissue layers in *Aurelia* physiology

Aurelia aurita can repair sustained damage from tentacle amputation through restoration of symmetry using non-regenerative processes to regain function (Abrams and Goentoro 2016). An undamaged *A. aurita* has eight appendages known as tenticulocytes forming its swimming apparatus, and the tenticulocytes symmetrically pulsate (Mayer 1910). The striated musculature of the tenticulocytes connected to *A. aurita*'s pulsating bell through epithelial tissue drives the recovery and power strokes of the pulsations as the organism swims (Abrams and Goentoro 2016; Costello et al. 2021). The

mesoglea's elastic properties are used in the recovery stroke to restore the bell to its original shape (Costello et al. 2021). Because the musculature architecture is symmetrically linked with the bell, any loss of symmetry, such as the removal of tenticulocytes, creates an imbalance in forces during pulsations (Abrams et al. 2015). Since radial symmetry is essential for propulsion, when any number of these tenticulocytes are removed from an ephyra, radial symmetry is expected to recover (Fig. 4; Sullivan et al. 1997). The process of recovering radial symmetry is known as "symmetrization" (Abrams and Goentoro 2016).

Aurelia aurita-symmetrization model

In the symmetrization model, Abrams and Goentoro (2016) suggest two repair strategies without increased cell proliferation in Cnidaria to restore symmetry; one that regenerates lost parts and one that does not regenerate lost parts. When appendages are not regenerated, symmetry is regained by shifting the position of the remaining appendages (Abrams and Goentoro 2016).

When *A. aurita* ephyrae tenticulocytes are amputated, individuals quickly begin a symmetrization response (Fig. 4C). The wound at the site of amputation closes in as little as 3 hours, and within 18 hours, full symmetrization—when the manubrium relocates to the center—occurs (Fig. 4D; Abrams et al. 2015). Ephyrae regain radial symmetry with as many as six of their eight total tenticulocytes removed. Even so, development into the medusae stage, where swimming is fully regained, is only possible with at least four remaining appendages. Hence, radial symmetry appears to play a vital role in facilitating further development of ephyrae (Abrams et al. 2015).

The symmetrization process proceeds independently from global factors such as the movement of water, light, or the orientation of *A. aurita* in the water column (Abrams et al. 2015). Symmetrization appears to be independent of wound closure, as evidenced by the faster time scale of wound closure when symmetrization occurs compared to when it does not occur. This was confirmed by treatment with an actin inhibitor, which revealed that wound closure is a necessary step before symmetrization, althouh wound closure does not drive symmetrization (Abrams et al. 2015). Finally, symmetrization also appears to be independent of cell death and cell proliferation. This was confirmed by treating ephyrae cells with Sytol, which does not cross the cell membrane and hence highlights dying cells, and/or by treating ephyrae cells with a caspace inhibitor (Abrams et al. 2015).

Because symmetrization appears wholly related to cellular rearrangement in the organism, it is imperative to look for contributions from the musculature network

of the ephyrae. Inhibition of muscle contractions using muscle relaxants resulted in complete absence of symmetrization, which leads to the conclusion that forces generated due to pulsations are linked to symmetrization (Abrams et al. 2015). An intuitive way to visualize muscle contractions as the driving force is that with each cycle of contraction and repulsion, the appendages relax to an increasingly stable state until their morphology is geometrically balanced. Asymmetrical contraction, due to amputation, might lead to pivoting of the appendages toward the injured sight due to lack of bulk tissue at the site (Fig. 4E; Abrams et al. 2015). Along with the recovery of radial symmetry, this suggests the existence of a mechanism by which asymmetry is detected (Abrams et al. 2015).

Abrams et al. (2015) derived a mathematical model for the timescale of symmetry recovery based on the above-mentioned intuitive idea. The model is based on the suggestion that the muscular contraction forces and the elastic response of mesoglea involved in the propulsion of the uninjured ephyrae can sufficiently explain the recovery of radial symmetry in injured ephyrae. Using the angular movement of each appendage with respect to the geometric center as a parameter, they apply Hooke's Law, which directly relates the total force needed to extend or compress a spring to the distance the spring will be changed by, to generate a recursive expression for the parameter. The simulation of the mathematical model with parameter values obtained by estimation shows the appendages of the ephyrae moving toward the injured site with each contraction and relaxation cycle until symmetry is regained. In other words, symmetry increases with each contraction. Additionally, the model predicts the speed of symmetrization to be dependent on the frequency of muscular contractions. The model suggests that muscular contractions play a dominant role in the mechanism and time required for symmetrization (Abrams et al. 2015).

