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ORIGINAL PAPER

Model and movement: studying cell movement in early morphogenesis, 1900 to the present

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Abstract Morphogenesis is one of the fundamental processes of developing life. Gastrulation, especially, marks a period of major translocations and bustling rearrangements of cells that give rise to the three germ layers. It was also one of the earliest fields in biology where cell movement and behaviour in living specimens were investigated. This article examines scientific attempts to understand gastrulation from the point of view of cells in motion. It argues that the study of morphogenesis in the twentieth century faced a major dilemma, both epistemological and pictorial: representing form and understanding movement are mutually exclusive, as are understanding form and representing movement. The article follows various ways of modelling, imaging, and simulating gastrular processes, from the early twentieth century to present-day systems biology. The first section examines the tactile modelling of shape changes, the second cell cinematography, mainly the pioneering work of the German embryologists Friedrich Kopsch and Ernst Ludwig Gräper in the 1920s but also a series of classic, yet not widely known, studies of the 1960s. The third section deals with the changes that computer simulation and live-cell imaging introduced to the modelling of shape change and the study of cell movement at the turn of the twenty-first century. Although live-cell imaging promises to experiment upon and represent the living body simultaneously, I argue that the new visuals are an obstacle rather than a solution to the puzzle of understanding cell motion.

Keywords Cell motion · Cinematography · Embryology · Gastrulation · Live-cell imaging · Simulation

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1 Introduction

Morphogenesis is the process by which the organism develops its shape. The most dramatic morphogenetic event in the developing embryo is gastrulation. Following the formation of the blastula (a hollow sphere made of cells called blastomeres), the single layer of the blastula becomes differentiated into the three germ layers, the ectoderm, mesoderm, and endoderm, by means of various types of inward folding, curving and bending. Gastrulation differs considerably in different groups of animals, but generally speaking the process brings inside the embryo cells that lie further outside in order to form the germ layers, which subsequently give rise to all future structures and organs of the animal. This process marks a period of major cell movements, translocations, and rearrangements, and enormous activity inside the ovum. Its common characteristics are changes in cell motility, cell adhesion, and cell shape; however, the ways that the cells move are manifold, showing great spatio-temporal variability and complexity both within and across the various species.

The aim of this article is to examine the history of attempts to analyse and understand early embryogenesis from the point of view of the study of cellular motion. I follow the study of gastrulation, arguably one of the most puzzling and fundamental biological problems, from the early twentieth to the beginning of the twenty-first century. As early as the end of the nineteenth century, cell movements were found to be of major relevance for the gradual shaping of the embryo's vessels, tissues, and organs. At the same time, making sense of cells in motion presented scientists with a substantial challenge. Cells could be observed in motion in the living specimen, but the organisms examined under the microscope were stained, fixed, and cut into slices. Working with dead substances, movement could not be seen. How, then, could it be framed? Conversely, if studied in the living specimen and hence visible but fleeting, how could movement be captured, traced, or archived? Tackling the question of how to make cell movement visible simultaneously meant making it intelligible. Even more importantly, once cells were seen and investigated as moving actors, a new and major problem immediately arose: How do cellular movements bring about the shapes of the developing organism? How should one understand the emergence of form out of hundreds of diverse, delicate, erratic movements?

Embryology was one of the first fields in biology to engage with these questions, and gastrulation one of the earliest problems to be examined with the help of cinematographic technologies. For a decade or two now, historians of science, especially of the life sciences, and media scholars have researched the use and adaptation of animating devices for scientific and educational purposes, ranging from Muybridge's and Marey's chronophotography up to modern computer animations (to name just a few: Banner and Ostherr 2015; Cartwright 1995; Coopmans et al. 2014; Curtis 2015; Dagognet 1987; Gaycken 2015; Landecker 2006; Olszynko-Gryn 2017). Recent technologies of live-cell imaging, which make it possible to follow and record the behaviour of cells live in action through fluorescent marking, led to whole new research agendas, revolutionizing biology in the twenty-first century both visually and epistemologically (Landecker 2012). Although such research has rightly stressed the entanglement of science and culture,

technology and understanding, media and scientific practices, little has been said about how exactly our framing and understanding of a particular scientific problem emerged, developed, was channelled, or broadened due to new perceptions, new strategies of experimenting with, and new visual renderings of organisms that were in motion instead of stilled.[1]

Art history has long pondered questions around the perception of movements or events, their representation in pictures (especially still images), cultural contexts, and the beholder's frameworks of knowledge, all of which prepare us to "see" movements or events in a picture (see, especially for Gestalt theory, Arnheim 1965, ch. 8; Gombrich 1960, 1964, 1982; also Panofsky and Saxl 1923; Warburg 1932). The art historian Ernst Gombrich explained that in order to read a still image as conveying motion, "the movement must result in configurations that can be easily understood"; there also have to be "clear contextual clues" (Gombrich 1982, pp. 79, 81–82). From our reading of spatial relations in a picture, Gombrich derives the "principle of the primacy of meaning" for our understanding of events: in order to assess a distance between objects in space, we need to identify the objects and estimate their sizes. Similarly, in order to understand "the passage of time in a picture", we have to "interpret the event represented" (Gombrich 1964, p. 302). In other words, the more clearly we understand the event we witness, the more likely we are to be able to see the movements depicted (Gombrich 1964, p. 304).

Gombrich's reflections on still images point to the intricate entanglement of seeing movement and understanding form, and vice versa. In this article, I will apply his acute observations to the scientific study of cell movements in still and moving pictures. This will take us to a problem crucial for the study of movement in the microscopical world but hitherto largely overlooked: in morphogenesis, we cannot easily discern either form or movement. This is not only a problem of seeing and interpreting, of making perceptible and intelligible at the same time. Rather, movement and shape, behaviour and form have to be worked out in relation to one another. Looking at the history of morphogenesis from this point of view, I will take the opposite stance to the prevailing research. There, *seeing* motion on a screen is generally considered equivalent to *understanding* motion, with moving images providing the seemingly obvious (technical) solution to the problem of understanding movement. I will argue instead that seeing and understanding cells' movement was hard scientific work. For the case of gastrulation, I show in this article that throughout the twentieth century the study of form and the study of motion were two distinct approaches. Either form was studied at the expense of movement or movement at the expense of form, each approach coming with its own very different methodologies, experiments, and epistemological frameworks.

Separating form and movement to look at them as two distinct perceptual and intellectual problems that have to be brought together in order to understand morphogenesis, I examine and juxtapose a series of pioneering works, all

[1] Landecker and Kelty first elaborated on the "helix of the perceptible and the intelligible" in studying the animated organism in biology in a paper that still serves as a point of reference (Landecker and Kelty 2004, p. 33). Landecker also argued that live-cell imaging started out in the 1990s as a program in genetics to see the "genetic code unfolding itself" on the screen, but after 2000 surpassed and abandoned the gene, turning instead into the animation of biochemical knowledge (Landecker 2012, pp. 379, 390).

referencing each other but not previously discussed together. The first section of this article examines the mechanical study of development by way of tactile physical models to track cell shape changes. The second section is dedicated to cinematographic experiments to capture gastrular cell movements, as introduced by the German embryologists Friedrich Kopsch and Julius Gräper, pioneers in the application of cinematography to embryology, but also as described by Tryggve Gustafson and Lewis Wolpert in a classic series of papers from the 1960s. The third section deals with developments following the introduction of computation, in simulating shape changes, and in live-cell imaging. In modern systems biology, fluorescent marking, live-imaging, heavy computation, and simulation all promise to integrate information across the different levels of the body's organisation (molecules, genes, cells, organs, environment) in a way inconceivable in the pre-computer era, and to access, collect, and display all this integrated information while the body is alive and unimpaired by the operations and procedures imposed on it (Boogerd 2007; Kitano 2002; Schneider 2013; Wake 2008). The new visuals, it has been argued, also open new epistemological paths—to a new, "molecular vitalism" (Kirschner et al. 2000) or a "new vitalism unfolding on the screen" (Landecker 2012, p. 381). I argue that the gap between the movements of life and the knowledge of science in the twenty-first century does not yet seem to be closing and that the visuals are an obstacle rather than a solution.

