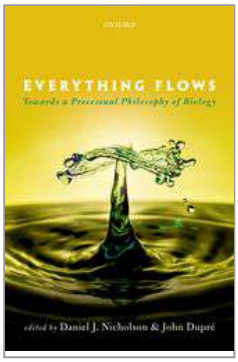

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Capturing Processes

The Interplay of Modelling Strategies and Conceptual Understanding in Developmental Biology

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Abstract and Keywords

While a processual view of biological entities might be said to be congenial to embryologists, the intractability and speed of developmental processes traditionally led to an epistemological abandon of processes in favour of the advantages of discretizing ontogenies in arrays of patterns. It is not until the turn of the twenty-first century that the digital embryos obtained from in vivo microscopy have started to replace developmental series as the reference representations of development. This chapter looks at how new microscopy, molecular, and computer technologies for reconstructing biological processes are contributing to a processual understanding of development. First it investigates how time-lapse imaging has brought with it a radical dynamization, not only of the images, but also of the theories of development themselves. Next it explores the role that imaging technologies have played in the return of organicism in developmental biology. Finally, it focuses on how quantitative imaging contributes to the explanatory modelling of developmental processes.

Keywords: developmental biology, imaging, modelling, organicism, process philosophy

1. Introduction

Historically, embryology (and developmental biology later on) has concerned itself with the process of development from egg or seed to adult. Following processes is a—if not *the*—characteristic activity of science, and visual representations play a major role in this endeavour (Griesemer 2007).

‘Developmental series’ are the main illustrations of ontogeny, and, since they emerged in the late nineteenth century, they have shaped the conceptualization, comparison, and explanation of developmental processes. As any other representation of natural processes, developmental series involve a form of abstraction or idealization wherein some features are selected while others are ignored, depending on the epistemic goals of the inquiry (Love 2010a; see also Griesemer 2007). Developmental series have undergone deep transformations in virtue of the different research goals they have served over the years (Hopwood 2005, 2007), but there are three main aspects of development that have been repeatedly abstracted away during their construction. First, in developmental series normal stages are meant to represent ‘normal’ development (i.e. the developmental pattern that is common to most members of a species) and thus explicitly exclude individual embryonic variation. Second, in representing ontogeny as a linear and temporally delimited sequence that covers a certain period of the life history of an organism, developmental series delimit the temporal boundaries of development, marking a beginning and an end of development. And, third, developmental series represent ontogeny as a sequence of successive forms or structures rather than as a continuous process.

These three dimensions of idealization have served different epistemic goals in different historical periods. In the comparative framework of pre-evolutionary morphology, individual variation needed to be abstracted away in the establishment of homologies, and the representation of development as a sequence of successive stages enabled embryologists to compare the structures characteristic of each stage and to trace them back to their embryonic precursors. With the advent of evolutionary biology, the identification of homological relationships (reinterpreted as evidence **(p.265)** of common descent) remained the main goal of morphology (Brigandt 2003). In Haeckel’s theory of recapitulation, ontogenetic stages were seen as a record of evolutionary patterns, and comparative embryology was devoted to uncover the parallelisms between series of ontogenetic and phylogenetic patterns. At the end of the nineteenth century, experimental embryology radically transformed the epistemic goals of embryology. Embryologists abandoned the description and comparison of developmental patterns subordinated to the study of evolution, and reoriented their efforts towards the experimental study of the causal processes responsible for the generation of form (Maienschein 1991). In this new disciplinary context, developmental series became a tool for standardizing the experimental work carried out by researchers in different laboratories (Hopwood 2005, 2007).

The multifaceted idealization of development embodied by developmental series has therefore been instrumental to the development of embryology as a discipline. However, abstraction practices can also constrain our ability to recognize and study certain phenomena (Love 2010a), particularly when the methods of representation are conflated with the phenomenon itself. For well

over a century, biologists have challenged the three aforementioned dimensions of idealization involved in the construction of developmental series. Probably the most recurrent concern has been with the first of these, that is, with the abstraction of inter- and intraspecific developmental variation. The exclusion of interspecific variation in Haeckel's comparative plates led to overestimating homological relationships and underrating the role of heterochrony as a mechanism of evolutionary change (de Beer 1958; Richardson 1995). As for intraspecific variation, Alan Love has investigated how the practice of developmental staging has led to a neglect of the phenomenon of developmental plasticity in contemporary evo-devo (Love 2010a). With regard to the second form of idealization, there is a long tradition in developmental biology, from Joseph H. Woodger to current evo-devo biologists, that has opposed the linear sequencing of development (Woodger 1929; Minelli 2003; Bonner 2015). Instead of viewing development programmatically, as a teleological phenomenon where the egg is the first stage of a process that leads to the creation of a mature organism, these authors take the life cycle to be the primary research subject of developmental biology, the egg and the adult no longer being the beginning and the end of a linear causal process, but rather temporal parts of a life history where change takes place at different speeds (Nuño de la Rosa 2010).[1] Finally, with regard to the third dimension of idealization outlined above, many authors have warned that the characterization of development as a sequence of disconnected morphological stages prevents the recognition of the profoundly dynamic nature of developmental processes. In this chapter I will focus on this particular idealization of developmental series.

