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REVIEW

‘The Forms of Tissues, or Cell-aggregates’: D’Arcy Thompson’s influence and its limits

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ABSTRACT

In two chapters of his book *On Growth and Form*, D’Arcy Thompson used numerous biological and physical observations to show how principles from mathematics and physics – such as pressure differences, surface tension and viscosity – could explain cell shapes and packing within tissues. In this Review, we depict influences that enabled the genesis of his ideas, report examples of his visionary observations and trace his impact over the past 100 years. Recently, his ideas have been revisited as a new field of research emerged, linking cell-level physics with epithelial tissue structure and development. We critically discuss the potential and the limitations of both Thompson’s and the modern approaches.

KEY WORDS: *On Growth and Form*, Cell packing, Cell shape, Surface tension, Tissues

Introduction

The diversity and beauty of shape in nature has been a source of inspiration over centuries. In his famous book *On Growth and Form*, D’Arcy Wentworth Thompson [first edition, Thompson (1917); second edition, Thompson (1942)] discussed the importance of physics in determining cell shapes within tissues. This book and its author have had a striking influence on scholars in several fields, and are still highly quoted 100 years later, an unusual destiny for scientific works such as this.

As Thompson observed and predicted, based on simple and specific observations, living matter seems to obey physical and chemical laws. From looking at the outer contours of cells within monolayers, Thompson claimed that the specific dimensions of cell-cell contacts and their respective angular orientations for each single cell within an epithelial tissue as a whole were set by rules that physics could address quantitatively. The link between small scale – the cellular contour – and large scale – the tissue – was thereby formulated with no *a priori* knowledge of the molecular actors. This simplification allowed him to propose an analogy with physical foams in two dimensions, that is, foams squeezed between parallel glass plates so that bubbles form a monolayer (Fig. 1, top). Although cells are hundreds of times smaller than bubbles in standard foams and are composed of living matter, Thompson assumed that the rules describing how bubbles organised geometrically within a foam (discussed further below) could extend to actual cells in epithelial monolayers. It is at this level that similarities between foams and tissues were initiated, and this eventually led to the emergence of new concepts for developmental biology. It should, however, be noted from the outset that Thompson’s principles contained ideas with oversimplified frameworks, particularly in terms of the geometries and tensions of cell walls, and should be treated with due care; we will explore these limitations in detail below. These oversimplifications sometimes impact the modern assumptions behind computer simulations and force inference measurements.

Thompson may not have been the only originator of the idea that tissues can be compared to foams, but he managed to present this conceptual analogy in an exceptionally clear manner, which contributes to the modernity of his century-old book. In many ways, Thompson’s ideas came ‘before their time’. Only recently have physicists and biologists come together to start a new field of research, now mature, linking cell-level physics with epithelial tissue structure and development. Particularly since 2004, his ideas on cell shapes and configurations in tissues have been revisited with the latest approaches to label the main molecular actors with fluorescent proteins such as green fluorescent protein (GFP) and to follow them by fluorescence microscopy in living embryos from a variety of species (Guillot and Lecuit, 2013; Heisenberg and Bellaïche, 2013). It is now clear that acto-myosin molecular motors drive shape transformation of cells and tissues through cell deformations, using the energy from ATP hydrolysis; cells move with respect to their neighbours, involving friction forces mediated by cadherin-based adhesive junctions; cell division and cell delamination contribute to mechanical stresses (see Glossary, Box 1), driving tissue convergence and extension, as well as other cell-mediated phenomena. More generally, it is now accepted that cell shape and cell-cell interactions and their dynamics can often be disentangled from cell fate, and generic rules for living matter can be formulated with new theoretical formalisms (Delanoë-Ayari et al., 2011; Prost et al., 2015; Popović et al., 2017). For example, reinforcements of focal contacts (Riveline et al., 2001) and cell-cell contacts (Brevier et al., 2007, 2008) illustrate how mechanical forces mediated by the cytoskeleton regulate cell adhesion. It might appear too simplistic to capture morphogenesis *in vivo* under tight regulation with physical laws of acto-myosin interactions. However, the striking conservation of the Rho signalling pathways (Hall, 1998) and their directed control of acto-myosin activity *in vivo* from yeast to humans, through *C. elegans*, zebrafish and *Drosophila*, support this vision. Of course, feedback mechanisms also operate *in vivo*, but they can often be identified based on their mechanical and/or signalling origins (Petridou et al., 2017).

As biophysicists working respectively in inter-cell and intra-cell physics, we here retrace the story of this field, with its successes and weaknesses. We revisit Thompson’s seminal

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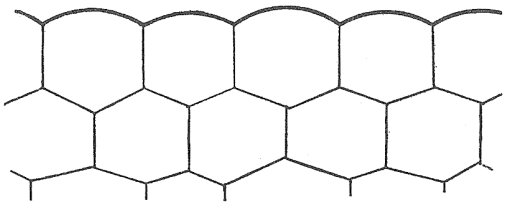

Fig. 177. A froth, with its outer and inner cells or vesicles

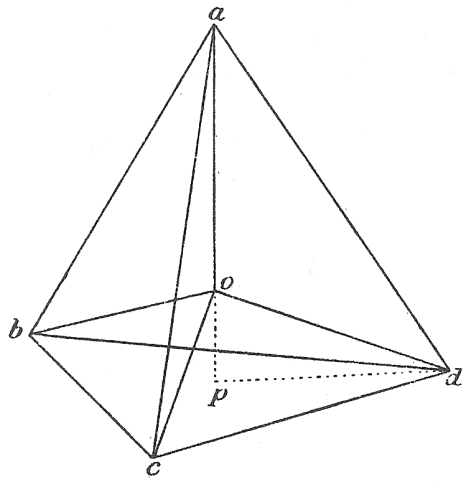

Fig. 178. A regular tetrahedron, with its centre of symmetry.

Fig. 1. Foam representations and geometric definitions (Thompson, 1942). (Top) Hexagonal bubbles, with slightly variable sizes, in a 2D foam (bubble monolayer), here with a free boundary. (Bottom) Meeting of four bubbles in a foam. Walls meet three by three at 120° along an edge; for instance, *aob* (in the plane of the figure), *boc* (in the front of the figure) and *bod* (in the back of the figure) meet along edge *ob*. In turn, edges meet four by four at 109.5° at a vertex; for instance, *ao* and *bo* (in the plane of the figure), *oc* (in the front of the figure) and *od* (in the back of the figure) meet at vertex *o*. The point *p* represents the projection of vertex *o* on the horizontal plane *bcd*. Reproduced, with permission, from Thompson (1942).

chapters on plant and animal cell shapes and packing in two-dimensional (2D) or three-dimensional (3D) tissues, trying to understand how and why his ideas emerged, and why his book allowed cross-fertilisation between the developmental biology of morphogenesis and the physics of living matter. We first explain, in modern terms, the basic concepts that underlie patterns in foams and tissues. We then comment on their original presentation by Thompson, summarising the origin and content of Thompson's chapters, and emphasizing his important observations of four-cell vertices. We discuss the limitations of his approach, distinguishing scientific breakthroughs from more descriptive claims. We then critically review subsequent improvements by his successors. We conclude by recalling the validity and limits of some analogies, and discuss possible research directions in developmental biology.