2 Shaping cells

The last decades of the nineteenth century brought a new experimental approach and mechanistic thinking to the study of embryogenesis. The *Entwicklungsmechanik* or developmental mechanics proposed by Wilhelm Roux (1850–1924) was among the most prominent articulations of search on the mechanisms of organ formation around 1900 (see Mocek 1998; for a broader perspective, Dupont 2017). In this tradition, Ludwig Rhumbler (1864–1939) applied mechanistic ideas to gastrulation in his 1902 treatise *Zur Mechanik des Gastrulationsvorganges insbesondere der Invagination.* Trained in Berlin, Strasbourg, and Göttingen, Rhumbler early on developed a notable interest in cell physiology, especially the study of protoplasm and cell division. Professor of zoology from 1906 until his retirement in 1929 at the Preußische Forstakademie Hannoversch Münden, at the time not a university but a provincial college, he was confined to the margins of German academe and aligned his later research with the study of forestry (Bartenstein 1964; Eidmann 1930; Spek 1939).

The aim of Rhumbler's treatise on gastrulation is to "dissect living events into their physical–mechanical factors". Mechanics, as Rhumbler defines it, is "the science of movement in time and space", and as morphogenesis is an event of the "mass movements" and "rearrangement of substances" in the developing egg, mechanics is the appropriate framework to study it (Rhumbler 1902, p. 401).[2] One way to apply mechanistic principles to the study of emerging form around 1900 was

[2] Unless otherwise noted, all translations from German are mine.

to build physical, tactile models, in which the different materials combined to mimic various mechanical properties of the organic structures in question (see, for example, the work of Wilhelm His, discussed in Hopwood 1999).

For the model Rhumbler devised for use in his lectures, he chose "corset bones", "cloth-covered steel slats with a hole at each end", like those "generally to be found in any ladieswear store" (Rhumbler 1902, p. 403). Rhumbler bent the corset slats into hoops of different sizes. The slats stood in for the cells, with broader ones at the vegetal pole and narrower ones at the animal pole. He lined the hoops up and bound them together with a thin, soft wire threaded through the holes at the ends of the slats (see Rhumbler 1902, p. 403).[3] In amphioxus (lancelet), the organism he studied, the blastula consists of only a single layer of cells, so that the model could mimic the "tight epithelial cohesion of the blastomere", the wedged cell shape and the flatness of the blastula at the lower side.

Rhumbler's investigation into the mechanics of gastrulation starts with a given form: the blastula. At the beginning of gastrulation, the blastula, a hollow sphere made of a single layer of cells, is slightly flattened at the bottom; by the end of gastrulation, as a result of the inward folding of the blastula, the gastrula has formed, which now consists of the three germ layers. The aim of the mechanical model of gastrulation is to account for the original spherical shape of the blastula at the beginning and explain its shape change, that is, the invagination or inward curving of the hollow sphere. The plate in Fig. 1 shows different variations of pulling strings, exerting pressure on the ring and its elements, and tracks the resulting shape changes. In Fig. 7 of the plate, for example, two outlines of different shapes are juxtaposed in a single depiction to compare them at a glance, one showing the original shape of the model, the other its deformation when pressure is applied by a weight pulling at the strings.

With the model, Rhumbler was able to test the various ways in which the shape could be deformed. More precisely, he simulated three different possible mechanisms driving invagination: (1) differential growth of entoderm and ectoderm, (2) differential growth of the egg membrane, and (3) reduction of the blastocoel fluid. The main mechanical problem he encountered was that exerting pressure on the sphere to cause deformation leads to protrusion, not invagination. For this reason, he concluded that none of these mechanisms alone explains the invagination of the blastula (Rhumbler 1902, p. 429). Rather, the individual cells first have to change into a wedge shape to enable the inward curving of the whole cell sheet, a process today known as apical constriction (Rhumbler 1902, p. 438). This change is caused by a shifting of substance inside the cell, reversing its shape so that the outward-facing cell border now becomes shorter than the one facing the cavity of the blastula (Rhumbler 1902, pp. 440, 438, 432).

Rhumbler set out to study the "mass movements" and the "living events" in morphogenesis. He was also much interested in how to draw the boundaries

[3] More precisely, the model consists of 20 hoops or circles altogether, six at the upper pole made of shorter slats 18 cm in length, followed on each side by two made from longer slats of 20 cm, three of 22 cm, and finally closing the ring with four circles made of 24 cm slats (Rhumbler 1902, p. 404).

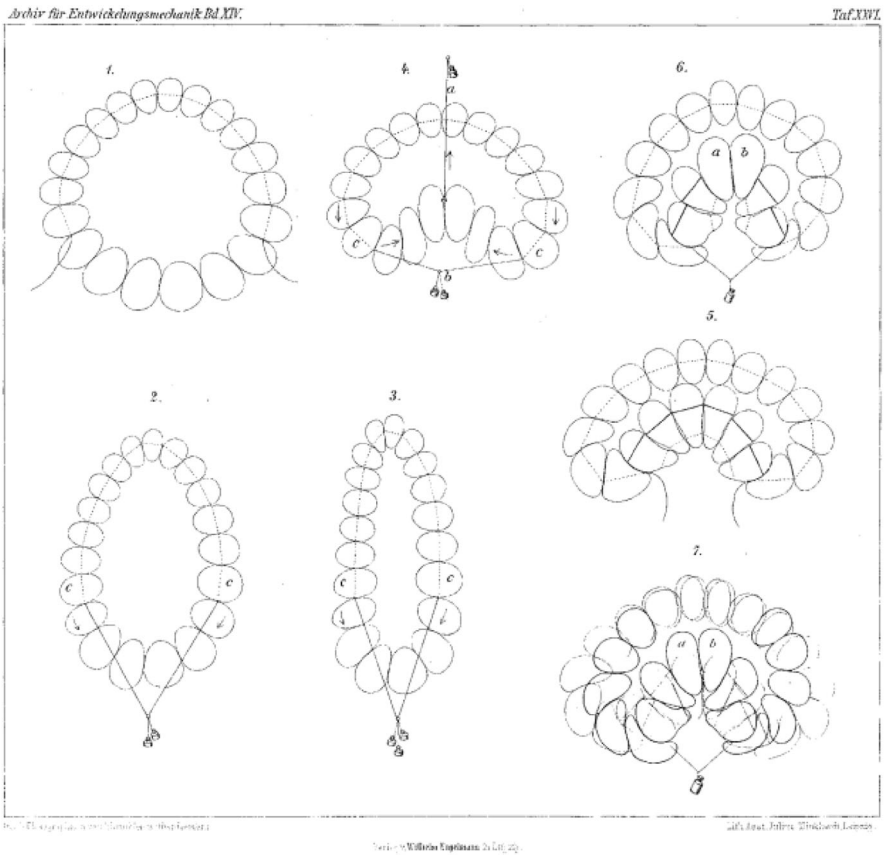


Fig. 1 Plate accompanying Rhumbler's 1902 publication. It shows the model fabricated of corset bones of different lengths, lacing, and wire. Rhumbler 1902, Plate XXVI

between living and dead substance and extensively studied protoplasm. He held that cells are made not of a "uniform liquid" but of "foamy structure". Living substances, thus, are not "simple liquids" but "plastic substances"—they are "variable" and "adaptive". Rhumbler also examined that "living cells under pressure act like plastic masses" (Rhumbler 1902, p. 421) and that only dead cell substance actually behaves mechanically like a fluid. "Rigid in its structures" (Rhumbler 1902, pp. 418–419), Rhumbler's corset bones, however, not only simulated living events and variable movements by framing them as the geometrical problem of shape change. They also only simulated the behaviour of the "cell contours", not the whole cell, because he postulated that the plastic inner cell substance did not affect the entire blastula's shape change (Rhumbler 1902, pp. 404–405). In other words, to reconcile his mechanistic approach with the malleability of living matter, Rhumbler simulated no living substance, but dead cells.

