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Animating embryos: the *in toto* representation of life

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Abstract. With the recent advent of systems biology, developmental biology is taking a new turn. Attempts to create a 'digital embryo' are prominent among systems approaches. At the heart of these systems-based endeavours, variously described as '*in vivo* imaging', 'live imaging' or '*in toto* representation', are visualization techniques that allow researchers to image whole, live embryos at cellular resolution over time. Ultimately, the aim of the visualizations is to build a computer model of embryogenesis. This article examines the role of such visualization techniques in the building of a computational model, focusing, in particular, on the cinematographic character of these representations. It asks how the animated representation of development may change the biological understanding of embryogenesis. By situating the animations of the digital embryo within the iconography of developmental biology, it brings to light the inextricably entwined, yet shifting, borders between the animated, the living and the computational.

In the preface to the tenth and latest edition of his authoritative textbook on developmental biology, Scott F. Gilbert states that the science of becoming is currently itself undergoing a 'metamorphic molt', at the end of which there will be an as 'yet unnamed developmental science'.[1] To a large extent, systems biology is responsible for this developmental science yet to come. Systems biology is the attempt to redefine the study of life by regarding life in its complexity, examining it computationally, and providing types of explanation different from those previously known in the history of biology.[2] According to Gilbert, the new science of development will 'integrate anatomy, physiology, genetics, cell biology, systems theory, genomics, and structural biology'.[3]

In fact, Gilbert traces the beginnings of modern systems biology itself to that same science of development, which was one of the first to apply 'principles of causation, integration, and context dependency'.[4] As a science of syntheses and relationships, embryology has from the outset asked the questions that will be asked by all the future life

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1 Scott Gilbert, *Developmental Biology*, 10th edn, Sunderland, MA: Sinauer Associates, 2014, p. xvi.

2 See Hiroaki Kitano, 'Systems biology: a brief overview', *Science* (1 March 2002) 295(5560), pp. 1662–1664; Marvalee H. Wake, 'Integrative biology: science for the 21st century', *BioScience* (2008) 58(4), pp. 349–353.

3 Gilbert, op. cit. (1), p. xvi.

4 Gilbert, op. cit. (1), p. 630.

sciences.[5] Prominent among systems approaches to developmental biology are attempts to create a 'digital embryo'. These proceed in two steps. One is to represent early embryogenesis in model organisms, such as drosophila or zebrafish, in animated visualizations of the movement patterns of cells, showing the organism's development by tracking every cell from every angle and moment by moment. The other is a quantitative assessment of the experimental data gained, in order to construct a model of embryogenesis. That model will be a 'set of mechanistic rules in a normalized morphogenetic scaffold', which will 'pave the way for a developmental computer model with truly predictive power'.[6]

In this article I investigate how modern systems biology conceives of this 'digital embryo'. At the heart of approaches like the one to be described here are a set of visualization techniques variously described as '*in vivo* imaging', 'live imaging', or '*in toto* representation' of the embryo. These terms designate the kinds of technique that allow researchers to image whole, live embryos at cellular resolution over an extended period of time.

Two questions about these methods seem to be of particular importance. First, in them, experimentation on and manipulation of the organism are inextricably entwined with computation. The transition of the living into the machine – the moment when the material becomes the virtual – is crucial to understanding what is actually done in live imaging.[7] My interest here is in the consequences of this crossing over into the realm of algorithms and numbers for the conception of development. Second, there would be no digital embryo without the visualization of developmental data. What is named 'embryo' in this setting is the trajectories of cells shown in animations. The animations give the impression of following the division and multiplication of the first cell into all its successors and the movements through which the embryo is created. However, what exactly is visualized in these movies – an organism, data, movement? We need to ask where life ends and the representation of life begins.

The inherently visual character of modern biotechnology has often been commented upon.[8] I will not go into the discussion of the representational, epistemic or ontological nature of the visualizations produced by particular technological set-ups.[9] There can be no doubt that modern imaging techniques 'simultaneously make and make visible, present and represent all at once'.[10] Instead, I want to focus on an effect of the type of visualization that is strikingly characteristic of computational biology today: the animation of life. Modern simulation and computer animation create the impression of seeing

5 Gilbert, op. cit. (1), p. 632.

6 Khaled Khairy and Philipp J. Keller, 'Reconstructing embryonic development', *Genesis* (2011) 49, pp. 488–513, 488.

7 See Hallam Stevens, *Life out of Sequence: A Data-Driven History of Bioinformatics*, Chicago and London: The University of Chicago Press, 2013.

8 Recent publications include Catelijne Coopmans, Janet Vertesi, Michael Lynch and Steve Woolgar (eds.), *Representation in Scientific Practice Revisited*, Cambridge, MA and London: MIT Press, 2014; and Annamaria Carusi, Aud Sissel Hoel, Timothy Webmoor and Steve Woolgar (eds.), *Visualization in the Age of Computerization*, New York and London: Routledge, 2015.

9 The different concepts of rendering, performativity, materiality, representation, enactment, ontology etc. have recently been discussed in Coopmans *et al.*, op. cit. (8); and Carusi *et al.*, op. cit. (8).

10 Lorraine Daston, 'Beyond representation', in Coopmans *et al.*, op. cit. (8), pp. 319–321, 321.

life as it moves, pulses and unfolds before our eyes. Animation permits development in the digital embryo to be presented not only in an image, but also in its quality of constantly changing. Indeed, some have claimed that the very nature and epistemic novelty of systems biology and simulations is their ability to tackle processes, relationships and the fluid, dynamic and ever-changing aspects of life.[11] Well into the twentieth century, biology was described as 'a science of the non-living',[12] in which techniques of staining, electron microscopy or histology predominated; these enhanced vision but were ultimately never able to go beyond framing life as a mere, albeit refined, still life. In comparison, the new visual techniques, which depict process and change, present themselves as a major revelation. This raises several questions. How are these animations realized in the computer? How do they affect our understanding of development? And finally, how does this particular algorithmic realization differ from previous modes of representing life as moving, especially through film? Are we witnessing the beginning of an era in which biology will, at last, really become a science of the living?