Packing rules in foams and tissues

When a pattern is made of an ensemble of domains tiling the space without gaps nor overlaps, the rules that dictate the way these domains are assembled are collectively termed packing rules. They include three classes: mathematical rules, generally pertaining to all types of cellular patterns; physical rules, usually referring to foams that are at mechanical equilibrium (see Glossary, Box 1); and biological rules, for epithelial tissues.

Box 1. Glossary

Interfacial tension. Also called surface tension, interfacial tension quantifies the tendency of two different materials to reduce their contact interface area. This is formalised by an energy per unit interface area (a positive energy, which means a cost), expressed in joules per square metre, or equivalently by the resulting force acting parallel to the interface and always tending to reduce it; this force is proportional to the interface perimeter and is expressed in newtons per metre. It results from collective interactions between individual constituents (here, cells) and is defined at a scale larger than its constituents. It applies for instance to: two different cell aggregates; an aggregate and the outer medium; or two tissue regions.

Mechanical equilibrium. In the context of cells and tissues during morphogenesis, mechanical equilibrium refers to a situation in which the pattern is static and all forces balance each other. In terms of equations, it can be described by an energy that is minimised. A slow enough perturbation (here, 'slow' means slower than all relevant time scales inherent to the tissue) is called a 'quasistatic' evolution, that is, a succession of quasi-equilibrated states in which mechanical equilibrium theorems and energy-based descriptions apply. In situations far from mechanical equilibrium, movements are described with other equations not based on energy and its minimisation. Mechanical equilibrium should not be confused with thermodynamical equilibrium, which means absence of fluxes of energy and matter, and is a property of inanimate material or dead bodies.

Mechanical stress. The result, coarse-grained over several cells, of cell-scale forces between neighbouring cells: pressures, wall tensions. Stress is a tissue-scale notion, and can be in traction (positive stress in all directions), in compression (negative stress in all directions), or in shear (positive in one direction and negative in another).

Topological changes. These are of two types. First, the change in packing, that is, the change in cell or bubble wall number, also called rearrangement, intercalation, neighbour exchange or wall swapping. Second, the change in bubble number, by creation, disappearance or wall breakage; corresponding processes for cells are division, apoptosis, extrusion or necrosis. Weaire and Rivier (1984) have shown that, from the formal point of view of topology, all these processes can be expressed as combinations of e.g. rearrangement (which they named 'T1') and disappearance (which they named 'T2') or their inverses.

Wall tension. A force acting within an individual thin wall. It is expressed in newtons when the wall is a line, as in a 2D foam or tissue, and in newtons per metre when the wall is a 2D sheet, as in a 3D foam or tissue. The wall tension can vary, as it depends on the state of traction of the wall. For instance, it can vanish for a given wall size, which then is the wall size at mechanical equilibrium: when the wall is larger, its tension is positive, and when the wall is smaller, its tension is negative.

Counting walls and edges

A branch of mathematics, called topology, deals with properties that are independent of the size, composition, mechanical equilibration or physical properties of any cellular pattern. In an ideal 2D pattern with a large number of cells, if at each vertex there are three edges that meet (as is the case in a 2D foam, and in several other 2D patterns), the average number of sides of each cell, $\langle n \rangle$, is always close to 6 (see Box 2 for mathematical details; Graustein, 1931; Weaire and Rivier, 1984). Importantly, this rule does not fix the number of sides of each cell, i.e. individual cells can have more or fewer sides.

To characterise the distribution of the cell (or bubble) side number, since the average $\langle n \rangle$ is fixed, it is more useful to focus on the distribution width, namely the standard deviation Δn. In a disordered foam, and in several epithelia, Δn correlates with, and often suffices to predict, the shape of the whole distribution. If Δn is zero, each cell is a hexagon (although this does not necessarily imply that it must be a regular hexagon). If Δn is small, there is a

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Box 2. Walls and edges

In 2D, Euler (Cromwell, 1999) found a relationship between the total number of cells or bubbles (N) and their numbers of walls (N_{walls}) and vertices ($N_{vertices}$):

$$N - N_{walls} + N_{vertices} = \chi_{Euler}.$$

This relationship is difficult to demonstrate but easy to check by simple counting. Here, the constant χ_{Euler} is a small integer number. It is typically 1, but may be 0 or 2 if the pattern is contained in a closed box or has a free surface. Importantly, this constant does not change if cells or walls are added or removed; for instance, when a cell divides, dies or changes neighbours.

A remarkable consequence of this formula was found by Graustein (1931). Denoting $\langle n \rangle$ the average of the number of walls of the cells (which in 2D is the same as their number of vertices), and $\langle z \rangle$ the average number of edges which meet at a vertex, we have:

$$N_{walls} = \langle n \rangle N/2,$$

$$N_{vertices} = \langle n \rangle N/\langle z \rangle.$$

When N is much larger than χ_{Euler} (which, as noted above, is typically 1), $\langle n \rangle$ and $\langle z \rangle$ are related:

$$1/\langle n \rangle + 1/\langle z \rangle = 1/2.$$

Hence, in an ideal 2D pattern with a large number of cells, if at each vertex there are three walls which meet, $\langle n \rangle$ is always close to 6. More precisely, $\langle n \rangle$ is equal to 6, less a small correction that depends on the periphery of the foam and on N:

$$\langle n \rangle = 6(1 - \chi_{Euler}/N).$$

In a real foam there are other, generally small, corrections, due for example to round corners between bubbles. In a real tissue, there is another generally small correction, if several cells meet by four instead of three.

Let us now turn to 3D. Cauchy (1813) and L'Huilier (1812-1813) extended Euler formula and established a relationship between the total number of cells or bubbles (N), and their numbers of walls (N_{walls}), edges (N_{edges}) and vertices ($N_{vertices}$), defined in Fig. 1, bottom:

$$-N + N_{walls} - N_{edges} + N_{vertices} = \chi_{Euler}.$$

One of the consequences of this relationship is that for each individual 3D cell, there is a link between its number of walls, N_{walls}, and its average number of edges per wall, $\langle e \rangle$. If, at each edge, there are three walls that meet (as is the case in a foam, and in several other usual patterns), a simple counting argument implies that:

$$6 - \langle e \rangle = 12/N_{walls}.$$

Whether the number of walls is very small or very large, $\langle e \rangle$ is thus always strictly less than 6. Put another way, no 3D cell has only hexagonal walls; there must be some walls with fewer edges. As an analogy, a soccer ball has, among white hexagons, exactly 12 black pentagons.

majority of 6-sided cells, with 5- and 7-sided cells in an equally small number. If Δn is larger, there are 4- to 8-sided cells, with a peak at n=5 or 6. Finally, if Δn is even larger, the distribution can become very asymmetric (the lower limit for side number is 3, while there is no upper limit and cells with more than 9 sides exist): to keep the average $\langle n \rangle$ at 6, there can be more 5-sided than 6-sided cells.

Shapes of walls and edges in foams

In a given foam, all bubble walls are made of the same water solution containing a small amount of soap, they all have two air-water interfaces, and all have the same constant, uniform wall tension, t (see Glossary, Box 1). At mechanical equilibrium, the foam minimises its total surface energy, which is the surface area multiplied by t. Whereas a single bubble minimises its area by being spherical, bubbles assembled in a foam reach shapes resulting from a compromise that minimises together their total surface area.