Almost fifty years later, the residual vitalism still palpable in Rhumbler's reasoning had disappeared. In 1947, Warren H. Lewis (1870–1964) redesigned Rhumbler's model, this time with brass bars and rubber bands (Lewis 1947, p. 140). Using the rubber bands, varying in number and variously distributed to exert different tensions on the brass bars (simulating the boundaries of the adhering cells), he tested apical constriction by physically simulating cell sheet changes as well. Like Rhumbler's, Lewis's model produced several possible epithelial sheet foldings, and he found that invagination occurred on whichever side of the cell was exposed to greater tensions (Lewis 1947, p. 155). Tactile models physically simulated various changes and conditions to test the range of mechanisms of cell sheet bending and their plausibility. But forms and models made from wire and rubber were difficult to calibrate and limited in range, and they soon started to be replaced by equations and finite element simulations. Scientists began frequenting computer shops rather than ladieswear stores.[4]

3 Filming cells

Around the same time as Rhumbler's tactile simulations, the German anatomists and embryologists Friedrich Kopsch (1868–1955) of Berlin and Ludwig Gräper (1882–1937) of Jena embarked on a different way to study gastrulation. Trained under Oskar Hertwig and Wilhelm Waldeyer, Friedrich Kopsch held a teaching position as prosector for the anatomy institutes at the University of Berlin for many years. He became a full professor of anatomy and embryology there only in 1935. His anatomical knowledge fed into the many editions of his handbook on human anatomy, for which he is mostly known today (Richter 1985; Waldeyer 1955). Ludwig Gräper is also a little-known figure in German embryological research. He studied in Leipzig under Carl Rabl and served as an assistant to Carl Hasse in Breslau. Although his extensive publications on embryology were internationally recognized (he was one of the few members of the Utrecht Institut d'embryologie), he was never appointed to a major post in Jena. Gräper himself suggests that this was due to the Jena tradition of comparative anatomy and morphology going back to Carl Gegenbaur, which did not welcome his experimental approach (Gräper 2004; Peter 1937). Kopsch and Gräper approached the problem of organic formation from the novel perspective of movement and with a new, cinematographic methodology. Their seminal work and major experimental and technological innovations, however, are largely forgotten today.

In his 1895 article *Ueber die Zellen-Bewegungen während des Gastrulation-sprocesses* Kopsch, like Rhumbler, conceives of gastrulation as an event of "cell displacement" (Kopsch 1895b, p. 21). Unlike Rhumbler, however, Kopsch does not interpret cell displacement as the deformation of the spherical blastula shape. He

[4] During his long scientific career in embryology, Warren H. Lewis also used cinematography for his research, starting in 1929 at the Carnegie Institution of Washington (Landecker 2004). For this late study of invagination, Lewis teamed up with the physics department at the Wistar Institute in Philadelphia, his home institution at the time. Along with Rhumbler's, his model continues to be a reference to this day (Davidson et al. 1995).

follows the inverse path, examining single cells and their trajectories throughout gastrulation to find out how their displacement creates the new form of the gastrula. Consequently, Kopsch invents a new method, one that can track the movement of single cells or cell groups during the whole period of gastrulation in the living egg and avoids artificial conditions to the greatest possible extent (Kopsch 1895a, p. 182, 1895b, p. 23). Around 1900, he was one of the pioneers in using serial time-lapse photography to explain gastrulation in axolotl and frog eggs—in fact, he provided the first concrete evidence for cell movement in gastrulation (Beetschen 2001, p. 781).

To discover the size of the cells and the direction and speed of cell movement, thereby following the changing form of the blastopore, Kopsch chose a continuous series of microphotographs, taken at intervals of one to several hours. What makes his photographic approach remarkable is that he exposed his photographs for 20–30 min. This exceptionally long exposure time—he terms his photographs "Daueraufnahmen"—inscribes moving cells as a blurred trace onto the paper, their nuclei taking the shape of strokes rather than spots, whereas immobile cells are clearly discernible by their sharp cell borders (Kopsch 1895a, p. 183, 1895b, pp. 24–25).

Studying the movement of cells is anything but self-evident, and it prompted major methodological reflection for Kopsch. He argued that working with histological sections, the usual approach at the time, yielded conclusions that were too "diverse" and "subjective" to be valuable. It was of prime importance to follow the displacement of cells "in one and the same egg" (Kopsch 1895b, p. 23). Due to the amphibian egg's size, opacity, and spherical shape, only movements on the surface of living eggs are discernible, Kopsch writes (Kopsch 1895a, p. 182). In addition, cell movements in gastrulation take place in the vegetal hemisphere of the egg, facing away from the observer (Kopsch 1895a, p. 182). To enable observations, therefore, the microscope has to be inverted (Kopsch 1895b, pp. 24–25). No less experimentally demanding is the need to ensure the visibility of each individual cell. Kopsch rejects placing experimental or natural marks and fixing the cells in a set position, as practised by his contemporaries Wilhelm Roux, Oskar Schultze, and Eduard Pflüger. This is because, firstly, the extent of destruction in the cells caused by these methods cannot be known, and, secondly, if the amount of dead cellular material is large it might modify the regular course of gastrular movements (Kopsch 1895a, p. 182, 1895b, p. 24).

Kopsch's observations and distinctions concerning the various cell types and their movements are precise and detailed.[5] He distinguishes between macromeres and micromeres. The former are larger cells, characteristic of the vegetal hemisphere of the blastula; they show the "liveliest and fastest movement", move along the "curvature of the spherical surface", and are pushed into the interior of the egg. The smaller cells or micromeres are found in the animal hemisphere. Some of them "fold into the interior of the embryo", and others, close to the lip of the

[5] In amphibians, gastrulation starts in the marginal zone, an area surrounding the equator of the blastula, where the animal and the vegetal hemispheres meet. It begins with the invagination of the epithelial sheet inward to form the dorsal lip of the blastopore. Amphibian gastrulation varies across different species. For a detailed account, see Beetschen (2001).

blastopore, move the opposite way (Kopsch 1895b, p. 26).[6] Kopsch characterizes macromere movement as a steady, "broad stream" of cells inside the blastopore, "swollen from the sides" by an influx of new cells; the movement of the macromeres close to the blastopore is accelerated and of those further away is slowed down (Kopsch 1895b, p. 26). Observing the formation of bottle cells, Kopsch describes their change of shape at the lip of the blastopore, where he sees them "elongating in the direction of their movement" (Kopsch 1895a, p. 183).[7] He also tells us that these movements continue until the blastopore attains a u-shape. The blastopore is later closed by the macromeres (forming the yolk plug, *Rusconi'scher Dotterpfropf*) and successively "contracts like a rubber band" (Kopsch 1895b, pp. 26–28) (Fig. 2).[8]

Thanks to this nuanced description of cells—their shapes, movements, directions, speed, and behaviour—Kopsch believes he has given sufficient proof of the "continuous invagination" of cells from "the very beginning of gastrulation… up to the disappearance of the yolk plug" (Kopsch 1895b, p. 28).

Starting from movement rather than from shape, Kopsch found a dynamics of cellular displacements during gastrulation that was much more complex than the deformation described by Rhumbler. Yet cellular movements were actually even more complicated. Kopsch had observed how cells change their trajectories and move in opposite directions when the micromeres move towards the dorsal lip of the blastopore, the macromeres away from it. This opposing directionality initiates a rotation of the egg that ultimately intensifies the downward displacement of the dorsal lip (Kopsch 1895a, p. 187). But to uncover the exact, manifold and three-dimensional cell trajectories inside the developing egg, Kopsch's "Dauerphotographien" did not suffice. In the mid-1920s, he therefore turned to cinematographic devices and time-lapse cinematography (Kopsch 1930).[9]

3.1 Polonaise

Antagonistic, multidirectional movements inside the egg also intrigued Ludwig Gräper, who started his own cinematographic investigations of chick embryos in

[6] The unequal size of the cells in the two hemispheres of the egg are the result of unequally rapid cell divisions at the animal and the vegetal pole (Kopsch 1895b, p. 22).

[7] The invaginating cells change their shape and are called bottle cells due to their elongated shape. These invaginating bottle cells initiate the formation of the archenteron (primitive gut).