The first section of this article is dedicated to the technological aspects of *in vivo* imaging. The second focuses on *in vivo* visualizations as animated visualizations. The techniques' names suggest life, liveliness and a totality of vision as regards the processes during embryogenesis – but what exactly are they representing? In the third section I discuss the notion of animation to frame the computer visualizations of development, and in the fourth I situate the animations of the digital embryo within the iconography of developmental biology. In particular, I ask what role animation and motion played in the conceptualization of change before the introduction of computer visualizations, focusing especially on cinematographic techniques in the early twentieth century.

Optics and algorithms

In 2008, the digital embryo made it to *Science*'s top ten scientific breakthroughs of the year.[13] Earlier that year, a set of animations of zebrafish development using a new microscopical technique, developed at the European Molecular Biology Laboratory, had been released on the *Science* website.[14] The ongoing project's objective is an *in toto* representation of the embryogenesis of an organism, which means viewing the full 3D structure of an embryo over time by means of multidimensional imaging techniques.

In terms of technology, *in toto* imaging requires (1) mounting and labelling as experimental techniques to keep the organism alive and make cells visible; (2) image acquisition, with an optical system able to optically section the specimen repeatedly over

11 See Irun Cohen and David Harel, 'Two views of a biology–computer science alliance', *CoSMoS*, Proceedings of the 2009 Workshop on Complex Systems Modelling and Simulation, 2009, pp. 1–8.

12 Evelyn Fox Keller, *Making Sense of Life: Explaining Biological Development with Models, Metaphors, and Machines*, Cambridge, MA and London: Harvard University Press, 2002, p. 218.

13 Bruce Alberts, 'Celebrating a year of science', *Science* (19 December 2008), 322(5909), p. 1757.

14 See Philipp J. Keller, Annette D. Schmidt, Joachim Wittbrodt and Ernst H.K. Stelzer, 'Reconstruction of zebrafish early embryonic development by scanned light sheet microscopy', *Science* (14 November 2008) 322, pp. 1065–1069.

time into thin 2D slices at the resolution of single cells; and (3) image analysis by software that can process huge data sets to generate animated 3D images from a series of 2D images.[15] The resulting animations thus rely on three epistemologically different, yet related, practices: intervening, looking and representing.[16]

Since Antonie van Leeuwenhoek's invention of the microscope in the seventeenth century, microscopy has been at the heart of the life sciences. It is a long-established, continuously developing tool of observation.[17] Research on *in vivo* imaging techniques has its own, though shorter, history. It faces several optical challenges, including the need for spatial resolution to cover both interaction between cells and intracellular processes, penetration depth to zoom deeper into the tissue or to image larger specimens, imaging speed to capture the rapid dynamics of cell movement, the danger of long light exposure causing phototoxic effects, and the period of observation time.[18]

Time-lapse microscopy to capture the dynamics of development in transparent organisms such as sea urchins or *C. elegans* (roundworm) met with a new interest in the 1980s.[19] The 1960s marked an important advance towards *in vivo* imaging, when naturally occurring green fluorescent protein (GFP) was extracted from the bioluminescent jellyfish *Aequorea victoria*. In 1994, the protein was introduced into the genome of a different organism, namely *C. elegans*, for the first time. Next came the invention of laser-scanning microscopy (LSM) and with it the possibility of generating 3D images.[20] In

15 See Sean G. Megason, 'In toto imaging of embryogenesis with confocal time-lapse microscopy', in Graham J. Lieschke, Andrew C. Oates and Koichi Kawakami (eds.), *Zebrafish: Methods and Protocols*, New York: Humana Press, 2009, pp. 317–332.

16 See Keller, op. cit. (12), p. 219; on microscopy see also Annamaria Carusi, 'Computational biology and the limits of shared vision', *Perspectives on Science* (2011) 19(3), pp. 300–336; Annamaria Carusi and Aud Sissel Hoel, 'Toward a new ontology of scientific vision', in Coopmans *et al.* op. cit. (8), pp. 201–221; Evelyn Fox Keller, 'The biological gaze', in George Roberston, Melinda Mash, Lisa Tickner, Jon Bird, Barry Curtis and Tim Putnam (eds.), *FutureNatural: Nature, Science, Culture*, London and New York: Routledge, 1996, pp. 107–122; Ian Hacking, *Representing and Intervening: Introductory Topics in the Philosophy of Natural Science*, Cambridge: Cambridge University Press, 1983.

17 See Jane Maienschein, *Embryos under the Microscope: The Diverging Meanings of Life*, Cambridge, MA and London: Harvard University Press, 2014; on the nineteenth century see Jutta Schickore, *The Microscope and the Eye: A History of Reflections, 1740–1870*, Chicago and London: The University of Chicago Press, 2007.