Aurelia aurita uses its radially symmetric musculature to produce power and recovery strokes for propulsion, aided by fast muscle contractions in the tenticulocytes and elastic recoil in the viscous mesoglea (Costello et al. 2021). Therefore, both propulsion and propulsion-linked recovery from amputation are tailored for the radial symmetry, tissue flexibility, and musculature of the animal. The symmetrization process is a fast self-repair strategy, adopting existing physiological machinery to drive the mechanical remodeling process. Symmetrization encapsulates the priority afforded to shorter time-scale functional recovery over longer time-scale tissue regeneration. It will be fascinating to investigate the notion that symmetrization is an energy-saving procedure that increases the organism's ability to survive. This procedure could motivate the development of biomimetic

materials and technologies that preserve functional geometries without the requirement to regenerate exact shapes and forms (Nawroth et al. (2012)).

General principles

Small-scale phenomena lead to emergent large-scale behaviors

In the ventral epithelium of *T. adhaerens*, micro-scale fractures appear first due to local regions of high tension or shear forces that arise from ciliary-driven traction forces (Bull et al. 2021a; Prakash et al. 2021). These micro-fractures subsequently coalesce to form a larger and stable ventral fracture hole (Prakash et al. 2021). Interestingly, dorsal epithelial fractures also begin with a very small fracture hole that propagates in a different manner and grows in size (Prakash et al. 2021). Eventually, the dorsal hole merges with the ventral hole, and an inside edge is created in the organism (Prakash et al. 2021). Thus, small-scale micro-holes propagate to form larger scale macro-holes in both the ventral and dorsal epithelium (Prakash et al. 2021).

Hydra vulgaris mouth opening requires the overcoming of dual sealing forces associated with septate junctions at the cellular scale and contractile myonemes, which act together to enable the large scale phenomena of mouth opening with precise control (Campbell 1987; Banerjee et al. 2006; Carter et al. 2016). Also, the changes in cellular and molecular properties at the local shoulder region of the *Hydra* result in differential tissue stiffness between the shoulder and body column. This differential tissue stiffness gives rise to the large-scale mechanics of the organism's locomotion (Mackie 1974; Han et al. 2018; Naik et al. 2020). Hence, phenomena at the cellular scales determine emergent behavior at the organismal scale.

Rapid tissue remodeling versus regeneration

This review focuses on rapid (minutes to hours) tissue remodeling phenomena in the three non-bilaterians. However, Cnidarians are also known for their regenerative abilities (Alvarado and Tsonis 2006; Vogg et al. 2019). In particular, *H. vulgaris* and *Nematostella vectensis* are popular model systems for regeneration (Layden et al. 2016; Vogg et al. 2019). Some jellyfish species are more regenerative than *A. aurita* discussed above. One such example is *Clytia hemisphaerica*, which exhibits wound healing and regeneration utilizing a combination of tissue reorganization, proliferation of cellular progenitors, and long-range cell recruitment (Sinigaglia et al. 2020). Further, in *C. hemisphaerica* rapid tissue remodeling is difficult to separate from

the regenerative mechanism in terms of recovery, even though the time scales differ (Sinigaglia et al. 2020).

The conflict between the cost-effectiveness of rapid tissue remodeling in relation to regeneration presents tremendous opportunities for further investigation (Chiou and Collins 2018). Additionally, quantifying the amount and type of mechanical forces that can trigger rapid tissue rearrangement and regeneration could shed light on the cost-effectiveness of both processes. Thus, it will be intriguing to look into the small scale, localized molecular mechanisms that translate forces from muscle contraction into tissue reorganization.

Tissue remodeling by fractures

The only known instances of physiological tissue fracture in organisms occur in *T. adhaerens* and *H. vulgaris*, as discussed in their respective sections. However, there are several differences in the tissue fracture phenomena between these two organisms. An important difference is the location of tissue fractures. In *H. vulgaris*, this location is always fixed at the mouth, but in *T. adhaerens*, fractures arise anywhere in the epithelium—an emergent phenomenon dependent solely on organismal-scale mechanical forces. Physiological tissue fracture and healing dynamics have not yet been observed in jellyfish, and it could be very interesting to look for them in future work.

Hence, *H. vulgaris* and *T. adhaerens* are powerful model systems for future cell and molecular biology investigations to determine specific components (e.g., proteins/molecules) that enable these unique tissue fractures and their healing dynamics.