[8] Today, the process Kopsch describes is known as involution. Involution describes the rolling inward of the epithelial sheet, forming an underlying layer: when the migrating cells reach the dorsal lip of the blastopore, they turn inward and travel along the inner surface of the outer animal hemisphere cells. At the dorsal lip, therefore, cells are constantly moving and new cells are entering the embryo. In the process, the blastopore lip expands, widens, and forms a circle, closed by a yolk plug which is eventually internalized as well. These movements bring the endodermal cells into the interior of the embryo; the ectoderm has encircled the surface and the mesoderm has been brought between the two layers (see Gilbert 2014).

[9] He first showed his films at a 1926 meeting of the Anatomische Gesellschaft in Frankfurt. Kopsch applied the uncommon practice of exposing his films for almost the entire period of filming (Kopsch 1930, p. 245).

Krümmung der Erdoberfläche folgend, sich durch den Blastoporus, gleichsam wie durch eine Pforte in das Innere des Eies begeben (Fig. 1).

Fig. 1.

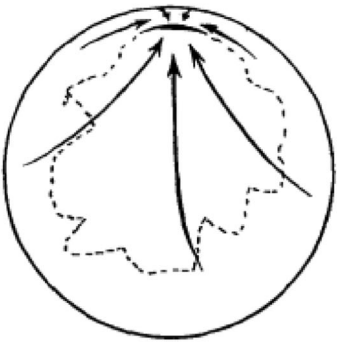


Fig. 2.

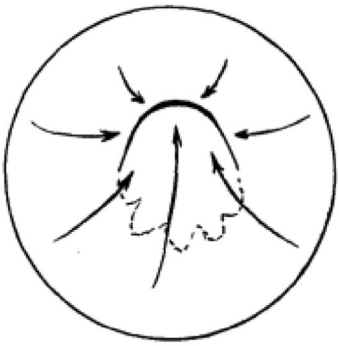


Fig. 3.

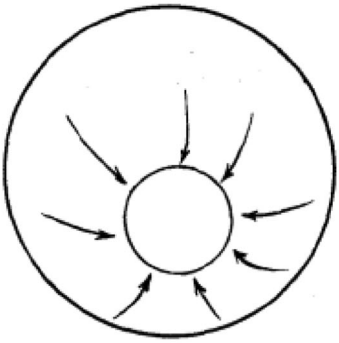
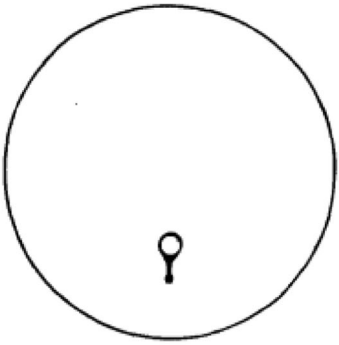


Fig. 4.



Aus der schmalen Spalte, als welche der Urmund im Anfang erscheint, bildet sich der U-förmige Blastoporus dadurch, daß die freien Enden desselben an Länge zunehmen, indem sich neuer Umschlagsrand bildet. Zugleich erfährt die dorsale Blastoporuslippe sowohl bei Eiern, welche in Zwangslage sich befinden, als auch bei normal gehaltenen eine Verlagerung derart, daß sie sich allmählich dem unteren Eipole nähert. Während dieser ganzen Zeit findet, wie schon oben erwähnt wurde, an der dorsalen Blastoporuslippe der Umschlag von Zellen statt, welcher am beträchtlichsten ist an den freien Enden des Blastoporus, nach der Mitte desselben allmählich abnimmt und dort am geringsten ist. Die Makromeren bewegen

Fig. 2 In these schematic drawings, Kopsch indicates the various cell movements at successive moments of gastrulation. Kopsch (1895a), p. 184

Leipzig and Jena around the same time as Kopsch. Like Kopsch, Gräper believed that time-lapse cinematography could resolve "points of scientific dispute" (Gräper 1926, p. 54). On film, he writes, the "flows and shifts of cell substance" inside the egg are rendered "with convincing clarity", and thus allow an "intimate glimpse" into the "morphology and physiology of development" (Gräper 1926, p. 55) as well as the opportunity to "truly 'take part' in the events" (Gräper 1929b, p. 383). Of all scientific methods, only continuous filming of a single living specimen can do justice to the enormous variability and individuality characterizing developmental processes—for though "descriptive", filming is a "research method", even one superior to experiments (Gräper 1928a, p. 90, also pp. 93–94). In particular, research carried out on large numbers of fixed specimens results only in "statistical" values (Gräper 1911, p. 323, 1929b, p. 387) and sections of embryos offer only a "dense succession of snapshots". These are insufficient to determine precisely "which points of a previous stage correspond to particular succeeding ones" or to track actual movements in living cells (Gräper 1929b, p. 387). More significantly, filming throughout the whole of embryogenesis is a more accurate way than experimenting to distinguish normal variability from pathological deviation (Gräper 1928a, pp. 90–91). The puzzle of countercurrent cell movements was one of the pressing scientific questions film should help to solve. After years of constant labour on experimental set-ups, imaging devices, and technological refinement, Gräper was the first to build and put to use a stereocinematographic apparatus (Michaelis 1955, p. 58). This finally enabled him to solve the mystery of cells moving in opposite directions and dimensions in the chick embryo. Stereocinematography revealed that they were dancing.

Gastrulation in birds is set off by the formation of the primitive streaks (Gräper 1929b, p. 400, also 1926, p. 55). To understand where the cells come from and how exactly they are exchanged between the surface and interior of the egg to form the two parallel streaks in the centre, spatial depth and differentiation are crucial. Stereocinematography provided the high degree of three-dimensionality needed to see and depict those movements. In stereocinematography, two images are taken separately for the left and right eye, and by taking them not simultaneously but sequentially, with a slight delay, Gräper could make the cells' movement visible in space (Gräper 1929a, p. 525, 1929b, pp. 383– 384).[10]

In this way, Gräper's investigation of chick embryos revealed that the primitive streak forms through a "double countercurrent", an elaborate, highly ordered, and carefully orchestrated cell movement (Gräper 1929b, p. 401). To make sense of it, Gräper compared the movement with a dance, more precisely the polonaise, which he describes as follows: "The couples move along in two columns on opposite sides of the ballroom, swing in toward the middle at the end and, joining hands, move forward through the middle in fours" (Gräper 1929b, p. 391). Just like couples on the dance floor, cells dance inside the egg, as the caudal cell masses "swing in toward the middle" and move upward at the same time as the cranial and lateral

[10] On stereocinematography, see Liesegang (1926, pp. 106–109, 1920, pp. 190–211). On Gräper's stereocinematographic investigation, see Liesegang (1920, p. 288); Michaelis (1955, pp. 31–32, 58, 116). Gräper himself gives a detailed account (Gräper 1928b).

masses move toward the tail end (Gräper 1929b, p. 398).[11] Through additional movements, cell material is exchanged between surface and interior: in the "layer closest to the surface", "forward-flowing material" is replaced by other material that flows from the centre and the sides (Gräper 1929b, p. 391) (Fig. 3).

In fact, cell movements during gastrulation are still more complex than that. Gräper also describes how, in order to form the medullary folds, material is pushed from the area opaca forward and sideways in an "arching" movement. He observes that the vessels in the area opaca are formed by cells of their own, but also by those of neighbouring areas, and that the cells forming the amnion are transported "both from behind and in a twirling movement from the front" (Gräper 1926, p. 56).

These early cinematographers regarded cinema as a novel research method. Studying form by aggregating information from many specimens, sections, or snapshots was a statistical approach, which they believed did not contribute to understanding movement and explaining morphogenesis. Promising to render cell movements visible in a single specimen, film seemed to be the prerequisite for the scientific analysis and explanation of the phenomenon of movement. Only with film as a descriptive device to trace movements did the phenomenon they wanted to examine begin to exist. Perhaps even more importantly, they understood that when gastrulation was studied from the point of view of the deformation of shape or from that of the movements contributing to organ formation, these were not just ways of looking at the same thing from different angles. Rather, movement (whether collective or of single cells) and development vary greatly not only between different species, but equally within one species: the same structures might be the result of many different chains of events. Hence, studying form did not necessarily provide the information needed to understand the process that brought it about; conversely, movements could be very diverse and still result in the formation of the same shapes.