18 See Philipp J. Keller, 'Imaging morphogenesis: technological advances and biological insights', *Science* (7 June 2013) 340(6137), pp. 1234168-1–1234168-10, doi: 10.1126/science.1234168. For an overview of the rapidly advancing field of visualization techniques, including other than laser-scanning and light sheet microscopy, such as magnetic resonance imaging (μMRI) or optical projection tomography (OPT), see Seth W. Ruffins, Russell E. Jacobs and Scott E. Fraser, 'Towards a Tralfamadorian view of the embryo: multidimensional imaging of development', *Current Opinion in Neurobiology* (2002) 12(5), pp. 580–586; Sean G. Megason and Scott E. Fraser, 'Digitizing life at the level of the cell: high-performance laser-scanning microscopy and image analysis for in toto imaging of development', *Mechanisms of Development* (2003) 120(11), pp. 1407–1420; Philipp J. Keller and Hans-Ulrich Dodt, 'Light sheet microscopy of living or cleared specimens', *Current Opinion in Neurobiology* (2011) 22(1), pp. 138–143; and recently Khaled Khairy, William C. Lemon, Fernando Amat and Philipp J. Keller, 'Light sheet-based imaging and analysis of early embryogenesis in the fruit fly', in Celeste M. Nelson (ed.), *Tissue Morphogenesis: Methods and Protocols*, New York: Springer, 2015, pp. 79–97.

19 See the literature in Ruffins, Jacobs and Fraser, op. cit. (18).

20 Melissa Phillips, 'Deciphering development: quantifying gene expression through imaging', *BioScience* (2007) 57(8), pp. 648–652, 648.

LSM, a specimen injected with a fluorescent marker (often GFP) is scanned by a laser.[21] By eliminating out-of-focus light, a single focal plane – the 'optical section' – is imaged.[22] A series of such optical sections, generated at different focal planes, can then be stacked, enabling three-dimensional images (*xyz* image sets) of the specimen to be reconstructed. Imaging a living specimen over time adds the time dimension (*xyzt* image sets).[23]

A second method is light sheet fluorescence microscopy (LSFM), the approach that gave rise to the enthusiastic acclaim of the *Science* community. This is an optical arrangement in which an entire, micrometre-thin volume of the specimen is illuminated: the laser comes from the side. In other words, scanning happens orthogonally to fluorescence detection. This produces advances in imaging speed while reducing the light exposure of the specimen.[24] The laser beam moves vertically while the fluorescence emitted by the zebrafish is detected by a camera, which creates an image slice. When the embryo is moved slightly but continuously on a horizontal line, a new image slice is created, and so on. By using a rotary stage, the embryo can also be recorded sequentially from multiple views. Once completely scanned from one viewpoint, the embryo is rotated 180° and scanned again. In every position, the embryo is scanned by the laser beam at intervals of between thirty and ninety seconds over a period of twenty-four hours.[25] Recently, a more advanced optical setting, called SiMView, has enabled simultaneous multiview imaging by overcoming the slight gap between images that is caused by rotation. In SiMView, the embryo is illuminated from two opposite directions and images are acquired by synchronized detection systems.[26]

My very brief description of image acquisition has bypassed the first two steps, labelling and mounting: the application of fluorescent markers and the provision of favourable conditions for keeping the embryo alive, both of which are fundamental to the functioning of image acquisition.[27] I would now like, however, to elaborate in more detail on the last step, image analysis.

21 On GFP and different markers see Megason and Fraser, op. cit. (18); Andrew Matus, 'GFP in motion CD-ROM. Introduction: GFP illuminates everything', *Trends in Cell Biology* (1999) 9 (2), p. 43.

22 This is done in confocal LSM by a pinhole aperture; in two-photon LSM, the fluorescent markers are excited only at the focal plane, making use of an optical property of the fluorescent dye.

23 For more technical detail, also on two-photon LSM, see Megason and Fraser, op. cit. (18), pp. 1408–1409; Megason, op. cit. (15). Before applications with drosophila and zebrafish, *in toto* imaging was done in *C. elegans*, for example by the Nobel Prize winner Andrew Z. Fire, 'A four-dimensional digital image archiving system for cell lineage tracing and retrospective embryology', *Computer Applications in the Biosciences* (1994) 10, pp. 443–447.

24 See Keller *et al.*, op. cit. (14); Keller and Dodt, op. cit. (18); Khairy *et al.*, op. cit. (18); Philipp J. Keller, 'In vivo imaging of zebrafish embryogenesis', *Methods* (2013) 62(3), pp. 268–278; Andrei Y. Kobitski, Jens C. Otte, Masanari Takamiya *et al.*, 'An ensemble-averaged, cell density-based digital model of zebrafish embryo development derived from light-sheet microscopy data with single-cell resolution', *Scientific Reports* (2015) 5(8601), pp. 1–10, doi: 10.1038/srep08601.

25 See Keller *et al.*, op. cit. (14).

26 For details see Khairy *et al.*, op. cit. (18); Raju Tomer, Khaled Khairy, Fernando Amat and Philipp J. Keller, 'Quantitative high-speed imaging of entire developing embryos with simultaneous multiview light-sheet microscopy', *Nature Methods* (2012) 9(7), pp. 755–763.

27 I will not go into detail here about the use of *in vivo* imaging and fluorescent markers for genetic research. See Megason and Fraser, op. cit. (18), pp. 1410–1411.

A microscope is an optical device: it enhances vision so that the observer can see what was previously undetectable by the unaided eye. *In vivo* imaging, in contrast, serves as a vehicle to 'digitize the information'.[28] It allows a qualitative (seeing) approach to developmental processes to be transformed into a quantitative (measuring) approach. Only quantitative data are computable, and quantification is the prerequisite for computational modelling.[29] 'Seeing' here becomes computational image analysis. This shift entails a transition from observing the single cell to observing the behaviour of all cells on the systems level; in other words, from a biological to a computational focus.