Paradoxically, while t is the origin of the foam structure at mechanical equilibrium, its exact value plays no role whatsoever in the bubble shape and foam structure. This explains why different foams share common shapes and properties (Fig. 1). Observations by Lamarle (1864) and Plateau (1873) led to the following 'Plateau rules' for the mechanical equilibrium of an idealised foam in 2D or 3D (for details, see Weaire and Hutzler, 1999; Cantat et al., 2013). They were only demonstrated a century later (Taylor, 1976; Almgren and Taylor, 1976).

The first rule, also called Laplace's law, is that each wall between two bubbles is smooth and has a curvature K, which balances the pressure difference Δp between both bubbles: $\Delta p = tK$. As a consequence, each wall has a uniform curvature (in 2D, it is an arc of a circle). Another consequence is that when three walls meet and have the same t, the sum of their curvatures is zero.

The second rule is that walls meet three by three; by symmetry they form equal angles, which are $\arccos(-1/2)=120°$. The angle between a bubble wall and a (smooth) solid wall is 90°. This is true in 2D (Fig. 1, top) and in 3D (Fig. 1, bottom). In 3D, edges meet four by four, forming equal angles of $\arccos(-1/3) \approx 109.5°$ (Fig. 1, bottom).

To fulfil the 120° angle condition, 2D bubbles with 5 sides or fewer must have walls that are mostly convex, bubbles with 7 sides or more must have walls that are mostly concave, and bubbles with six sides have walls that are flat on average. Note that 6-sided bubbles can (but need not) have flat walls (Fig. 1, top).

Cell wall tensions vary over space and time

The balance of forces in epithelial tissues involves various scales, as in foams, but it requires a more detailed examination. In several monolayered epithelia, cell shape and packing are mostly determined by the balance between two antagonistic effects (Lecuit and Lenne, 2007; Käfer et al., 2007; Farhadifar et al., 2007; Hilgenfeldt et al., 2008). First, contractility of the acto-myosin cortex resists cell deformation and tends to yield regular, 'roundish' cell shape. Second, adhesion via cadherin-based adherens junctions tends to favour contact between cells, and thus results in cells spreading on each other. It should be noted that other adhesion structures – such as desmosomes, hemidesmosomes, tight junctions, gap junctions, focal contacts – also play important roles (Alberts et al., 2002). Moreover, for a given type of contact, they differ from species to species (for example, for adherens junctions see Meng and Takeichi, 2009). However, the main adhesive anchor to the acto-myosin cytoskeleton between cells is ensured by adherens junctions, and this simplification allows epithelia from different species to be considered generically, despite their variability and the many types of junctions.

At the scale of cell walls, cell-cell mechanical interactions are described by a cell-cell wall tension and by the difference between cell pressures. The cell-cell wall tension t is positive and results from the balance between adhesion and contractility mentioned above. A simple description based on these ingredients turns out to be a surprisingly efficient means to describe, and sometimes predict, cell shapes (Käfer et al., 2007; Hilgenfeldt et al., 2008).

However, the analogy with foams has several limitations (discussed further below in the section 'Since 2004: modern renewal of the field'). First, if there are two different cell types A and B, there are five different wall tensions: two between same cell

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types, t_{AA} or t_{BB}; one for dissimilar cells, t_{AB}; and the two wall tensions of A and B with the medium, t_{Am} and t_{Bm}. Second, due to cytoskeletal activity powered by ATP hydrolysis and regulated by the Rho GTPases, cell walls fluctuate in position: only in average can their shape appear as almost at mechanical equilibrium. Third, and most important, cell wall tensions depend on cell shape, so that cell shape and wall tension feedback on each other.

As a consequence, cell wall tensions are usually neither uniform in space nor constant in time. When cell shape is controlled by wall tension and pressure, Laplace's law holds, walls have an uniform curvature, and angles reflect mechanical balance between wall tensions. However, the rule of 120°, as well as the rule that walls which meet have curvatures of sum zero, are only approximate for cells, the approximation being better if all cell walls have a similar tension value. Fourfold vertices, although less frequent than threefold ones, can be observed under some circumstances in 2D tissues (see below), unlike in 2D foams. Energy minimisation can remain a good approach to predict shape, but the energy involves adhesion and cortex contractility (Ouchi et al., 2003; Käfer et al., 2007; Hilgenfeldt et al., 2008), so is less simple than the energy in foams which is proportional to the total surface area of cell contacts.

In summary, tensions in cell walls are well defined but can vary in space and time, so that cell shapes are similar to bubble shapes but much more varied.

Thompson's chapters 'The Forms of Tissues, or Cell-aggregates'

Having laid the groundwork with the mathematical and physical principles, we now comment on how Thompson presents these rules, and why. In the revised edition (Thompson, 1942), to which all page numbers here refer, chapter VII comprises 100 pages. It mostly deals with cell shape, wall tension and surface area minimisation. It is entitled 'The Forms of Tissues, or Cell-aggregates'. Chapter VIII, almost as long and curiously entitled 'The same (continued)', examines how surface area minimisation affects cell division and growth.

Interdisciplinary influences at the origin of these chapters

As early as 1889, Thompson had already began to work on mathematics; he wrote to a student: 'I have taken to Mathematics, and I believe I have discovered some unsuspected wonders in regard to the Spirals of the Foraminifera' (Thompson, 1889; Jarron, 2017). Can we identify some scientists who have influenced him in this direction?

At this date, Anatole-Henri-Ernest Lamarle and Joseph-Antoine-Ferdinand Plateau had recently published their works on soap bubble shapes (Lamarle, 1864; Plateau, 1873). By 1917, Plateau was well known, as was Henri Bénard and his work on flow patterns in liquids heated from below. Thompson duly quotes them in these chapters. Since Plateau was dead, Thompson's source could have been Lord Rayleigh, who was working on the subject while Rayleigh and Thompson were simultaneously at Trinity College, Cambridge (I. Falconer, personal communication). In addition, Thompson exchanged numerous letters with Plateau's son Félix, the zoologist; however, they discussed the museum specimens more than bubbles (M. Jarron, personal communication).

The French biologist Stéphane Leduc (a contemporary of Thompson) had an agenda to reproduce biological patterns, such as trees, flowers or tissues, using only physical and chemical materials. Thompson quotes Leduc and reproduces his pictures. There seems however to have been no reciprocity, although Leduc perceived he had a better audience in the UK than in France (Keller, 2002); despite their similar interests and the close temporal proximity of their publications, Leduc and Thompson apparently did not correspond (M. Jarron, personal communication).

Later, Frederic T. Lewis, heavily influenced by Thompson's 1917 edition, underwent a thorough analysis of cell shapes and packings. In 1923 he sent an article to Thompson (Thompson, 1923) and they corresponded intensively up until Thompson's death; Lewis received a visit from Thompson in 1936 (M. Jarron, personal communication). The material provided by Lewis strongly influenced the 1942 edition.