3.2 Cell behaviour

With World War II, the pioneering work in cell cinematography in Germany came to a halt. A generation of researchers died—Gräper died in 1937, though he continued to make films until then—or only briefly returned to the university, as did Kopsch when Berlin's university reopened in 1946.[12] After the War, it was in laboratories in the rest of Europe and the United States that cinematographic

[11] Gräper points out the same countercurrent movement in amphibians (Gräper 1929b, pp. 399–400).

[12] More research remains to be done in this field. Beetschen holds that Kopsch's findings, which ought to have changed the course of research, failed to convince his contemporaries (Beetschen 2001, p. 781). Kopsch and Gräper, on the other hand, were both devoted teachers, though we know little of their many students and their careers. Involvement with National Socialism may also be a reason why there has been little research on Gräper: he seems to have been a member of Stahlhelm and the SA, and from 1932 to 1938 the Jena Anatomical Institute was headed by a member of the Nazi Party and SS, Hans Böker (1886–1939), see Hoßfeld et al. (2003). Three of Gräper's films were commissioned in 1936 and 1937 by the Reich Office for Educational Film, which was created in 1934.

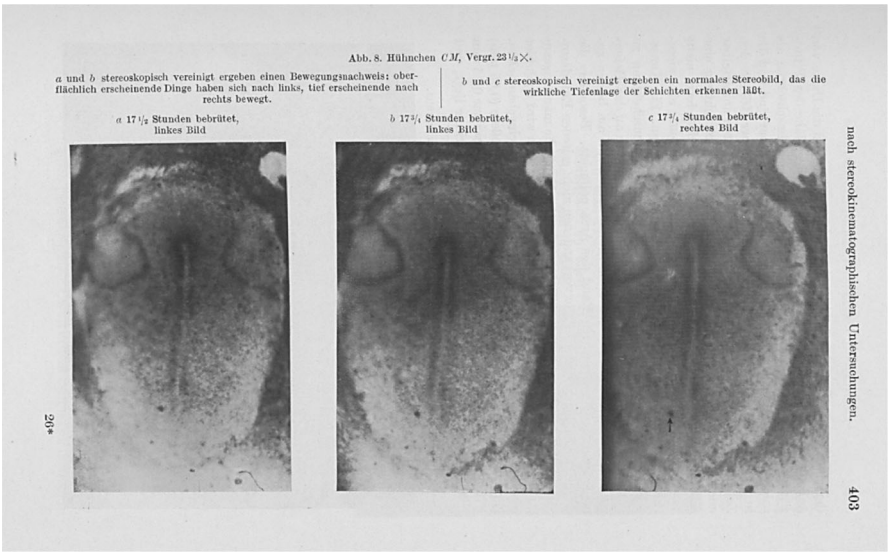


Fig. 3 The arrow in **c** of Gräper's series of stereocinematographic images shows the displacement of cellular material in the depths of the embryo. Gräper 1929b, Fig. 8, p. 403

research into cell movement and cell behaviour thrived.[13] In the field of embryology, Tryggve Gustafson from Stockholm University and Lewis Wolpert at University College London were among its leading proponents. In the 1960s, they dedicated a series of highly influential papers to sea urchin morphogenesis, work that can be considered classic but is largely forgotten today (Gustafson and Wolpert 1961, 1963, 1967).[14] For the purposes of this article, their investigations are especially relevant. Firstly, Gustafson and Wolpert approached morphogenesis as a problem of cellular morphological events. As such, they contradicted molecular and biochemical research of their time, arguing instead that understanding morphological events is a prerequisite for the biochemical and molecular study of development, as opposed to using "morphological events… only as indicators of biochemical changes" (Gustafson and Wolpert 1963, pp. 139, 206–209). In their view, the "neglect" of research into cell movements and activities in previous decades "may have hindered progress in developmental physiology" as a whole (Gustafson and Wolpert 1963, p. 141). Secondly, they identify pseudopod formation as one of the main mechanisms of cellular movement in morphogenesis. They show that despite resulting in the same morphological shapes, cellular movement is highly

[13] Research on the scientific use of film in the period around 1900 far exceeds research on the period after World War II. On early film, see Curtis (2015), Gaycken (2015), Ostherr (2012), Wellmann (2011), in the context of cell culture Landecker (2007). On the pioneer Warren Lewis, see Landecker (2004), on Ronald Canti, Foxon (1976), on Julius Ries, Wellmann (2017), on Jean Comandon, De Pastre and Lefebvre (2012). On the technological advances in cinematographic research in biology after World War II, see Michaelis (1955, pp. 47–57, ch. 3); on Michael Abercrombie and the Strangeway Laboratories, Stramer and Dunn (2015); Landecker (2011).

[14] http://thenode.biologists.com/forgotten-classics-principles-morphogenesis/research/, Accessed March 5, 2018.

variable—underlining the difficulty of drawing conclusions on movement from the study of form and vice versa.

Gustafson and Wolpert studied sea urchin morphogenesis using time-lapse film. Like Kopsch and Gräper, they stress the need to trace movement continuously in a single living specimen, because "statistical" observations of living or fixed material "make it extremely difficult to correlate cellular activity with a morphogenetic event". Furthermore, the cinematographic acceleration in time-lapse can deal with processes so slow that they do not exist for us until becoming visible "by virtue of their movement" (Gustafson and Wolpert 1963, p. 143). Gustafson and Wolpert argue that gastrulation is an "example of both a change in curvature and long range translocation of a cell sheet" (Gustafson and Wolpert 1963, p. 183). It can, then, be reduced to two basic cellular activities: changes in cell contact, and cell motion (1963, p. 198). The two activities drive different phases of gastrulation, of which there are two in the sea urchin. Primary invagination leads to the formation of the archenteron (primitive gut) and brings it up to about one-third of the way across the blastocoel. It is brought about by a loss of contact and adhesion between cells and a subsequent change in the packing of the cells in the epithelial sheet (Gustafson and Wolpert 1963, pp. 183–185, 148–155). Primary invagination is thus "a special type of change in curvature" (Gustafson and Wolpert 1963, p. 199). In this context, Gustafson and Wolpert refer to Lewis's and Rhumbler's modelling of epithelial cell sheet change, but consider cell shape changes to be not the cause, but the result of invagination (Gustafson and Wolpert 1963, p. 185).

Secondary invagination involves directed movements and translocations of cells (Gustafson and Wolpert 1963, p. 199). It sets in only after a pause: the archenteron elongates further across the blastocoel and attaches near the animal pole of the embryo (Gilbert 2014, pp. 225–232; Kominami and Takata 2004, p. 309). In this movement, pseudopods play a major role. Pseudopods or filopodia are contractible extensions at the cell surface, here cells located at the tip of the archenteron (Gustafson and Wolpert 1963, pp. 155, 185). Gustafson and Wolpert postulate "a direct correlation" between pseudopod formation and secondary invagination, as the latter only starts when new pseudopods form and it is the pseudopods' contraction that pulls the archenteron toward the future mouth region. More precisely, once they have made contact with the ectoderm, the pseudopods exert tension on the archenteron, thus extending it. As proof of the tension exerted by pseudopods, Gustafson and Wolpert cite the cellular deformation at the points of the pseudopods' attachment to the ectoderm (Gustafson and Wolpert 1963, pp. 186–188). To illustrate how cell movement via pseudopod formation may be directed, Gustafson and Wolpert offer a schematic drawing (Fig. 4).

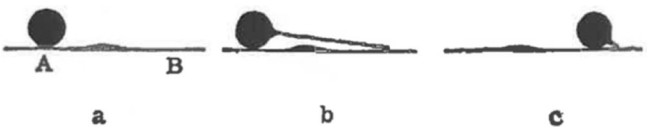


Fig. 4 Pseudopod formation. Gustafson and Wolpert 1963, p. 156, Fig. 6

Figure 4 shows a simple scheme of how a cell can move from A to B by extending a pseudopod that attaches at point B, exerts a tension that is greater than the cell's adhesion at A, and, by contracting, moves the cell in the direction of the extended pseudopod to B. In reality, the direction of this movement is far more complicated: a single cell can extend pseudopods in opposite directions, leading to a "tug of war" between them; the substrate along which the cell moves might not be uniform; the tension and length of attachment of pseudopods can vary; forces of adhesion differ; the surface varies in its contours; and there are actually not one but two or more cells extending pseudopods (Gustafson and Wolpert 1963, pp. 156–157).