The process approach to development has deep roots in the history of embryology. Historians of biology have recently shown that the principles of development worked out by the founders of modern embryology went far beyond the mere temporalization of ontogeny. For example, Karl Ernst von Baer aimed not simply to explain **(p.266)** temporal changes, but to inscribe the generation of new organisms into a continuous process (Vienne 2015). In this respect, the notion of 'rhythm' played a major role in his explanation of morphogenesis (Wellmann 2015). After a long period of supremacy of the morphological approach to development, in the 1950s, organicist biologists, deeply influenced by Whitehead's process metaphysics, revolted against the anatomist's timeless concept of the organism.[2] Adopting a radically dynamic perspective on the living organization, they defined the organism as a spatio-temporal process and understood organic form 'as a cross-section through a spatio-temporal flow of events' (Bertalanffy, quoted in Rieppel 2006: 531). Opposing the view of development as a series of discrete patterns, Conrad H. Waddington became the main advocate of a new 'diachronic biology', which understood organisms as developmental systems that undergo an endless process of becoming. To be able to account for this essentially dynamic character of the living organization, Waddington needed to introduce a whole range of new dynamic terms such as

‘chreod’, ‘canalization’, and ‘homeorhesis’ (Waddington 1957), together with new visual representations of development such as his influential epigenetic landscape. After suffering a long period of exclusion from mainstream biology, Waddington’s process approach to development and evolution has been recovered and taken up by current developmental and evolutionary biologists (Gilbert 2000; Jamniczky et al. 2010).[3]

Nevertheless, the process approach to development has not resulted in a transformation of the major representations of development—at least not until very recently. While the dynamic understanding of development has had an impact on the formal explanatory models of development and on the graphical illustrations used to represent such models (Baedke 2013; Fusco et al. 2014), developmental series of normal stages have remained the main visual representations of ontogeny. Time-lapse microscopy was introduced in developmental biology all the way back in the early twentieth century, and Waddington himself declared, already in 1962, that films of development were necessary for counteracting the deanimating effects of the microscope (Landecker 2006: 126). However, not until the first decade of the twenty-first century have the new ‘digital embryos’ (Keller et al. 2008), built from in vivo microscopy, started to replace the static series of normal stages as the standard representations of development. The recent convergence of microscopy, molecular, and computer technologies in live imaging is at present prompting a shift in our perception of development and in the theories we use to conceptualize it. Taking into account the radical interweaving of technological and conceptual advances in the history of embryology (Hopwood 1999), this chapter looks at how new techniques for reconstructing developmental processes are contributing to a processual understanding of development.

I proceed as follows. First, I investigate how time-lapse imaging has brought with it a radical dynamization, not only of the descriptive models of development, but also of the theories of development themselves (section 2). Next, I explore the role played **(p.267)** by imaging technologies in the return of organicism to developmental biology, and I argue that the reduction of the methodological trade-off between spatial and temporal resolution rendered by 4D imaging has also served to shorten the theoretical distance between processual and structural approaches to development (section 3). Finally, I focus on how the revolution in computational imaging and visualizing techniques is opening up new ways of explaining (not only describing) developmental processes (section 4).

2. In Vivo Imaging and the Four-Dimensional Conceptualization of Life

A fundamental aspect of the descriptive modelling of developmental processes is the construction of ‘embryological time’ (Griesemer 2000, 2002). One of the main motivations for building staging systems has been the desire to ascertain the age of an embryo. Individual organisms develop at different speeds, and

therefore the chronological age of an embryo (typically defined as the number of hours or days after fertilization) is not an accurate indicator of its structural age. This lack of correlation between chronological and structural age makes developmental stages the very markers of embryological time. In other words, it is the qualitative morphological features, not the chronological age of an embryo, that indicate the phase of development (i.e. the developmental stage) an embryo belongs to. In the staging systems based on morphological criteria, embryological timing is reduced to temporal 'ordering', that is, to the coordination of sequential events in time, which tends to assume an underlying causal relationship between the successive states (Webb and Oates 2015).