William C. Graustein demonstrated in 1931 that cells tiling a plane without gaps or overlaps have six sides on average (Graustein, 1931). Lewis, who was his colleague at Harvard, wrote twice to Graustein, around 1923 and in early 1940 (as mentioned in Lewis, 1940, 1943). However, Thompson does not seem to have been much interested in Graustein's work: in the 1942 edition, he quotes this article in passing (p. 516), incorrectly writing the name as 'Goldstein', and no letter between them has been found. Thompson also overlooks Graustein's sources: he quotes Euler only on other subjects, and quotes neither Cauchy nor L'Huilier.

Thompson's approach

Despite the title of these chapters, Thompson does not investigate the forms *of* tissues and cell aggregates by themselves (except for the shape of a compressed foam, p. 506 for instance). Rather, he investigates in detail the forms of cells *within* tissues and cell aggregates.

In line with the whole book, this chapter is a synthesis of enormously wide scope in terms of the forms and organisms considered, questions asked, and ideas drawn upon. The text is abundantly illustrated, containing as many figures as the six preceding chapters together, with photographs and careful drawings from his own work and from decades of others' observations. He reports cellular patterns from inert to living matter: packed soap bubbles or oil drops; flow patterns in a liquid heated from below; cracks in dried clay, basaltic lava, or porcelain bowls; patterns in frogs eggs and the wings of fly and, with a special emphasis, honeycombs.

To interpret such a variety of patterns, he proposes a simple, unified, quantitative framework. He documents and emphasizes the striking analogies between cell shapes and patterns for foams and tissues: 'we see the cell-walls everywhere meeting, by threes, at angles of 120°, irrespective of the size of the individual cells' (p. 487). Among many physical parameters, he mostly emphasizes the importance of surface tension and pressure differences.

To support his vision he provides some theoretical demonstrations, deriving equations, some of which are geometrical (e.g. demonstrating values of angles), and frequent visual analogies. For example, he explains the rules about numbers of sides (pp. 515-517), shapes of walls in 2D (pp. 464-475, 483-487, as well as p. 596 for cell divisions) and in 3D (pp. 496-499, 549-552). He also outlines exceptions when needed (for example, see below). Another patient observer wrote to him: 'I marvel at the care with which you must have gone through the material that was sent to you' (Matzke, 1948). This suggests that he was indeed carefully considering each single specimen but, perhaps for the sake of clarity, he seems to have purposely selected some simplifications first before progressing to more detailed explanations.

The case of the four-cell vertex

In biological tissues he observes four-cell vertices (Fig. 2, top), which, as he explained, are unstable in foams. He discusses the case

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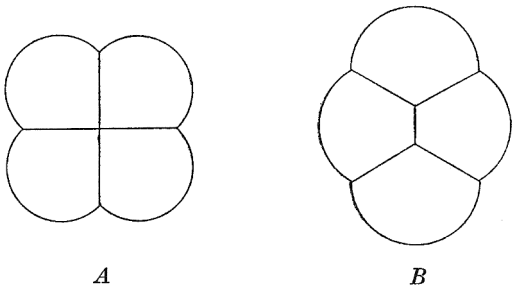

Fig. 172. A, an unstable arrangement of four cells or bubbles. B, the normal and stable configuration, showing the polar furrow.

Fig. 2. Arrangements of four cells. In all schemes, the contours of cells and their meeting points are extracted and drawn from actual experiments, and their specific shapes are proposed to be informative for the organisation and dynamics of the tissue. (Top) The four-cell vertex (A) and a relaxed state (B) observed in bubbles and cells. (Bottom) Various configurations (A-C) in a frog's egg. Reproduced, with permission, from Thompson (1942).

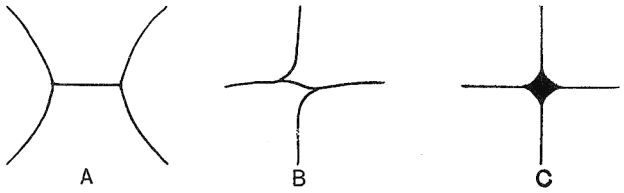

Fig. 175. Various conjunctions of the first four cells in a frog's egg. After Rauber.

in 2D (pp. 486-493) and later in 3D (pp. 557-560). Facing this important exception to the foam-tissue analogy, he writes (p. 491):

> '*I was wont to attribute to error or imperfect observation all those cases where the junction-lines of four cells are represented* [Fig. 2, top] *as a simple cross. As a matter of fact, the simple cross is no very rare phenomenon, even in the frog's egg; but it is a transitory one, and unstable. Viscosity and friction may enable it to endure for a while, but the partitions inevitably shift into the stable, three-way, configuration. In such a case, the polar furrow manifests itself slowly and as it were laboriously; but in the more fluid soap-bubble it does so in the twinkling of an eye.*'

He emphasizes that this is a difference in degree, not in quality, since in both cases the duration is non-zero.

On the one hand, it seems that Thompson recognises that the foam-tissue analogy, which underlies the whole explanation of cell shapes by surface tension, fails in the current case. He attempts at hand-waving to reconcile his observation and his intuition. His somehow self-contradicting usage of words such as 'stable' and 'unstable', here and in other places, might be disputed by a theoretical physicist.

On the other hand, for an experimentalist, these approximations are understandable at a stage when the focus is the discovery of the phenomenon itself. Along these lines, Thompson performs several important observations: (1) he identifies the location within the tissues where relevant phenomena occur and draws only the meaningful traits; (2) he compares them to the similar configuration in foams; (3) he deduces a difference in dynamics; (4) he proposes that viscosity and friction in tissues are responsible for this difference. He even envisions the potential dynamics of these peculiar vertices in another scheme where he draws the 'various conjunctions of the first four cells in a frog's egg' (Fig. 2, bottom).

In summary, Thompson's penetrating intuition and pioneering observations recognise the importance of four-cell vertices, but his interpretations need to be reworked in modern times, as discussed below.

Limitations of Thompson's work

As noted above, Thompson's work, although influential, does have a number of limitations. Here, we discuss key caveats with these chapters, many of which come from Thompson's quest for simple explanations, which sometimes led him to imprecisions.

The search for order and perfection

As James A. Glazier commented (Glazier, 1989):

> '*The fundamental weakness of Thompson's approach, which carries over to later writers as well is an obsession with the crystal, with a regularity and symmetry which he assumed to be the Platonic form for imperfect natural structures. Sir Thompson had no room for probability in his*

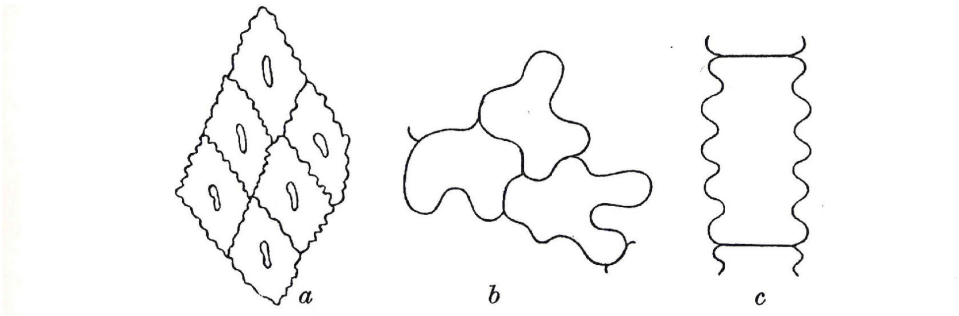

Fig. 186. Sinuous outlines of epithelial cells. *a*, endothelium of a blood-vessel; *b*, epidermis of *Impatiens*; *c*, epidermal cells of a grass (*Festuca*).