In other words, cell movement is highly variable, and contingent upon a variety of circumstances—to such a degree that the pseudopods seem to be "exploring" their environment, as shown in Fig. 5 (Gustafson and Wolpert 1963, p. 186). It is this great variability that Gustafson and Wolpert repeatedly stress as the most salient feature of cell movement in gastrulation. Not only, they point out, can pseudopods "form in any direction" and cells "move along an infinite number of paths" (Gustafson and Wolpert 1963, p. 199); the "pattern of pseudopod formation", all the "pathways of invagination", and the "time lag" between primary and secondary invagination are also quite variable. Yet the "end result appears unaffected by this variability" (Gustafson and Wolpert 1963, pp. 188, also 201–202, 142–143). Given their general conclusion "that a relatively constant end result may be achieved by a variety of pathways" (Gustafson and Wolpert 1963, p. 202), they argue that the actual, specific "time–space distribution" of the cellular activities should become the focus of research. It makes a difference at what point in space and time a specific cellular event happens, or how "pseudopods develop at the right place and time" (Gustafson and Wolpert 1963, p. 141). Gustafson and Wolpert note that this

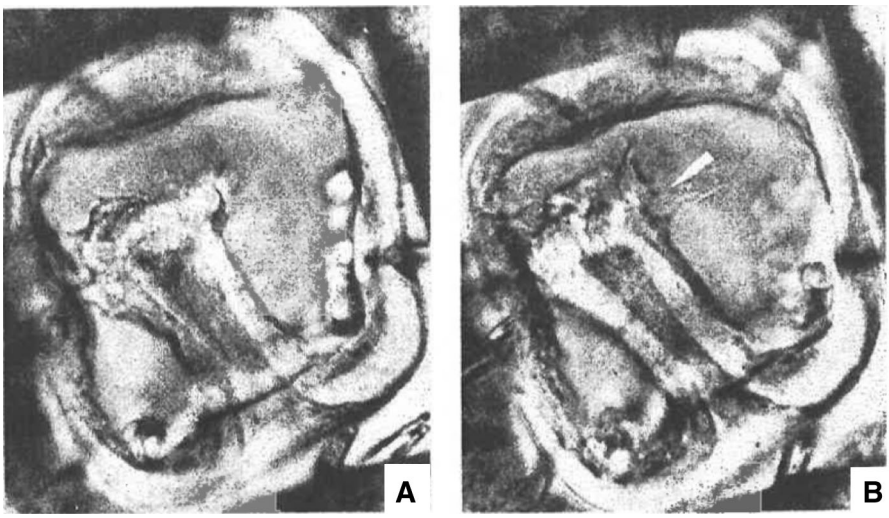


Fig. 5 The image in **b** (taken 10 min after the images in **a**) shows an "exploring pseudopod" indicated by the white arrow. Gustafson and Wolpert 1963, p. 186, Fig. 19 (detail)

question of the "precision or imprecision of developmental events" has hitherto received too little attention: "How cellular events are specified remains a fundamental question" (Gustafson and Wolpert 1963, pp. 203).

4 Computing cells

A concern with variety and specificity animated cinematographic research, its methodology of continuous tracking of movement, and its insistence on investigating the living organism. Research into shape change, in contrast, was guided by an interest in geometry, mechanics, and general principles. With the advent of computation at the end of the twentieth century, both fields of interest gained new momentum. Computer experiments introduced methodologies and epistemologies that call into question demarcations between theoretical and actual, dead and alive, descriptive and explanatory.

4.1 Differential equations and finite-element simulations

In the early 1980s, G. M. Odell and collaborators developed one of the first computer models of gastrulation to solve the same question that had plagued Rhumbler: why the epithelial sheet bends inward in invagination. Odell's paper clearly sets research into morphogenesis via movement apart from research via form, on the grounds that one offers descriptive filming, the other explanatory modelling; one "only" traces "movements of cells recorded", the other explains "the forces which drive the movements" (Odell et al. 1981, p. 446). Odell's computer simulation, like Rhumbler's and Lewis's tactile equivalents, approaches morphogenesis as a problem of geometric form and its deformation. The particular aim of his simulation is to show that invagination of the whole epithelial sheet can be explained by the local change in individual cell shape alone (Odell et al. 1981, p. 450).

For a problem to be solved by a computer, it has to be framed as a set of differential equations (Odell et al. 1981, p. 455). In Odell's case, a mechanical model of a cell is first constructed, then the "shape history" of each cell is computed by solving a set of differential equations (Odell et al. 1981, pp. 448–449, equations on p. 457). Subsequently, the "dynamical behavior" of assemblies of cells is examined by varying the geometrical and mechanical parameters, making it possible to simulate the behaviour of the cell shape changes over a certain time period (Odell et al. 1981, p. 449). The two major assumptions of the model are that the cytoskeleton can be represented by a number of "hypothesized mechanical properties", and that any morphogenetic dynamics can be described by Newton's laws of motion (Odell et al. 1981, pp. 446–447, 455).

For organisms with an epithelial sheet consisting of a single layer, such as the lancelet (Kopsch) or sea urchin (Gustafson and Wolpert), the simulation predicts an invagination as shown in Fig. 6: the succession of shapes in a–f shows the

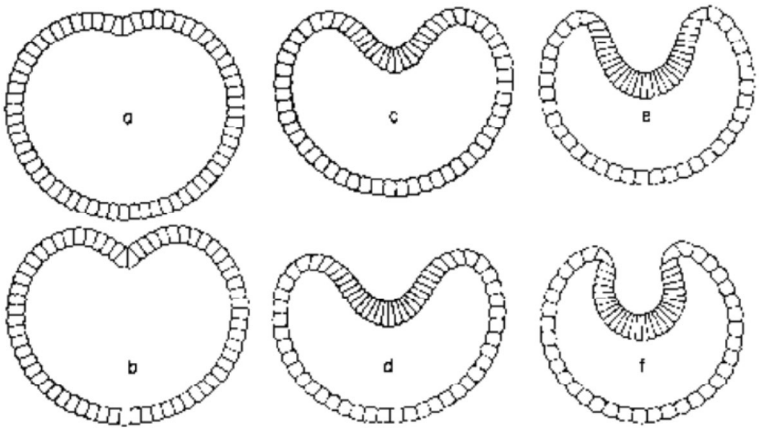


Fig. 6 A computer simulation of gastrulation in sea urchin. Odell et al. 1981, Fig. 7

invagination of the blastula caused by a spreading wave of contraction in each cell initiated by the contraction of the apical surface in a trigger cell.[15] The computational model is not designed to be applied specifically to gastrulation, or a single organism. It can "produce a variety of geometrical configurations", of which folding and invagination are only two (Odell et al. 1981, p. 455). The "global time history of the cell sheet geometry" (Odell et al. 1981, p. 455) is determined by how the initial geometric configuration of the cells and the parameters in the model are set—thus, how the differential equations are solved. Consequently, Odell can apply the model to simulate various forms of shape changes in various organisms, such as ventral furrow formation in drosophila and neurulation in amphibians. Gastrulation in sea urchins is just one, comparatively easy case.

This early computer simulation, thus, described morphogenetic change in terms of cell sheet deformation due to mechanical forces "generated locally by each cell" (Odell et al. 1981, p. 450). Based on the solution of mathematical equations whose parameters can be freely changed (ranging from the actual to the impossible), the simulations create various possible geometric configurations, disregarding the organismic specificity and variability that were so persistently highlighted in the cinematographic accounts of the earlier twentieth century. Not surprisingly, then, Odell's study refers to Lewis's 1947 model and Wolpert's 1969 theory of positional information (Odell et al. 1981, pp. 453–454), but does not mention Gustafson and Wolpert's earlier research on sea urchin morphogenesis, in which they had claimed the exact opposite: that in order to address "physical forces", such forces had to be "accounted for in terms of cellular activities" (Gustafson and Wolpert 1963, p. 140).