However, classical staging systems based on morphological criteria are not without problems (Boehm et al. 2011). First, embryonic parts may develop at different speeds, so that the same embryo may simultaneously belong to different developmental stages, depending on the organ that one takes as a reference. Second, some developmental events occur in shorter time frames than those captured by time-point microscopy and are therefore excluded from the characterization of normal developmental stages. Finally, there are also dynamic traits of embryos that cover longer periods of development but cannot be captured by time-point microscopy. This is the case of those types of biological timing, such as interval timing and rhythms, that cannot be reduced to a mere sequence of events (Webb and Oates 2015). Interval timing is a process with a well-defined duration between two events. Here the key feature is not so much the sequence of successive states as the kinetics of the process. Intracellular developmental timers, for example, control when vertebrate precursor cells stop dividing and start differentiating. Rhythms are continuous sequences of repetitive events with regular periods. A classical example is the sequential formation of body segments characteristic of most animal phyla.

A continuous description of the developmental state of an embryo over time is the obvious way to overcome the limitations of time-point microscopy. In this regard, the introduction of live imaging constitutes a radical revolution in developmental biology. While the sequential representations of normal stages involve thousands of **(p.268)** individuals, each of them fixed at different moments of its life, in vivo imaging makes it possible to witness the development of one and the same organism (Kelty and Landecker 2004). More importantly, in vivo imaging renders a much more accurate temporal resolution of development than in vitro microscopy. One of the main advantages of in vivo imaging over time-point microscopy is that it allows us to capture developmental processes over time through the use of time-lapse imaging. While traditional microscopy acquires images at distinct time points (e.g. daily), in time-lapse microscopy living embryos are cultured on an imaging device that captures images almost continuously, at much shorter intervals (e.g. a minute). The resulting film (a series of film frames) is then projected at a much higher speed (e.g. sixteen frames per second; see Wong et al. 2013). The ability to manipulate the time of

observation through projection (minutes) compared to the time of the experiment (hours or days) turns time-lapse imaging into an instrument for the investigation of biological time (Landecker 2006). The biologist and cinematographer Jean Comandon was particularly aware of the theoretical potentialities of microcinematography as an instrument of research. According to Comandon, just as microscopes had opened up the spatial dimension of investigation, the film camera enhanced the *temporal* dimension of perception, allowing us to see well-known phenomena in a new way or to discover previously imperceptible processes (Landecker 2005, 2006, 2009).[4] Ever since the introduction of time-lapse imaging, the development of methods for acquiring, analysing, and understanding images in order to generate numerical information has been the main technological breakthrough in enhancing the manipulability of time. With the so-called 'computer vision', filming allows the observer not only to see events that are not visible in static images, but also to subsequently deal with time as a measurable variable in experiments (Stramer and Dunn 2015).

The origins of time-lapse imaging go back to the invention of the cinematograph in the late nineteenth century and were intimately intertwined with the study of life, particularly of morphogenesis. In fact, one of the first time-lapse films (made in 1907 by the Swiss biologist Julius Ries) was a two-minute film of the process of sea urchin fertilization and development (Landecker 2009). A century later, making movies of cells, tissues, and embryos has become a familiar practice in the laboratory, to the point that it can be said without exaggeration that 'most cell biologists these days are also cinematographers' (Stramer and Dunn 2015: 9).[5] The ability to track in real time the dynamic processes that take place at the cellular and tissue levels has revolutionized developmental biology over the last two decades. Since the middle of the last **(p.269)** decade, examples of continuous live recording of single organs have increased greatly, and the visualization in real time of the early development of whole embryos is revolutionizing the field of human-assisted reproduction, where non-invasive methods are imperative (Wong et al. 2013). For instance, using time-lapse videography, Connie Wong and co-workers have demonstrated that two morphologically identical eight-cell human embryos that would have been classified under the same developmental stage in a time-point analysis were actually products of different developmental processes (Wong et al. 2010).

Nonetheless, in toto imaging, or the dynamic imaging of whole embryos over the entire course of development, remains a major challenge (Keller et al. 2008). There are still many species, especially mammals, whose development can be studied only by interrupting it at static time points; and representing ontogeny as a continuous process is not a trivial task for bioinformatics (Davidson and Baldock 2001). As a consequence, most embryo atlases still present a stage-by-stage view of development. Nonetheless, in the last few years, new methods have appeared that reconstruct the continuity of development in embryos whose growth cannot be recorded in vivo (Wong et al. 2015) and light sheet-based

fluorescent microscopy has been applied to analyse cellular dynamics in the early development of two model organisms: zebrafish (Keller et al. 2008) and drosophila embryos (Tomer et al. 2012). In both cases, the application of automated image analysis provides ‘digital embryos’, that is, ‘comprehensive databases of cell positions, divisions, and migratory tracks’ of the early development of entire embryos (Keller et al. 2008: 1065). Although the dynamic imaging of whole embryos over the entire course of embryogenesis is still an unrealized project, in toto imaging promises to replace the static and discontinuous views of ontogeny rendered by developmental series.