Automatically identifying and tracking a cell, or more generally a biological 'object of interest' (such as cell nuclei or cell membranes) in an image, over time with the help of software and algorithms, is called segmentation. Systems biologist Sean Megason found that there were around 20 million segmented objects in a twenty-four-hour time-lapse film of zebrafish development.[30] Segmented objects are referred to as 'traces' and are subdivided into different classes: figures (2D), meshes (3D), tracks (4D, including the time dimension) and lineages (branched trees representing cell lineages).[31] By means of segmentation, pixel-based images, such as those resulting from the optical slicing of the organism by a laser beam, are 'converted' into collections of traces. As traces – that is, numerical data sets – the segmented objects can be annotated with additional data such as 'cell width, cell type, cell location, and cell velocity'.[32] Powerful software is needed for the millions of cells that have to be identified and subsequently tracked over time during embryogenesis, and to gather all the information extractable from the images for quantitative analysis. Managing this huge amount of data is only possible through the use of databases, where the information can be stored and managed, retrieved or researched.

Traces, systems biologists argue, 'allow research to be focused on the cell rather than the pixel'.[33] In such statements, a distinction is made between a visual object (the pixel or the pixel-based image) and the computational object (the trace), whereas no further distinction is made between the 'cell' as a biological entity (in the organism) and as a computational object (the cell segmented by an algorithm). The 'conversion' that the authors identify is solely one from pixel to trace, from image to data, not one from the organism to the computer. There is yet another conversion, or more precisely reconversion, to make: from the trace back into an image, or from the data back onto the screen. Now the traces can be annotated with colour, for example, in order 'to mimic the original fluorescent colors of the cells or to visualise an annotation such as cell type or cell velocity'. This process is called rendering, in which commercial software is often adjusted to the specific needs and purposes of the research in question.[34] Reconstructing 3D

28 Phillips, op. cit. (20), p. 649.

29 See Fengzhu Xiong and Sean G. Megason, 'Abstracting the principles of development using imaging and modeling', *Integrative Biology* (2015) 7(6), pp. 633–642.

30 Megason and Fraser, op. cit. (18), pp. 1412–1413.

31 Megason, op. cit. (15), p. 329.

32 Megason and Fraser, op. cit. (18), p. 1413.

33 Megason and Fraser, op. cit. (18), p. 1413.

34 Megason and Fraser, op. cit. (18), p. 1415.

images from stacks of optical sections and rendering them over time as animated representations that permit rotation or zoom, again, demands high computing power.[35]

Discussing the technical requirements and computational approaches in live imaging, it has become clear that the 'images' we look at are the result of several conversions and translations between the biological organism, its computational modelling and its visual presentations. In the following, I discuss the animate and live quality of the imagery produced by these techniques and referred to in their names.

In vivo visualizations

In another *Science* article featuring the digital embryo project, entitled 'Lights! Camera! Action! Zebrafish embryos caught on film', *in vivo* imaging is repeatedly described as producing 'movies' – even a 'set of potential blockbusters'.[36] What makes the *in vivo* animations visually appealing enough to deserve these epithets?

Development starts with a single cell that divides into millions of cells, shaping the future organism by their divisions, movements, changes in cell shape, cell interaction and cell death. The single-view images (Figure 1), for example, show the increase, with every division, in the number of cells in the zebrafish embryo. Each illuminated dot represents a single cell. As their number multiplies during embryogenesis, the visualization becomes more and more dense, ultimately impenetrable, and the dots become indistinguishable to the observer. By rotating the embryo during imaging, multiple views are generated. In animations such as 'movie 2' released on the *Science* website,[37] the lateral and dorsal views of the zebrafish are represented side by side. Another movie (movie 4) shows a view of drosophila development at different angles, each differing by 90° from the previous one (at 0°, 90°, 180° and 270°). In movie 6 of the drosophila embryo, a third animation joins the lateral and ventral view, so that we see the fusion of the two previous views into a rotating vision of the embryo. Different views are assembled into a montage, creating a multiview perspective either in juxtaposition or blended into one animation.

The background is entirely black in all the films. That is to say, there is no space indicated into which the action of cell motion is embedded. This is true for both the 2D and the 3D images. Instead, the movement of the cells brings about the space in which they move; the dots circumscribe a perfect sphere by their motion alone. Furthermore, the density of the dots, their clustering in some parts and wide gaps in others, hints at a certain spatial dispersion. Due to the black background, the absence for the eye of any spatial orientation, the gradual coming-into-being of form acquires the character of an almost ghostly apparition: as the dots suddenly appear out of nowhere (their

35 See in detail also Khairy and Keller, op. cit. (6); Khairy *et al.*, op. cit. (18).

36 Gretchen Vogel, 'Lights! Camera! Action! Zebrafish embryos caught on film', *Science* (10 October 2008) 322(5899), p. 176.