Fig. 3. Cells with sinuous walls. Whatever their shapes (a-c), and despite their fundamental difference from regular hexagons, as long as their walls meet three by three their average number of sides is six (Weaire and Rivier, 1984; Carter et al., 2017). Reproduced, with permission, from Thompson (1942).

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ordering of the natural world. For him, disorder was merely a deviation to be characterised and dealt with as an unavoidable inconvenience, but not of interest in itself.'

Thompson marvels at 'the widespread appearance of the pattern of hexagons', while in reality the only rule is that cells have six sides on average (in patterns with threefold vertices, see above and Box 2). He shows photographs of Stéphane Leduc's 'artificial tissues' obtained by diffusion of a coloured liquid in a less dense one (p. 501) as if they were a beautiful illustration of perfectly symmetrical regular hexagons, although in practice cell shapes are visibly irregular and some pentagons appear. He underlines the universality of 120° angles (p. 487), which is correct in foams, whereas significant deviations from 120° are frequent in cells. He presents a compressed foam drawn as if it were a crystal-like pattern of regular hexagons (p. 506), whereas the reality must have been far from it. On the same picture, the bubble walls at the outer surface of the foam are drawn as flattened, which he probably knows is wrong, since he correctly draws them curved on another figure (Fig. 1, top). However, despite occasional confusions between hexagons and regular hexagons, he distinguishes them when needed, quoting examples of extreme differences (Fig. 3).

The search for an optimal, unified explanation

Throughout his work, Thompson usually assumes there is one, and only one, explanation, and favours the simplest hypothesis. This search for parsimony, typically reminiscent of Ockham, is valuable in physics, and also in biology whenever it is experimentally testable and refutable. However, its general application to biology without control can lead to dead ends.

On the one hand, a physical determinant such as tension could act during the development of an individual. On the other hand, an optimisation principle such as area minimisation could act during trait selection. This ambiguity between ontogeny versus phylogeny is hidden throughout the text and is never clarified.

Thompson suggests that tension explains the observations he reports. He also honestly alludes to the possibility of other explanations, in addition to tension or instead of it. However, he seems to be biased in his choice of samples – quoting more examples than counterexamples. The effect is to make the reader believe that tension is the general determinant of cell shape.

Approximate claims arise in several places. In most cases, Thompson does correct them in passing later in the book, but since the information is dispersed through the chapter, this correction is not always perceived by the reader. Some of his statements are valid only in 2D, some only in 3D, and some are valid in both, but this is not always clearly stated. The same applies for ordered versus disordered patterns; or for patterns with finite versus infinite (or periodic) boundary conditions; or for patterns with constant uniform tension, such as in foams, versus variable heterogeneous tension, such as in tissues. He often considers visual analogies as if they provided evidence of a common underlying causal mechanism. In mathematical demonstrations, he enjoys pedagogical shortcuts, even when he knows the complete and correct demonstration (pp. 485, 515-516).

For instance, in 2D, Thompson considers each cell wall as an arc of a circle. However, sinuous cell walls exist (Fig. 2, bottom, B): these cannot have been shaped by cell wall tension and cell pressure differences only. Other factors, such as bulk cytoskeleton, viscous dissipation or extracellular matrix, may contribute to determine cell shapes. An expert eye can also detect that factors beyond wall tension and pressure intervene, by looking at angles or curvatures; for instance, if three cell walls that meet have curvatures that do not sum up to zero, at least approximately. Thompson recognises that some cells are so sinuous that another explanation is required. For animal cells (Fig. 3a) he suggests an analogy with the wrinkles in a compressed rubber sheet, which physicists would call a buckling under negative tension: this is far from being the only possible explanation. For plant cells (Fig. 3b,c) he is more cautious, writing that it is 'another story, and not easily accounted for'. Note also that, in 3D, Thompson treats each bubble or cell wall under tension as a portion of a sphere; this is approximately true since each wall has a constant mean curvature, but, except when symmetry imposes it, it is not a general rule.

On the very first page of chapter VII a confusion appears between wall tension, at cell scale, and interfacial (or surface) tension (see Glossary, Box 1). Such confusion is natural for persons acquainted with foams, where both concepts happen to overlap by coincidence, since the wall tension is equal to twice the air-water interfacial tension. It is reinforced by the fact that wall and interfacial tensions obey the same laws of balance at mechanical equilibrium. This has contributed to a long-standing confusion between the two concepts, with 'surface tension' often used instead of 'wall tension'.

Moreover, in using the word 'tension', Thompson refers both to tension in a material bulk and at an interface: that is, to liquid materials, which have an interfacial tension, and to solid materials such as adult animal or plant tissues, with their bulk elastic tension or fractures. Despite this confusion between wall tension and interfacial tension, these patterns are all static and in mechanical equilibrium, and so the concept of tension makes sense. This is not the case for the figures of sand grain accumulations on vibrating plates (p. 472), diffusion of a coloured liquid in a less dense one (p. 501), or flows in liquids heated from below (p. 504), which all result from dynamic movements and are not subject to any type of tension. In short, Thompson treats different systems collectively by their patterns, as if the underlying physics were the same, which is not the case.

Altogether, Thompson seems guided by intuition, and his text might not pass a peer-review filter of modern times. However, as a pioneer and as a source of inspiration for others, his influence still lasts, as we now discuss.

Thompson's influence over the past 100 years

We chronologically retrace four different phases (corresponding to slightly overlapping periods) of Thompson's legacy since 1917. In each period, we review how physical mechanisms are invoked to explain cell shapes and packing.

Although Thompson's work has clearly been influential in this field, only some of the papers listed below explicitly quote *On Growth and Form*. Even if they quote it, is it more often for a general statement in the introduction, rather than for a specific result. The motivations of the studies discussed fall into four classes: description of packing and shapes; roles of mechanical stress and forces such as pressures and tensions; energy minimisation in analogy with foams; and, more broadly speaking, physical approaches to biological patterns.

~1920s to 1970s: descriptive observations of cell shapes and packing – a search for general laws

In the decades following publication of *On Growth and Form*, four researchers were particularly active in promoting Thompson's approach and keeping his ideas alive.

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Lewis, heavily influenced by the 1917 edition (see Box 3), followed Thompson on all four classes defined above. He engaged in a long-term, thorough descriptive investigation of cell packing and shapes in 2D and 3D, in animals and in plants. He was fond of visual analogies between tissues and foams, and was looking for perfection in patterns, which did not prevent him from carefully recording actual observations. This resulted in an abundant body of work, mostly remembered for his remark that large cells tend to have more sides than small cells do (see e.g. Lewis, 1928, 1948; for reviews see e.g. Chiu, 1995; Glazier, 1989).

At Columbia, Edwin B. Matzke, inspired by the second edition (Box 3), analysed and demonstrated experimentally the role of wall tension in 3D plant cells. He undertook painstaking manual searches and observations of 600 3D bubbles, looking for the ordered patterns or regular bubble shapes put forward by Thompson (Matzke, 1945, 1946). Having failed to detect them, and having rather proved the prevalence of disorder, he jokingly warned of the dangers of leaping from mathematical models to real-world conclusions 'in the twinkling of an eye' (Klarreich, 2000).