With computer power increasing, finite-element simulations pushed the geometrical framing of shape change in morphogenesis another step further. In 1995, L. A. Davidson et al. applied the simulation approach to gastrulation in sea urchins, just as Gustafson and Wolpert had done. More interested in shape change, however,

[15] For the mathematical formulation of the simulation, see Odell (1981, pp. 459–461).

Davidson looked only at primary invagination, as marked by changes in the epithelial sheet curving, and not at cell translocations and pseudopod activity during secondary invagination. More precisely, Davidson wants his simulation to test five mechanisms previously put forward, Lewis's and Gustafson and Wolpert's among them. The aim of Davidson's model is to predict the cell shape changes caused by each mechanism.[16]

Davidson's study first formulates a general model able to calculate "the early movements" produced by each mechanism (Davidson et al. 1995, p. 2006), and uses finite-element simulation, an engineering method now common in the sciences (Panagiotopoulou 2009). Finite-element simulation addresses a complex geometry by breaking it into smaller parts, called finite elements. It is a numerical approach to problems that cannot be solved by classical analytical methods. In the case of the shape changes in the cell sheet, the elements do not have to correspond to cells. Each finite element "has a simple geometry which permits a simple solution for its deformation" (Davidson et al. 1995, p. 2007). As the aim is to compute the deformation not of a single element but of the whole cell sheet, all the deformations of the subunits are "numerically assembled" and computed (Davidson et al. 1995, p. 2007). The commercial program Nastrans is employed for the simulation. Davidson models the "initial geometry" on a single embryo—on the morphology of the *Lytechinus pictus* (a short-spined sea urchin) blastula—and the embryo is actually modelled on one half only, as a rotational symmetry of the embryo is assumed (Davidson et al. 1995, p. 2007). Once the geometric design of the embryo is set in this way, serving as the template for all the simulations, the simulation is run on changing parameters, describing "different elastic material properties" of the embryo (Davidson et al. 1995, pp. 2007, 2014).

Apical constriction, as hypothesised by Lewis, is implemented by "imposing a gradient of constriction along the cell axis". The simulation shows that this mechanism can "indeed produce gastrulae whose invagination matches that of embryonic shapes" (Davidson et al. 1995, p. 2010). The same holds true for all five mechanisms, which can all "generate geometrically correct invagination" (Davidson et al. 1995, p. 2014). Each simulation, thus, is successful when its results resemble the geometry of the actual cell sheet shape in the embryo (Davidson et al. 1995, p. 2007). The simulation helps identify a "range of mechanical parameters" specific to each mechanism (Davidson et al. 1995, p. 2014), but says nothing about either the "actual causes" of invagination or actual cell shapes. It only tells us about shape *change*, given that natural cell shapes in the blastula "are not in the least like the purely columnar shapes of the finite elements" used in the simulations (Davidson et al. 1995, p. 2016).

In the 1960s, Gustafson and Wolpert had criticized the mechanics of morphogenesis proposed by Rhumbler or Lewis as "impotent" (Gustafson and Wolpert 1963, p. 140) for reasons that apply in equal measure to computer simulations. Such

[16] The five hypotheses are (1) apical constriction of vegetal plate cells, (2) cell tractoring of cells lateral to the vegetal plate, (3) contraction of a cycoskeletal bundle, (4) apicobasally aligned contraction of the cell cortex within the vegetal plate (this contraction is a mechanical effect of the adhesion hypothesis put forward by Gustafson and Wolpert and was modelled instead of the adhesion hypothesis itself), (5) swelling of a polyelectrolyte gel secreted by vegetal plate cells (Davidson et al. 1995, pp. 2005–2006).

mechanisms must, in Gustafson and Wolpert's view, "be discounted" as inadequate in major respects: any of them can "in principle" produce the bending of the cell sheet, and more importantly, all of them fail when "considered in the light of the actual behaviour of the cells during morphogenesis" (Gustafson and Wolpert 1963, p. 148). Watching cells actually move suggests, instead, that none of the mechanisms is in fact operative (Gustafson and Wolpert 1963, p. 185). And indeed, Davidson et al. concede that after running these simulations, "we still do not know how sea urchins invaginate" (Davidson et al. 1995, p. 2016).

4.2 Polonaise, again

In science from 1900 to the present day, modelers and simulators regarded cinematographers' work on cell movement as merely descriptive; cinematographers, in turn, considered the modelers' work impotent, offering merely aggregated, statistical and possible scenarios without elucidating the actual situation. The introduction of live-cell imaging into biology, however, seemed to herald a collapse in the distinctions between the individual and the statistical, the specimen and the model, the living organism and the computation, and ultimately between movement and shape.

At the beginning of the twenty-first century, the cellular movements leading to primitive streak formation in the chick embryo were still not well understood. To study cellular dynamics inside the living organism, live-cell imaging applies dyes and fluorescent markers to label cells, which are then tracked over time using time-lapse microscopy (Goldman and Spector 2005; Papkovsky 2010). In a 2005 study, Cheng Cui and his collaborators injected the fluorescent dye Dil into small groups of up to 30 cells at an early developmental stage and at multiple locations in the embryo. Using simple brightfield and advanced fluorescent microscopy, they took pictures every 4 min over a period of 12–15 h, then assembled and processed them into "movies" using Matlab, a commercially available software and programming toolbox to model and visualize data (Cui et al. 2005, pp. 38–39). To extract information from the material thus generated, the images have to be analysed—in particular, cell movement has to be identified. This is also done computationally. To compute movement within a tissue, an information flow is calculated for every image pixel using vector calculus. Each pixel is assigned a vector and a vector field is visualized as, for example, a field of arrows of different sizes and directions (Fig. 7). Now movement is mathematically quantifiable in terms of the direction and speed of the elements in different locations or at different moments in development, and trajectories can be calculated (Cui et al. 2005, p. 39).

The result of these experiments with labelled cell groups, time-lapse image sequences, and tracking algorithms is that cells move "in two large-scale counter-rotating streams which merge at the site of streak formation" (Cui et al. 2005, p. 37). As the streak forms "it elongates in both the anterior and posterior directions", and cells from the lateral epiblast continuously flow toward and supply the streak during its formation (Cui et al. 2005, p. 37). Live-cell imaging thus confirmed Gräper's observation of "Doppelwirbel" or polonaise movements in streak formation. In addition, it showed that the cells not only move toward the site

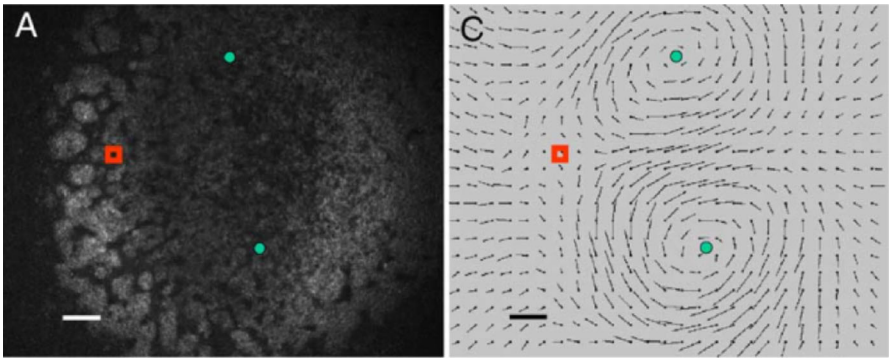


Fig. 7 **A** shows a brightfield microscopic image; **C** shows the corresponding calculation of a vector field based on ten consecutive such images. The red square on the left of each image indicates the merging and bifurcation of cell flows. Cui et al. 2005, p. 40, Fig. 2