37 To view the movies and for additional material see Keller *et al.*, op. cit. (14); and www.embl.de/digitalembryo.

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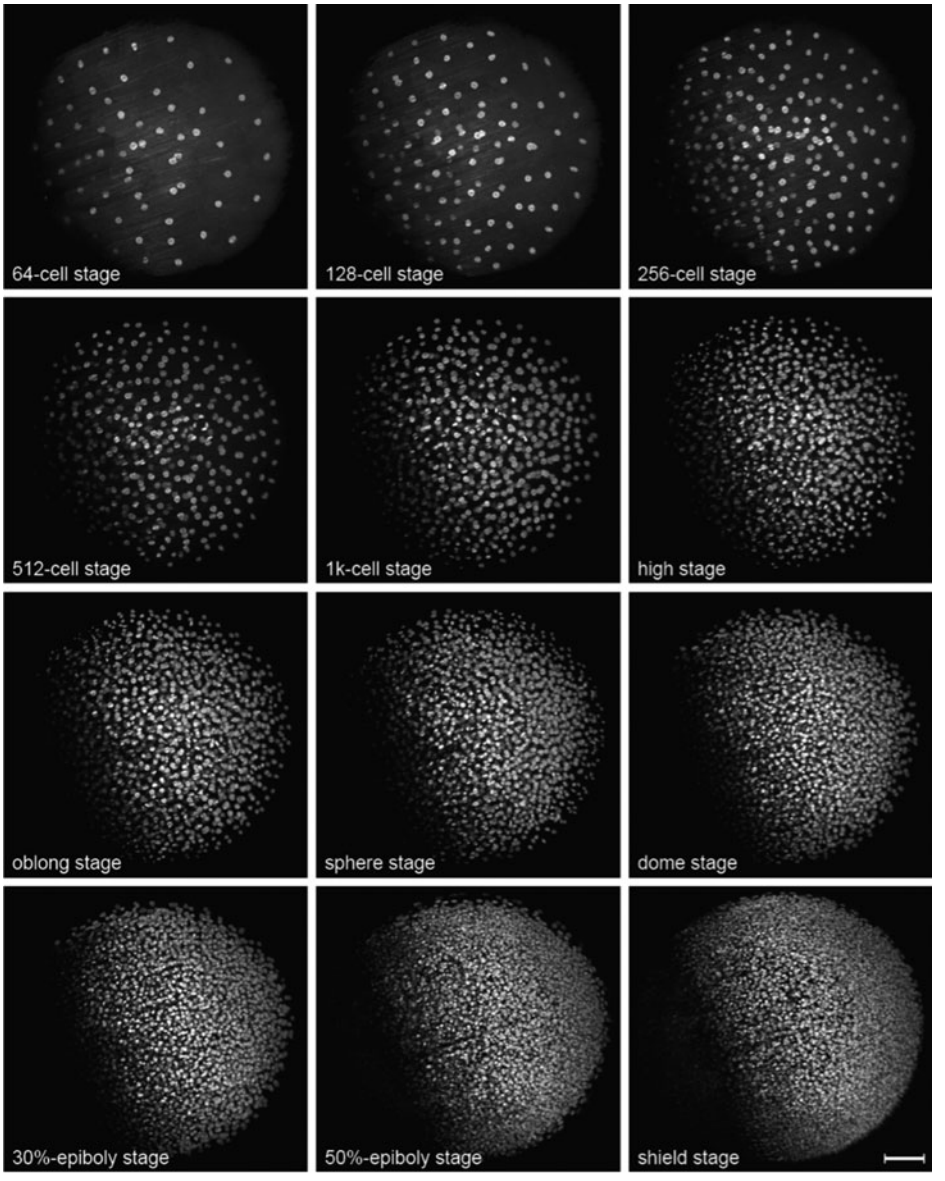

Figure 1. Reprinted from Philipp J. Keller, 'In vivo imaging of zebrafish embryogenesis', *Methods* (2013) 62, pp. 268–278, 274, copyright 2013, with permission from Elsevier.

origin in cell division cannot be discerned), the eye perceives the shaping of form as an invisible soap bubble gradually filling up with action. The movements define their own space, without the viewer being able to know quite what delimits them and whether their boundaries are intrinsic to the objects or set by an invisible border. While there clearly

are contours, the space inside and outside them is indistinguishable and of no quality. This impression is intensified by the rotation of the sphere about its own axis: in animations such as movie 3, a long-term imaging of the zebrafish embryo over sixty-seven hours condensed into a forty-four-second animation, we gaze into development as if it were revealed inside a crystal ball. We see it taking place in the encapsulated space of the rotating sphere. We are holding the future in our hands: all we have to do is look at it.

The dots do not just move around erratically, however. In Figure 2, the microscopical and the computationally reconstructed views are juxtaposed in the right and left halves of the image respectively. Different qualities of the cells can be encoded in the choice of different colours. The colouring of the dots not only introduces different levels of information into the images, but also brings about the most lively effects.[38] In part A of the figure, the colours code different directions: dorsal migration is coloured cyan, ventral migration green, motion toward the body axis red, motion away from the body axis yellow and motion toward the yolk pink. In part B, colouring indicates the speed of motion: bright orange indicates an average speed, blue standstill and colours between the two the range of intermediate speeds. Although commercial programs are available for some of the tasks in image processing, most features of these animations are customized to the specific research questions, technique and model organism used.[39]

Besides the question whether the colourful dots have a reference in 'real' cells, their motion poses an even bigger challenge to the mind of the observer. It is important to stress that the animations created by *in vivo* imaging have to be considered in their quality as visual products. They form a visual imagery of their own that is rooted in computational modelling or, more precisely, a back-and-forth between organism, algorithm and image. In addition, they introduce a sensual motion perception and quality characteristic to this particular imagery. In her study on systemic images, art historian Inge Hinterwaldner asks what happens between processing the algorithms, resulting in columns of figures, and the iconization of those figures.[40] In this context, philosopher Annamaria Carusi speaks of computer visualizations as 'the perceptual form of a mathematical idea'.[41] Hinterwaldner makes it clear that these two processes are not congruent: in the example of cell movement, a continuous organic process is first discretized in order to be analytically tractable for the computer, then resynthesized into an animate visualization, whose parameters are set to the human sensory apparatus.[42] The animations are, therefore, related to modelling. But unlike computation, which tackles the problem of how to model organic processes, they serve as visual solutions to the

38 See Keller, op. cit. (24), Figure 5.

39 Keller, op. cit. (24), Figure 5.

40 Inge Hinterwaldner, *Das systemische Bild: Ikonizität im Rahmen computerbasierter Echtzeitsimulationen*, Munich: Fink, 2010, p. 126.