How have these new dynamic modes of representing ontogeny impacted our understanding of development? On the one hand, the introduction of time-lapse imaging in biological research has rendered visible a whole new realm of processual phenomena that were too slow to reach the threshold of human perception and that escaped static means of representation such as histology, photography, or drawing (Landecker 2006). But the adoption of time-lapse imaging does not only allow us to see new phenomena hidden by the static representations of development generated by in vitro microscopy. A much more telling indicator of how the introduction of new dynamic modes of representation has influenced *theories* of development is how they have allowed embryologists to see well-known phenomena in a radically new light. Hannah Landecker has shown how, when the first films of biological processes were projected in the early twentieth century, the experience of watching living processes on screen enabled the perception of familiar phenomena as dynamic entities rather than as fixed structures. This shift in perception was seen as the result of a kind of ‘reanimation’ of the still images of biological phenomena rendered by static means of representation, and the resulting films were interpreted as a manifestation of the (processual) essence of life (Landecker 2005). Also in botanical research, the first time-lapse images of plant growth were seen as providing evidence of the vitality of plants (Gaycken 2012). Importantly, we should not interpret the visualization of processes as a mere illustration of dynamic theories of life. Rather, these new images involve a ‘reanimation’ of the actual theories themselves **(p.270)** (Landecker 2012). Since the introduction of in vivo imaging, embryologists have endorsed the realistic character of embryo films in place of the static representations of ontogeny rendered by developmental series. The representation of development as a series of still images of embryos at different discrete developmental stages is now seen as an artificial representation of what is actually a continuous process. Embryo films have put into motion (and have therefore reanimated) the series of sections, photographs, and drawings of dead, fixed embryos that had previously been the only perceptual evidence of ontogeny.

In her research on the evolution of biological theories in the field of cell biology, Landecker has argued that the introduction of fluorescent imaging has been the main technological breakthrough in the development of a new dynamic

perception, and hence conception, of life. The visualization over time of molecular structures through fluorescence first allowed us to ‘watch the genetic code running’, but has ended up challenging the gene-centred view of biology altogether:

> [P]rocesses which were thought to be programmed…—particularly those unfolding in organismal development—are shown by live-cell imaging to arise out of a messier, looser set of molecular relations and interactions… With live-cell imaging and a host of other developments in protein sciences, it seems that the cell composed of functional structures is dissolving into molecular entities that constantly but always changeably constitute structures. It is not so much that the structures begin to move, but movements—for example in the assembly and self-organization of the cytoskeleton—begin to constitute structure.
>
> (2012: 393–4)

The dynamic visualization of subcellular processes has radically changed contemporary theories of development, bringing with it new process-based theories of ‘the inner life of the cell’, to use the title of the famous Harvard animation of the workings of a blood cell. According to Landecker, these new theories of life endorse a new ‘molecular vitalism’ (Kirschner et al. 2000) where the gene has lost its causal supremacy with regard to the other molecules of the cell (RNA, proteins, or calcium ions), and explanations are sought in terms of macromolecular self-organization (Landecker 2012). While this might certainly be the case for cell biology, I do not think that the major theoretical issue that is at stake in the new dynamic images of development is ‘the molecular foundation of life’ (ibid., 393). As I will argue in the next section, biological disciplines, notably developmental biology, deal with different levels of organization, and the new modes of capturing biological processes are playing a major role in characterizing and understanding the dynamic nature of biological hierarchy, particularly at the cell and tissue levels.

3. Resolution, Contextuality, and the Return of Organicism

Organicism flourished between the First and the Second World War as a materialist but non-reductionist alternative to the dichotomous explanations of life given by mechanicists and vitalists (Nicholson and Gawne 2015). The organism was conceived of as an integrated whole whose parts, essentially related to one another, cannot be understood in isolation. Furthermore, organicists conceded a central role to the **(p.271)** irreducible hierarchical nature of biological organization: the principles that govern the behaviour of the parts at a higher level cannot be deduced from principles that apply to lower levels of the hierarchy. After the rise of molecular biology in the 1950s and the ascendancy of the modern synthesis view of evolution, organicist philosophy of biology was expelled from mainstream biology. However, since the early 1980s,

an increasing dissatisfaction with adaptationism and genetic reductionism has led to a revival of organicism in several fields of biology (Gilbert and Sarkar 2000).