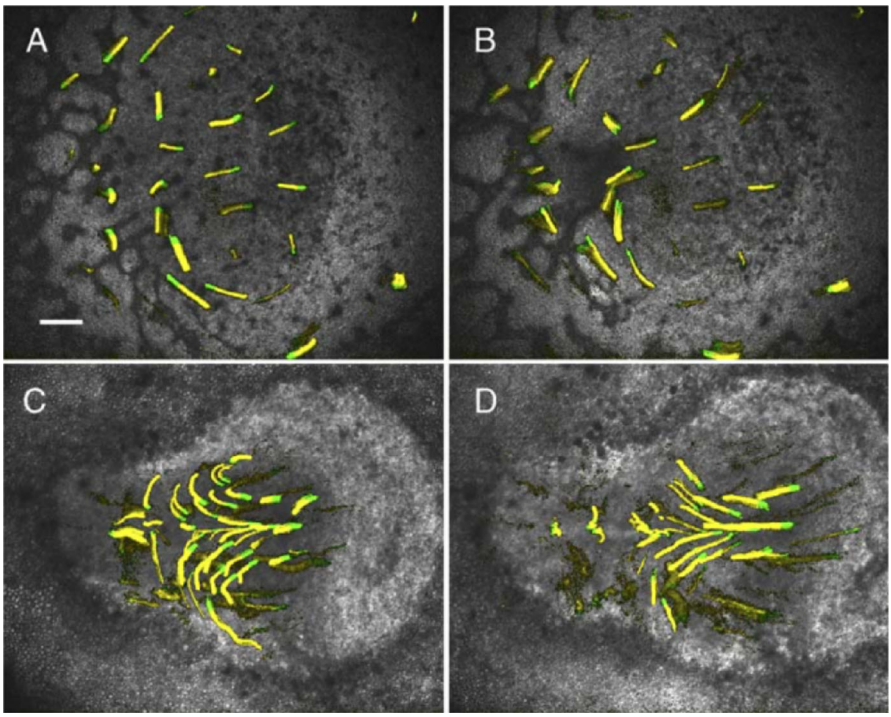


Fig. 8 In **A**–**D**, brightfield microscopic images are juxtaposed with the calculated trajectories of cells labelled with the fluorescent marker Dil. Cui et al. 2005, p. 40, Fig. 1

of streak formation, but also "anteriorly and laterally away" from it in "large-scale closed loop flows" (Cui et al. 2005, p. 39) (Fig. 8).

Live-cell imaging combined with experimental methods also confirmed the cells' polonaise movement at the level of single cells. In experiments conducted by Manli

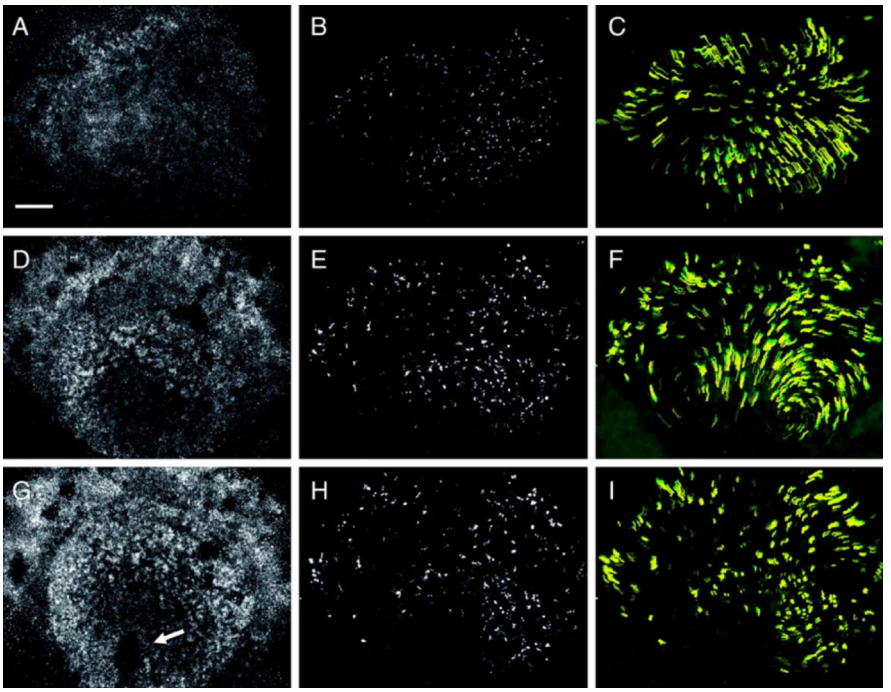


Fig. 9 Transfected embryos. Chuai et al. 2006, p. 141, Fig. 2

Chuai and collaborators, randomly distributed epiblast cells in the chick embryo at an early developmental stage were transfected, a procedure which introduces new genetic material into an organism, leading to the expression of GFP fusion proteins that then can be traced under the microscope (Chuai et al. 2006, p. 137; see also Lippincott-Schwartz et al. 2001; Miyawaki et al. 2003). Optical sectioning using an inverted confocal microscope creates images at varying depths, which then can be computed into three-dimensional representations of the embryo. Out of successive time-lapse images, single cell trajectories can be calculated with commercial software, as shown in 'C', 'F', and 'I' of Fig. 9. The images in the horizontal rows 'A', 'D', and 'G' show the same embryo at different stages of development (4, 15, and 18 h). They present different media and visualizations: brightfield microscopy, fluorescent microscopy, and the single cell trajectories calculated over 4 h.

The researchers were able to confirm Gräper's counter-rotating flows and to trace these flows even before "any optically-dense structure in the streak" could be detected. They showed that the cells of the two different streams "rarely appear to cross and or merge". Cell speed could be calculated as well, "from 0 to 2 μm/min, with the highest speeds at the periphery of the vortices" (Chuai et al. 2006, p. 139). On the basis of the cell tracking, the team planned further experiments aiming to alter the trajectories by interfering with signalling pathways (Chuai et al. 2006, pp. 144–147).

Visualization in live-cell imaging involves complex translation processes, a constant back-and-forth between the organism and computation: from visual material gained by experimenting with an actual specimen, data are computationally extracted and processed in order to turn them back into images (as in Fig. 9). In Cui's case, the imaging technique used to visualize the countercurrent movement of cells during primitive streak formation involves a highly complex mathematical operation, but fundamentally, the method to extract velocity vector fields implies that what is shown in the animations are average directions and velocities of movements for every pixel (Siegert et al. 1994). In these animations, then, we see *individual* entities (the pixel being a rendering of a morphological structure, such as the cell, not to be confused with the actual cell) featuring *average* properties.

5 Conclusion

During the twentieth century, cinematographers brushed aside statistical, mechanical approaches, insisting instead on the spatio-temporal specificities and variability of cellular behaviour. Model and simulation builders, in contrast, considered their findings explanatory rather than descriptive, and therefore more valid.

In this paper, I have framed morphogenesis and historical approaches to understanding organ formation as a struggle between form and movement, understanding and representing, modelling and visualizing, and have argued that live-cell imaging is a form of visual motion simulation that features an individual specimen with statistical properties. The images taken first, in experimentation, are optical images of the specific movements of individual cells, but the images calculated, rendered, and animated are not congruent with that first set of images. They are visual simulations, in which individual entities display properties calculated and aggregated from data sets, in this case showing cells moving at a certain speed and in a certain direction. Different scientific practices, the individual and the statistical, the organic and the mathematical, are here fused into one artefact. For gastrulation, this implies that form is pattern formation, and, ultimately, that form *is* movement.

In terms of understanding morphogenesis, one might say that this poses a problem rather than offering a solution, because it leaves aside one difficulty that, arguably, is central to morphogenesis: the final shape, as Gustafson and Wolpert point out, has numerous properties that are "not directly specified" in the movements moulding it, while conversely, multiple pathways can create the same form (Gustafson and Wolpert 1963, p. 209). Put differently: the gap between form and movement may have disappeared from the screen, but it still persists. Ernst Gombrich noted the "strange paradox" that "the understanding of movement depends on the clarity of meaning but the impression of movement can be enhanced by lack of geometrical clarity" (Gombrich 1964, p. 304). In live-cell imaging, this paradox seems to be turned upside down: computation leads to a gain in geometrical clarity, but we still lack the clarity of meaning.

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