41 Carusi, op. cit. (16), p. 329.

42 See Hinterwaldner, op. cit. (40), p. 83.

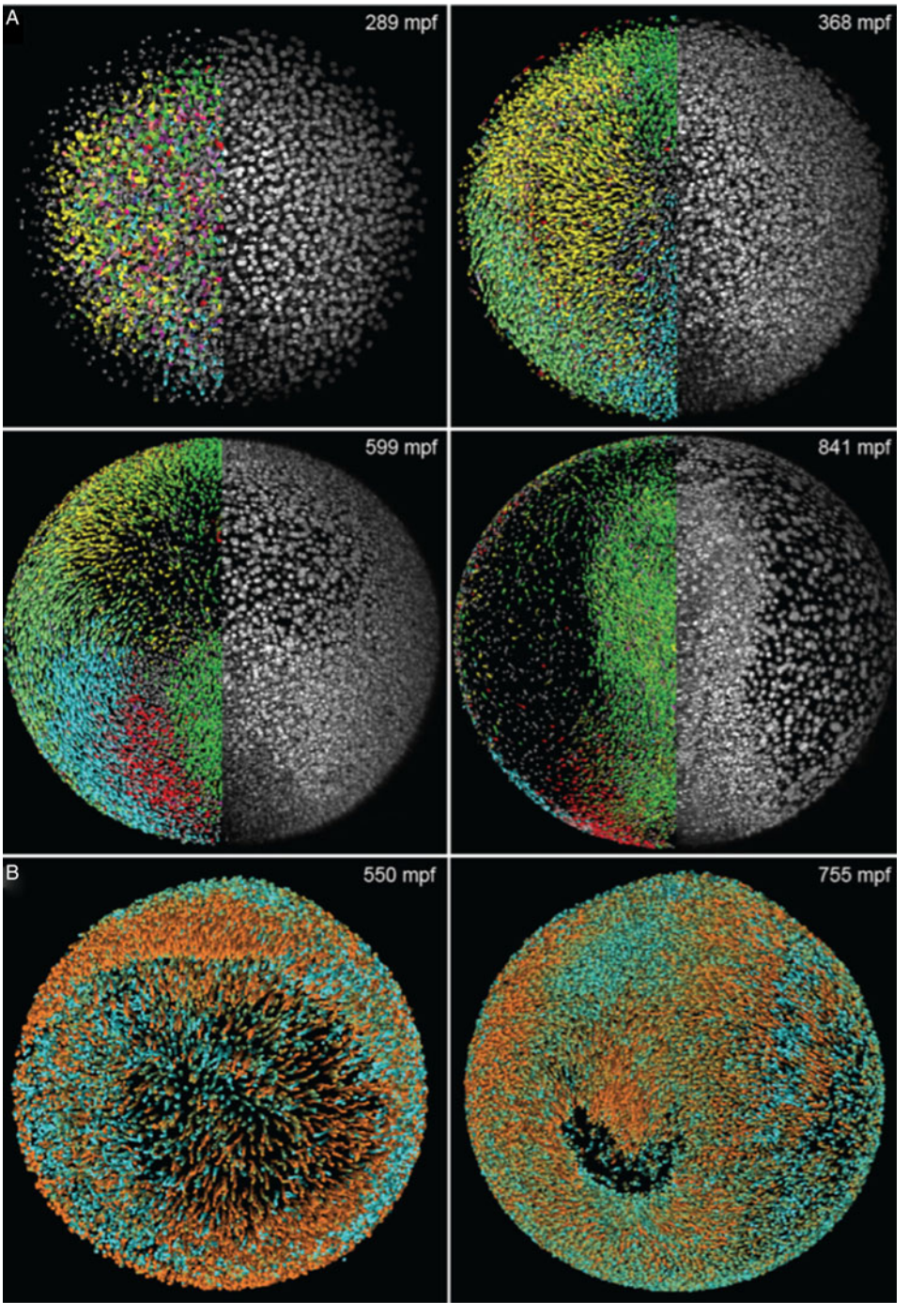

Figure 2. Reprinted from Keller, op. cit., p. 276, copyright 2013, with permission from Elsevier.

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problem of representing constantly changing forms. The question thus arises, as philosopher of science and media Gabriele Gramelsberger has put it, 'Where does the form get its gestalt?' Is it experimental data or the constraints of software programs that shape the visualizations?[43]

Animation

In this study of live imaging, I have not adopted the familiar use of the notions of films or movies to describe the *in vivo* visualizations, but speak of animations instead. Research on animation has so far taken its departure from chronophotography, cinema and special cinematographic techniques (notably cartoons) originating at the beginning of the twentieth century, and has been of interest primarily to film and media scholars.[44] Animation's other meaning of 'enlivening' or 'transforming into something living', however, covers more than endowing cartoons with life. Employing the notion of animation in the context of biological research in general and live imaging in particular, I pose the question of how the living organism is given an animate quality by being set in motion.

I take animation to mean, as film scholar Tom Gunning puts it, 'moving images that have been artificially made to move, rather than movement automatically captured through continuous-motion picture photography'. Furthermore, animations are not only 'displaying but also *playing* with the production of motion'. They create a sense of wonder as they draw our attention to the conditions of their own making.[45] At the same time, Landecker and Kelty characterize animations of biological events as the 'interplay of the perceptible and the intelligible', and hence always as an 'animation of theory'.[46]

What does this framing of live imaging as animation mean for the understanding and visualization of embryogenesis? Turning to the visual history of development in the next section I will show that it allows attention to turn to a hitherto neglected phenomenon in the study of embryology: the representation of movement.