Malcolm Steinberg focused on cell-sorting experiments, in which two aggregates made of different cell types are placed in contact; they can separate, touch, mix, or one may surround the other. By building upon Johannes Holtfreter's notion of cell affinity (Holtfreter, 1939) that could drive cell movements (Townes and Holtfreter, 1955), Steinberg proposed that these mutual arrangements are driven by differences between homotypic and heterotypic adhesion: the so-called 'differential adhesion hypothesis'. The key underlying idea, which Steinberg promoted until the 2000s, was that all cell-cell interfaces, despite their varieties, could be quantified by a single number (measuring their adhesivity), compared and ordered (Steinberg, 1963; Foty and Steinberg, 2005). This assumption was disputed by Albert K. Harris, who rather emphasized the role of differences in cell wall contractility (Harris, 1976). This debate has only recently been resolved, as discussed further below.

Finally, Hisao Honda developed multiscale studies linking cell packing with tissue dynamics. He introduced bottom-up computer simulations of cell assemblies and their dynamics by neglecting most details of cell contents and shapes, except for their polygonal nature; a cell was represented by its centre, the line midway between two cell centres representing the cell wall (Honda, 1978). In parallel, he tracked individual cell shapes and movements within various epithelial tissues (for a review, see Honda and Nagai, 2015).

Box 3. Thompson's influence

Thompson's immediate influence and the intensity of debates are illustrated in some of the letters that he received:

'*I am coming to realize that your book is regarded as the last word on the subject of cell shape. Unless I can point to some difference there, I can not obtain a hearing!*' (Lewis, 1925)

'*Of course, it* [the book] *presents problems and raises issues on which opinions differ in lively fashion.* […] *At Columbia* [Matzke team] *they have worked assiduously at this problem, and … your Growth and Form was the primary incentive.*' (Lewis, 1942)

'*It must be a satisfaction to you to realize that the work on cell shapes which has gone on in the last several decades has resulted from the stimulating discussion which you presented in the first edition of your book in 1918.*' (Matzke, 1948)

Between them, these four researchers, along with others, developed the ideas laid out in chapters VII and VIII of *On Growth and Form*, which were otherwise largely ignored by the broader cell and developmental biology communities for many years.

~1950s to 1990s: exchanges of ideas with foam physics

Meanwhile, Bragg and Nye (1947) had produced picturesque photographs of orderly assembled bubble monolayers floating at the surface of water, and used them to teach crystal structures. Together with the natural history descriptions of Lewis and Matzke, these pictures have influenced the modern study of foam physics, launched by the metallurgist Cyril Stanley Smith (Smith, 1952). The physics of foam structure became an active field of research (for reviews, see Glazier, 1989; Weaire and Hutzler, 1999; Cantat et al., 2013). It was during this time that Thompson's followers developed the bases that were later taken up by developmental biology (also discussed further below).

A toolbox for statistical description of cell assemblies

Researchers first investigated 2D packing of several bubbles (Weaire and Rivier, 1984; Rivier, 1991). They quantified distributions of cell size and number of sides (Rivier, 1991), as well as their spatial correlations and their disorder (Rivier, 1994); change in packing or in bubble number, also called 'topological changes' (see Glossary, Box 1) (Weaire and Rivier, 1984); and cell shape (Graner et al., 2001). David A. Aboav and Denis Weaire observed that when a cell has many sides, its neighbours tend to have few sides, and vice versa (for reviews, see Rivier, 1994; Chiu, 1995). Rather than looking for perfection, these studies emphasized the importance of disorder and correlations in actual patterns. Some were extended to 3D (Avron and Levine, 1992; Klarreich, 2000).

Computer simulations of disordered assemblies in 2D or 3D

The 'Potts model', in which surface energy is minimised while all bubble shapes are described in detail with as many pixels as in experiments, was adapted for cells in 1993 (Glazier and Graner, 1993). A cell contour changes when one of its boundary pixels is assigned to another cell, and such movements are executed in order to decrease an energy designed to mimic the cell-scale ingredients. This model captures in detail the cell contour fluctuations when the cell wall is 'floppy' (Magno et al., 2015). Two other models for bubbles were introduced around this time. First, 'the Surface Evolver' is similar in principle to the Potts model, with wall discretisation being refined as much as is needed to obtain a better accuracy in equilibrated bubble shapes (Brakke, 1992). Second, in the 'vertex model' each vertex is a point that moves according to prescribed forces (Nagai et al., 1988), and vertices are connected by straight lines to defined polygonal bubbles. Such a model can incorporate friction and viscosity, and thus can simulate a rapid dynamic evolution.

During this period, we feel (on the basis of numerous conversations) that the rare attempts by mathematicians and physicists to apply their results to biology, in the style of Thompson, were rarely successful. They were often received coldly by biologists, who in turn were not motivated to apply such principles in their own work. A turning point was reached when Masatoshi Takeichi, a specialist of cell adhesion, validated with Steinberg the possibility of quantifying cell adhesion in agreement with the differential adhesion hypothesis (Steinberg and Takeichi, 1994).

Since 2004: modern renewal of the field

As experimental techniques were developed that allowed researchers to fluorescently label proteins involved in

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morphogenesis and to image them in living and developing embryos, new questions and needs arose in developmental biology. Alongside the advances in foam physics (see above), this created a situation in which physicists and developmental biologists were ready to join their efforts. In 2004, in the space of under four months, three groups published pioneering articles using *Drosophila* and its genetics that revived and renewed Thompson's approach. Bertet et al. (2004) linked germ band extension of the embryo with changes in cell contacts, in turn due to an increase in cell wall tension that was related to the local enrichment of cell walls in myosin II. Hayashi and Carthew (2004) observed visual analogies between cell packing in retina ommatidia and soap bubbles, including in mutants of cell numbers or of adhesion molecules. Zallen and Zallen (2004) compared the distributions of the numbers of cell sides in normal and mutant embryos: they showed that some results from foam packing were general enough to be transposed to tissues almost without adaptation.

Starting with these papers, biologists and physicists began to combine their questions, and developmental biology expanded beyond the gene-centric view that had been dominant over preceding years. They jointly searched for mechanisms to explain numerous old and newer observations, bridging scales from nanometer-scale molecular motors to tissue-scale readouts. For example, cell morphology studies involved the quantitative description of cell packing (Classen, 2005; Gibson et al., 2006), cell elongation and changes thereof (Graner et al., 2008), and were also extended to plants (Hamant et al., 2008). Live imaging of tissue with GFP-fused proteins in wild-type strains and in mutants enabled kinetic studies in developing organisms (Blankenship et al., 2006; Rauzi et al., 2008; Butler et al., 2009). This period was marked by interdisciplinary review articles (e.g. Lecuit and Le Goff, 2007; Hutson and Ma, 2008; Oates et al., 2009) and by the appearance worldwide of new interdisciplinary teams, articles, meetings and courses.