Tissue remodeling by cellular rearrangements

Tissue remodeling by local cellular rearrangements is a ubiquitous and well-known mechanism during the development of model species (Blankenship et al. 2006; Lecuit and Lenne 2007; Guillot and Lecuit 2013; He et al. 2014; Mongera et al. 2018). In *T. adhaerens*, we have observed ductile tissue deformations that suggest local cellular rearrangements (Prakash et al. 2021). In-silico models have indeed revealed the presence of fast cellular rearrangements in the ventral epithelium (Prakash et al. 2021), but this has not yet been observed in experiments.

Unlike *T. adhaerens*, studies of *H. vulgaris* have not reported any fast time-scale cellular rearrangements. Given the dynamic movements of *H. vulgaris*, in future work, it would be interesting to look for localized tissue remodeling events involving cell–cell rearrangements.

The symmetrization model proposed for recovery in *A. aurita* is based on cellular rearrangements due to forces from contractions that lead to recovery of radial

symmetry (Abrams et al. 2015). It was found that cellular rearrangement drives symmetrization, independent of wound healing at the site of injury (Abrams et al. 2015). Despite different tissue structures and morphologies, different species (Abrams and Goentoro 2016) and life-stages of jellyfish, notably the hydromedusae (Hargitt 1897), also utilize such a reorganization process in their recovery.

Tissue mechanics in other non-bilaterians

We have so far described interesting tissue mechanics phenomena in the phyla of Placozoa and Cnidaria, but non-bilaterians also include two other phyla—Porifera and Ctenophora. Species belonging to these two other phyla also have the potential to be good candidates as tissue mechanics models, given their simple body plans and morphologies (Dunn et al. 2015).

Members of the phylum Porifera, commonly referred to as sponges, consist of cells in an extracellular matrix, and occasionally have stiff scaffolding (Van Soest et al. 2012; Kraus et al. 2022). A recent study dissected their tissues and studied their response to mechanical forces in a rheometer (Kraus et al. 2022). It was found that sponge tissues revealed interesting properties, such as anisotropic elasticity, and it was suggested that these properties were linked to the sponge's flow sensitivity (Kraus et al. 2022). The phylum Ctenophora is characterized by several hundred species of ctenophores, which are soft, gelatinous, freely swimming predatory animals (Pang and Martindale 2008). It has been shown that the ctenophore *Mnemiopsis leidyi* is capable of rapid wound healing when their tissues are cut (Tamm 2014; Traylor-Knowles et al. 2019).

There is a huge diversity in Poriferans and Ctenophores, and there are hundreds of different species in both these phyla, with unique adaptations (Haddock 2004; Van Soest et al. 2012). The few studies on them described above give a glimpse of the promise of these animals to serve as model systems to investigate tissue remodeling phenomena, particularly tissue rheology and rapid wound healing.

Conclusion

In this review, we described interesting tissue mechanics phenomena in two non-bilaterian phyla—Placozoa and Cnidaria. We reviewed how these organisms have stretched our perspective and understanding of tissue mechanics. We revealed how organisms in these phyla, particularly the Placozoan *T. adhaerens*, and Cnidarians *H. vulgaris*, and *A. aurita*, utilize rapid tissue remodeling for their physiological functioning (Abrams et al. 2015; Carter et al. 2016; Prakash et al. 2021). We also illustrated how small-scale cellular reorganization events

give rise to phenomena at the larger scales of tissues. We presented several examples of how these understudied non-bilaterians present a wealth of opportunities to improve our understanding of rapid tissue remodeling phenomena such as cellular rearrangements, fractures, and wound healing. Hence, these non-bilaterian tissue mechanics model animals complement and contribute to the broader field of biological physics of tissues (Harris et al. 2012; Bi et al. 2015; Park et al. 2015; Wyatt et al. 2016; Noll et al. 2017; Latorre et al. 2018; Mongera et al. 2018; Xi et al. 2019; Krajnc 2020; Armon et al. 2021; Bull and Prakash 2021; Kim et al. 2021; Bull et al. 2021b; Bonfanti et al. 2022; Duque et al. 2023).

We adopted a comparative approach to allow for a rigorous contribution to the search for general biophysical principles. We hope to have made a strong case for studying these early divergent non-model organisms as their extreme examples of behavior and morphology present a unique opportunity to study fundamental properties of tissue mechanics from a bottom-up perspective. These important studies can help us arrive at a comprehensive framework of tissue mechanics in animals.

Author contributions

S.G., G.M., M.R., and V.N.P. discussed ideas, wrote and reviewed the manuscript. V.N.P. conceived the project.

Conflict of interest

No conflict of interest is declared.

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