43 'Woher bezieht die Form ihre Gestalt?', Gabriele Gramelsberger, 'Semiotik und Simulation: Fortführung der Schrift ins Dynamische', dissertation, Freie Universität Berlin, 2001, p. 93, quoted in Hinterwaldner, op. cit. (40), p. 132.

44 For a recently renewed interest in animation see Karen Beckmann (ed.), *Animating Film Theory*, Durham, NC and London: Duke University Press, 2014; Suzanne Buchan (ed.), *Pervasive Animation*, New York and London: Routledge, 2013; or the special issue of *Animation* (2011) 6(2).

45 Tom Gunning, 'Animating the instant: the secret symmetry between animation and photography', in Beckman, op. cit. (44), pp. 37–53, 40, original emphasis. Here my use of the term is more precise than in Ostherr and Gaycken, where it is used interchangeably with 'cinematography'; see Kirsten Ostherr, 'Animating informatics: scientific discovery through documentary film', in Alexandra Jahusz and Alisa Lebow (eds.), *A Companion to Contemporary Documentary Film*, New York: John Wiley & Sons, 2015, pp. 280–297; Oliver Gaycken, '"A living, developing egg is present before you": animation, scientific visualization, modeling', in Beckman, op. cit. (44), pp. 68–81.

46 Christopher Kelty and Hannah Landecker, 'A theory of animation: cells, l-systems, and film', *Grey Room* (2004) 17, pp. 30–63, 42, 36.

Iconography of development

Understanding and depicting constant change has been at the core of research into development since its beginnings. How does one portray the elusive 'in-between' of representation – that which has just come to an end or is just about to start?

For the last two hundred years, developmental series have been the main means of visual representation in embryology. Typically, a developmental series consists of a sequence of images, each depicting a different stage in the genesis of the embryo, which taken together convey the complete process of embryonic development from homogeneous matter to a highly differentiated, fully functioning organism. Today, representing a developmental process by a sequence of images is part of the standard iconography of the life sciences. Indeed, the serial arrangement seems to offer the quintessential pictorial representation of any process, not only developmental processes.[47]

Chronophotography and cinematography are a continuation of the same pictorial procedure by technically advanced means. Film has been described as a 'cinematographic method' of science due to the 'natural affinity' between film and the sciences.[48] Many, if not most, physiological processes inside the animal or plant body escape immediate human perception. They take place too slowly or too fast, or are too small to be seen in the first place. With the advent of cinematography at the beginning of the twentieth century, at last processes became visible as such – as events in time that have a beginning, usually come to an end and cover a certain time span. This constitutes the important difference from chronophotographic depictions such as Marey's and Muybridge's, or the 'unquantifiable quality' of film that surpasses chronophotographic analysis: in the moving image, the movement of the depicted and of the medium are inextricably entwined. Only when both are animated in the same act are we able 'to convince ourselves of the truth of life'.[49]

Embryologists were among the first to adopt cinematic technology.[50] Often they had a long training in classic histological approaches, staining techniques and dyes, which they improved continuously. Accustomed to crafting and adjusting their devices – as diverse as incubators, microneedles, nutrient solutions, slides or lamps – to suit their delicate objects of study and specific research needs, they welcomed photographic and cinematographic practices and applied the same approach to the new apparatus.

47 See the work of Nick Hopwood, most recently *Haeckel's Embryos: Images, Evolution, and Fraud*, Chicago: The University of Chicago Press, 2015; also Nick Hopwood, Simon Schaffer and James Secord (eds.), *Seriality and Scientific Objects in the Nineteenth Century*, special issue, *History of Science* (2010) 48(3–4).

48 Scott Curtis, 'Die Kinematographische Methode: Das 'bewegte Bild' und die Brownsche Bewegung', *montage/av* (2005) 14(1), pp. 23–43. On the rich entanglement of film, modernity and culture see Janina Wellmann (ed.), *Cinematography, Seriality, and the Sciences*, special issue, *Science in Context* (2011) 24(3); recently Lisa Cartwright, 'Visual science studies: always already materialist', in Carusi *et al*., op. cit. (8), pp. 243–268; Scott Curtis, *The Shape of Spectatorship: Art, Science, and Early Cinema in Germany*, New York: Columbia University Press, 2015; Oliver Gaycken, *Devices of Curiosity: Early Cinema and Popular Science*, Oxford: Oxford University Press, 2015.

49 Kelty and Landecker, op. cit. (46), p. 38.

50 See Ostherr, op. cit. (45); Gaycken, op. cit. (45).

As early as 1909, the Swiss Julius Ries filmed fertilization and cell division in sea urchins.[51]

The literature on embryology and developmental series, in particular the use of chronophotographic and cinematographic devices, has widely discussed the dimension of time as well as its manipulation that the new technology opened up at the turn of the twentieth century. Film made it possible to exceed the limits of human perception and address the dimension of time in the living world. With microcinematography, for the first time a technology turned the inside of the body towards the outside and simultaneously into time. Because of film's manifold relations to time, historians have distinguished between 'the time of experiment, the time of recording, and the time of demonstration'.[52] In addition, time can be manipulated – it can be condensed, stretched out and speeded up, and the film played forwards or backwards or stopped.