Adapting results regarding bubble shapes to biological contexts required some effort, addressing three debates dating from Thompson: (1) do cells in epithelia minimise their surface area, like in foams, implying that all cell walls have the same tension (Hayashi and Carthew, 2004); (2) are cell-cell contacts dominated by the role of adhesion (Steinberg, 1963) or cortical contractility (Harris, 1976); (3) can four-cell vertices last and be stable (see above)? These questions were solved together, when the idea that both adhesion and cortical contractility simultaneously contribute to cell wall tension (see e.g. Brodland, 2002; Ouchi et al., 2003) reached a consensus. Four contemporary articles (Lecuit and Lenne, 2007; Käfer et al., 2007; Farhadifar et al., 2007; Hilgenfeldt et al., 2008) showed that the tension, t, in a cell wall should not be reduced to adhesion only; in fact, adhesion usually has a negative contribution to t, which is made positive by the contribution of cortical contractility.

The interfacial tension $T_{AB}=t_{AB}-(t_{AA}+t_{BB})/2$ between aggregates made of cell types A and B results from the difference between the heterotypic wall tension t_{AB} and the average of the homotypic wall tensions t_{AA} and t_{BB}; similarly, with the medium: $T_{Am}=t_{Am}-t_{AA}/2$ and $T_{Bm}=t_{Bm}-t_{BB}/2$ (Graner, 1993). It is this interfacial tension that drives cell-sorting and the formation of boundaries between different tissue regions during morphogenesis (Fagotto, 2014). A larger interfacial tension between two aggregates, A and B, leads to partial or complete detachment. A larger interfacial tension between aggregate A and the outer medium results in B engulfing A. When the interfacial tension between A and B vanishes, they mix. This could be called the 'differential wall tension hypothesis' or, equivalently, the 'interfacial tension hypothesis'.

The analogy with foams thus applies, in the sense that cell packing can be described as being in mechanical equilibrium, with its shape minimising an energy. However, the analogy is limited; since cortical contractility is larger when the cell is deformed, the wall tension itself must be variable. Thus, the energy that the cell shape minimises is not just proportional to the contact surface area.

Nurturing exchanges to and from foam physics, this period revised and critically discussed former empirical observations. Rather than the correlation between cell side number and area suggested by Lewis, it can be the cell radius that helps predict cell side number (Hilgenfeldt, 2013; Durand et al., 2014) and the proportion of hexagons (Hilgenfeldt, 2013). The standard deviations of cell sizes and cell side numbers correlate (Durand et al., 2014). Also, the Aboav-Weaire anti-correlation between neighbours (see above) has been used to quantify the assembly disorder (Cantat et al., 2013).

In the spirit of Thompson's idea that physical mechanisms explain cell shape or dynamics, several possible 2D or 3D representations of cell assemblies on a computer have been introduced (Maclaren et al., 2015; Sharpe, 2017). In addition to the Potts model, there have been adaptations to epithelial tissues of the vertex model introduced by Honda (Nagai and Honda, 2001; Honda and Nagai, 2015), which improve on his former attempts, and of the Surface Evolver (Hilgenfeldt et al., 2008). These simulations could be validated against experiments, enable interpretations, and suggest how a cell-level mutation affects the tissue-level phenotype. Simulations also fit experimental data to infer the measurement of a parameter (Rauzi et al., 2008) and even sometimes lead to testable predictions (Krieg et al., 2008; Bardet et al., 2013).

Although the basic principles from foam physics apply to tissues, some theorems do not translate. As mentioned above, in 2D, cell walls are arcs of circles as in foams, but when three walls meet at a vertex their angles are not necessarily 120° (whereas they are in foams) and the sum of their curvatures is not necessarily zero (in contrast to in foams). More importantly, four- and even five-cell vertices can be observed for a long time and in large numbers, both in experiments and in computer simulations (Blankenship et al., 2006; Bardet et al., 2013); in fact, theoretically, under some circumstances they can be stable (Tamada and Zallen, 2015; Spencer et al., 2017). Finally, during development soft cell walls may rigidify, and the adult pattern retains only reminiscences of the mechanisms that affected the course of its development (Fig. 4).

In summary, image analysis based on modern microscopy, complemented with genetics experiments and computer simulations, led to a better understanding of the analogy between foam and tissue patterns, both described as resulting from wall tension. It also clarified the limits of the validity of this analogy: since the tensions of cell walls are not constant, some theorems valid in foams are only approximate, or wrong, in tissues.

The current state of the field: dynamical studies

The recent period has seen the introduction of exhaustive studies of cell processes and their effects on whole-tissue morphogenesis. Theoretical physics models with computer-aided data analysis and predictive models have been combined with genetics and live imaging of tissue dynamics across several scales (Etournay et al., 2015; Guirao et al., 2015). These studies have led to the determination, beyond visual analogies (Savin et al., 2011), of causal mechanisms for cell packing (Salbreux et al., 2012) and cell rearrangements (Guirao and Bellaïche, 2017).

Such merging of theoretical physics and morphogenesis dynamics increasingly relies on mechanical measurements of forces

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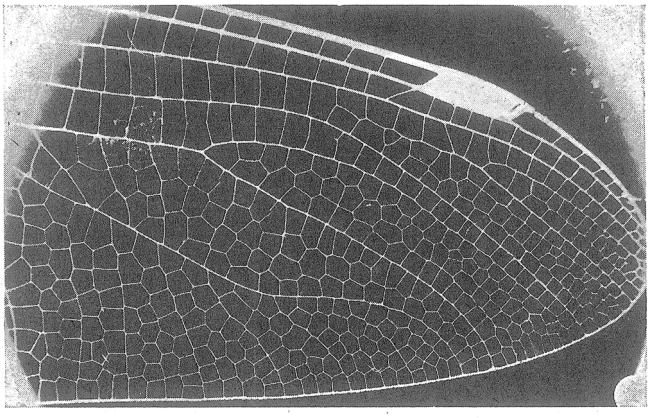

Fig. 162. Part of a dragonfly's wing.

Fig. 4. Adult dragonfly wing with visible veins, visualising contours of former cells from which they originate. Reproduced, with permission, from Thompson (1942) (not present in the 1917 edition).

(Heisenberg and Bellaïche, 2013), stiffness and viscosity (Serwane et al., 2017). Biology and physics have also combined their tools to manipulate and to measure these quantities. Several techniques, each with several variants, are currently tested to probe mechanical forces and stresses within living tissues: contact manipulation, manipulation using light, visual sensors, and non-mechanical observation techniques (Sugimura et al., 2016; Campàs, 2016).

Most of these techniques are in the spirit of Thompson, but this is particularly true for one of them: force inference (Ishihara and Sugimura, 2012; Chiou et al., 2012; Brodland et al., 2014). This consists of measuring cell wall shapes and angles, then explicitly assuming that they are determined solely by mechanical equilibrium dictated by the balance of cell wall tensions and cell pressure differences, to eventually infer wall tensions and pressures. When three walls meet at unequal angles, one can infer that their tensions should be unequal; the difference between observed angles and 120° provides information on the ratios of wall tensions. This can be implemented on thousands or millions or cells and generate space-time maps of mechanical stress fields within a developing tissue (Guirao et al., 2015).