How the various visualization techniques represented and conceptualized motion, however, has escaped scholarly attention.[53] Although pictorial sequences were first introduced into biology only around the year 1800, the convention of serial drawing was not new. As I have shown elsewhere it dates back to early modern instructions for bodily motion, in handbooks and military manuals that used images to teach skilful fencing, vaulting, shooting or dancing. When the new notion of epigenetic development (which would give rise to the science of embryology at the turn of the nineteenth century) entered biology, it was conceptualized as motion.[54] Motion, thus, was an object of research in embryology from the outset, but it proved very difficult to study. Among the first things to be seen in the developing chick egg, for example, was the formation of blood islands. Caspar Friedrich Wolff, in his seminal *Theoria generationis* of 1759, already described the formation of blood in terms of the motion of corpuscles, oscillating between states of solidification and fluidity.[55] Similarly, the theory of germ layers introduced by Christian Heinrich Pander and Karl Ernst von Baer, which laid the groundwork for modern embryology at the beginning of the nineteenth century, was the two scientists' painstaking endeavour to make sense of motion, to bring order to a world of constant flow and seemingly erratic change, and instead to see the well-ordered

51 Julius Ries, 'Kinematographie der Befruchtung und Zellteilung', *Archiv für mikroskopische Anatomie* (1909) 74, pp. 1–31; Janina Wellmann, 'Plastilin und Kreisel, Pinsel und Projektor: Julius Ries und die Materialität der seriellen Anschauung', in Gerhard Scholtz (ed.), *Serie und Serialität: Konzepte und Analysen in Gestaltung und Wissenschaft*, Berlin: Reimer, 2017, pp. 77–93.

52 Hannah Landecker, 'Microcinematography and the history of science and film', *Isis* (2006) 97, pp. 121–132, 123.

53 This paper is part of a bigger research project on the history of concepts, images and ways of moving in the life sciences. On the terminology of 'migration', 'motion' or 'locomotion' see Wolfgang Alt and Gerhard Hoffmann (eds.), *Biological Motion*, Berlin, Heidelberg and New York: Springer, 1989; Miguel Vicente-Manzanares and Alan Rick Horwitz, 'Cell migration: developmental methods and protocols', in Claire M. Wells and Maddy Parsons (eds.), *Methods in Molecular Biology*, New York: Humana Press, 2011, pp. 77–106.

54 See Janina Wellmann, *The Form of Becoming: Embryology and the Epistemology of Rhythm, 1760–1830*, New York: Zone Books, 2017.

55 Janina Wellmann, 'Wie das Formlose Formen schafft: Bilder in der Haller–Wolff–Debatte und die Anfänge der Embryologie um 1800', *Bildwelten des Wissens: Kunsthistorisches Jahrbuch für Bildkritik* (2003) 1(2), pp. 105–115.

movements of cells into layers, folding in three dimensions, repeatedly in time and space, all carefully orchestrated.[56]

When embryologists such as Ludwig Gräper and Roland Canti in the first half of the twentieth century, or Michael Abercrombie and Marcel Bessis in the latter half, directed their film cameras towards the embryo, they not only followed embryogenesis over time. To understand the formation of the embryo, they researched the origins of cells, their movements and their fate. They drew maps, diagrams and itineraries of single cells and reconstructed whole lineages. The film camera was a tool to help them follow the cells' displacements, to measure distances and sketch trajectories over time.

Film and photography made a world present that first had to be extracted from the body in order to become accessible. The embryo, however, remained part of the hidden inner world of our bodies and a morphological entity made of tissues, cells and liquids. The process of change that the embryo underwent could be visually displayed by delegating the movements inside the body to the projection machine. But movement itself was not placed under scrutiny in the era of cinematography. In the digital embryo, in contrast, motion becomes the object of computational modelling and visualization. But now the embryo has disappeared: it is extracted from our bodies and its organic form dissolved into coloured moving dots.

Conclusion

The embryo is not lost, though. It is resurrected. In the words of systems biologist Sean Megason, the embryo is 'uploaded' into a 'digital recreation that can be quantitatively and comprehensively studied with the same transparency and facility as a complex computer program'.[57] The benefit gained from that resurrection inside the computer is the annotation of the organism with information. In this respect, the *in vivo* visualizations bear no resemblance to the traditional depictions of development.

Instead, I hold that the *in vivo* animations introduce a new visual quality to the study of development. First, movement is no longer displayed along the continuous transformation of forms, along the change of shapes, the comparison of lines and angles, the measurement of distances. Now, it is movement that brings about form. Second, the representation of development works without gaps for the first time. Both in traditional pictorial series and in photography or film, the spaces between the pictures – the frames, leaps, blanks or black bars – were constitutive for constructing movement. In live imaging, discretization is still present as regards computation, but as regards visualization, discrete frames and gaps are absent. Finally, and more importantly, understanding 'live imaging' in terms of animation points to the epistemic assumptions of these visualizations and their techniques: other than their names suggest, 'live' or '*in vivo*' imaging does not automatically capture movement in a specimen while being observed alive but

56 Janina Wellmann, 'Folding into being: early embryology and the epistemology of rhythm', *History and Philosophy of the Life Sciences* (2015) 37(1), pp. 17–33.

57 The quotation is taken from Megason's website at https://zfin.org/ZDB-PERS-970109-5, last accessed 8 August 2016.

creates movement computationally. If the quality of movement is essential to our understanding of life as process and continuous change, however, we have to ask whether we can still look at the *in vivo* animations the way we have learned to look at moving images over the last centuries. Is it still true that live imaging can convince us of the truth of life as early cinematography convinced the pioneers of moving pictures in biology? Speaking of animation, I suggest, instead, being sceptical, that it draws our attention to the fact that the images were designed to move, to the conditions of their making, and to our knowing that producing motion is not necessarily displaying life but also the illusion of life.