In chapter VIII of *On Growth and Form*, Thompson echoed an already long-standing debate on what determines the orientation of symmetric cell division: a purely geometrical rule, where division occurs along the long cell axis, a principle of energy minimisation possibly controlled by tension, or an effect of mechanical stress orientation? The predictions of these three hypotheses usually coincide, making it difficult to disentangle them. However, a series of recent articles has addressed this question, indicating that all three can participate, probably with a dominant role of cell shape, encoded in molecular signals, and an indirect effect of stress (which in turn orients the cells) (Besson and Dumais, 2011; Minc et al., 2011; LeGoff et al., 2013; Campinho et al., 2013; Wyatt et al., 2015; Bosveld et al., 2016).

Thus, with force measurements complementing image analysis, Thompson's intuition about the role of mechanics can progressively be experimentally tested in various contexts, including the orientation of divisions. Reciprocally, forces can sometimes be inferred from image analysis.

Conclusions

Why did developmental mechanics take a century to flourish? Many factors probably contributed and only ideas can be suggested at this stage. The genetics and molecular biology approach has facilitated a revolution in our understanding of living matter and this became the almost exclusive focus of the developmental biology community. Since mutants could predictively change the shapes of cells, tissues and embryos, there was no real need after the 1950s to look with interest at the mechanics of the system. The sequencing of whole genomes probably also contributed to challenging the hypothesis that limited sets of genes could satisfactorily explain shape.

However, the lack of physical explanations began to be felt. Meanwhile, physics changed: 'soft matter' physics flourished in the 1960s and thereafter, and opened the way to the physics of living matter. Quantitative and predictive models appeared for reconstituted systems such as lipid vesicles and membranes; cells and tissues came next as a natural consequence. Experiments with physics designs and hypotheses appeared on living matter, first at the cell scale. In addition, developmental biology as a field has culturally deep roots in the engineering community (e.g. Wolpert, 1969; Brodland, 2002), and is probably receptive to accounting the contribution of mechanics in morphogenesis. This convergence of scientific interests set the stage for the modern renewal of the field.

Summary: considering Thompson's legacy…with due care

Over the 100 years since the publication of *On Growth and Form*, there has been a continuous lineage of ideas and research based on the hypotheses introduced by Thompson that were sometimes, but not always, made explicit. His legacy currently stimulates active research in which developmental biologists and physicists join their efforts. A century later, Thompson's intuitions are vivid in researchers' minds: for example, at least two articles have even included 'on growth and form' in their title (Hutson and Ma, 2008; Savin et al., 2011); while Brodland et al. (2014) chose Thompson's dragonfly wing picture (Fig. 4) to illustrate how their force inference method works. The effect of mechanical forces on gene regulatory pathways to specify cell fate is recognised as a contribution to robust tissue patterning during morphogenesis (Chan et al., 2017).

Overcoming disciplinary barriers, as a theoretician, Thompson provided guiding concepts of physics for living matter, and, as an observer, he taught researchers to perceive carefully what the system does. His idea that forces, and especially contact forces (wall tension, pressures), act to assemble cells and determine tissue shapes is now a generally accepted explanatory mechanism yielding testable predictions. Both adhesion and cortical contractility have been shown to contribute to cell wall tension. As cortical contractility depends on cell shape, shape feedbacks on wall tension, which is not uniform. Cells minimise an energy, which is not strictly proportional to wall surface area, and fourfold vertices can sometimes be stable. Tissue stress affects cell shape and orientation, which in turn affect wall tension and division orientation.

However, analogies between tissues and foams or liquids, whether regarding their packing or their flow, should not all be taken at face value. Each analogy has a limited domain of validity, and although some of them reach far enough to be fruitful and predictive, most are only valuable for the methods and approaches that they suggest. As a pioneer, Thompson certainly made approximations and simplifications. His search for order and perfection has had to be replaced by characterisations of actual disorders and imperfections, which is scientifically as rewarding. Matzke, among others, has experimentally demonstrated the dangers of leaping from mathematical models to real-world conclusions (Klarreich, 2000).

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Other oversimplifications have been propagated throughout the literature. We warn that intuitive correlations, such as those observed by Lewis, Aboav and Weaire regarding the relationship between the numbers of sides of neighbouring cells, should not be instilled as rigid 'laws'. Computer simulations are powerful only if they are used in line with the question under consideration, keeping in mind their specific advantages and drawbacks, as well as their underlying hypotheses. Force inference should be used only within a context in which its hypotheses are valid. The important role of tensions and their differences in shaping cells and tissues will benefit from recognising the distinction between wall tension and interfacial tension.

While Thompson's principles certainly guide intuition and suggest research directions, we must apply them, and/or generalise them, only with critical examination, and using standard experimental control methods.

Perspectives: extending Thompson's legacy

A century after the writing of the book, Thompson's vision can be revisited with fresh eyes. The main molecular actors are known (acto-myosin, cadherin, the Rho signalling regulatory pathways), the physics of living matter has matured, and mathematical models of tissues can be implemented using computers. Shapes can be followed in developing embryos over long time-scales with cellular resolution and quantitative measurements of cell shapes, protein densities and localisations, and local and global rheological measurements. The coming years should see the emergence of predictive models testing experimental readouts, such as adhesion and motor protein density and localisation, cell and tissue shapes, cell sorting, and local and global mechanical characterisations. This situation in which formalisms meet experimental tests through theoretical approaches and computer simulations has always been a good moment in physics to promote new interdisciplinary ideas. We would argue that, a century after publication, the influence of Thompson's work has been instrumental in this endeavour.

Still, a key issue involves keeping in mind scales and biological functions: proteins and nucleic acids contribute to changing mesoscopic parameters such as wall tension and friction, which have relevance at the micrometer scale, a scale 1000 times larger than a single molecule. A physical model will highlight conservation laws, symmetries, and use these mesoscopic parameters. As such, mutual expectations between biologists and physicists should be frankly formulated: mutants isolated from screens can be essential to probe new morphogenetic events, but links between the deleted genes and the model will have to be complemented by renewed measurements of motor/adhesion densities, cell shapes, and mechanical characterisations. On the other hand, the model will need to take into account the inherent specificity of living matter and the degree of adaptation; cells can change adhesion and motor activity over the course of morphogenesis events, and this feature is not yet encoded in either the founding hypothesis or the equations of some models. In other words, the systems biology of the Rho pathway/cytoskeleton should be appropriately merged with the equations of the physics of active matter to highlight the specific nature of tissues. This should lead in turn to formalisms encoding information of the signalling pathway and changes in shapes, with predictive power and experimental tests. A truly multiscale approach is appearing and should be encouraged, where each scale is given equal importance, and with special emphasis on both bottom-up and top-down mutual feedbacks between scales.

This shift in paradigms in the biology and in the physics communities calls eventually for new education programs and revised research strategies. To what extent could the example of Thompson be a source of inspiration? Thompson had an authentic double education. He interacted closely with a small community with mutual trust and patience in probing ideas. He also tested hypotheses with a thorough exploration over decades of available observations and measurements. This slow pace in thinking might be a prerequisite in progressing in this interdisciplinary adventure and, beyond the scientific legacy of Thompson, through the clarity and visionary nature of his book, his own style in being a scientist could be exemplary for the modern scientist as well.

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Competing interests

The authors declare no competing or financial interests.

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