In developmental biology, the two main arguments against the reductionist and deterministic view of development as programmed in the genes echo the major theoretical tenets of early organicism. First, developmental biologists have emphasized the importance of the cellular, tissue, and organismal context in understanding the role of genes in development (Laubichler and Wagner 2001). Moreover, when we aim to explain global patterning, local specification alone is not enough to explain the generation of the functionally coordinated structures that make up an organism. Taking the context of the organism as a whole is essential to identifying the mechanisms responsible for orchestrating the time and place of local factors (Winslow et al. 2007). This reference to the various contextual levels where gene action needs to be situated leads to the other major theoretical argument against genetic reductionism. The ontogeny of an organism is conceived of as ‘a hierarchy of developmental processes at different levels of organization’ (Hall 2003: 226). The properties at one level of complexity (e.g. cells or tissues) cannot be ascribed directly to their component parts (e.g. genes), because they emerge through interactions among the parts at different levels of organization. A cell interacts with its neighbours and with the extracellular medium, cells aggregate in germ layers and tissues, tissues interact in organogenesis, organs interact with the rest of the body, and the organism itself interacts with the surrounding environment. In this explicitly hierarchical view, presuming that the molecular level is the most fundamental ontological level in biology is an unwarranted metaphysical assumption (Laubichler and Wagner 2001; see also chapter 1 here). Rather, different rules are appropriate for each level of the irreducible hierarchy of the living organization (Gilbert and Sarkar 2000). In short, development cannot be reduced to the mechanisms of gene activity, and a new *holistic* and *multilevel* approach to developmental processes is needed (Salazar-Ciudad and Jernvall 2004).

This multilevel and systemic view of development has been articulated before, quite independently of the recent advancements undergone by imaging technologies. Still, the descriptive modelling of development seems essential if we are to capture both the holistic and the hierarchical dimensions involved in the development of complex multicellular organisms. For one thing, imaging captures embryological data in their full living context. Moreover, if we aim to understand how different regimes of causality operate at each scale of organization in the developing embryo, the first essential methodological step is to accurately characterize these organizational levels. Depending on which biological phenomenon we aim to explain, we will pay attention to one or another level of organization, and therefore to one or another developmental mechanism. In this context, modelling should be understood as ‘the art of…

choosing an appropriate level of abstraction' (Wolkenhauer and Ullah 2007: 164; see also Brigandt 2015). This approach to modelling, widely endorsed in the **(p. 272)** philosophical discourse on explanatory models, is equally valid for descriptive models. Depending on the organizational scale one is interested in studying, different microscopy methods will be chosen for reconstructing development at the anatomical, histological, or cellular level.

As I noted at the start of this chapter, any mode of representation involves a form of idealization wherein some features are selected and others are ignored, in accordance with our descriptive and explanatory needs. In particular, the dynamic dimension of development has traditionally been abstracted away in the static representations of development rendered by developmental series. However, the difference between still modes of representation (histology, drawing, and photography) and dynamic ones (film) cannot be reduced to a conflict between true and false representations (Landecker 2012). Both static and dynamic modes of imaging represent the same developmental phenomena, and therefore the split between structural and processual approaches to development should be analysed (as Griesemer has argued for the research styles of genetics and embryology) as 'a matter of what is represented in the foreground versus the background of attention' (Griesemer 2007: 382). Importantly, the underlying ontological commitments of biologists differ according to whether the biologists in question hold pattern-based or process-based philosophical views: the former mainly consider timeless structures, whereas the latter perceive reality as consisting of systems in a permanent state of flux (Nuño de la Rosa and Etxeberria 2012). It can be argued that the theoretical distance between process and structure reflects the methodological trade-off between spatial and temporal resolution: time-lapse imaging allows higher temporal resolution, but images with higher spatial resolution take longer to collect (Brainered and Hale 2006).

Still, the methodological trade-off between spatial and temporal resolution has been steadily weakening in the last decades. At the beginning of the twentieth century, one of the main limitations of applying time-lapse imaging to the study of development was precisely its lack of resolution. As living cells are translucent, the only way to see cells under a traditional light microscope was to stain and therefore to kill them. Embryologists were faced with the dilemma of having to decide between representing high-resolution but dead structures or visualizing live yet structureless processes. The structural and the processual modes of description seemed to be, as Nils Bohr (1933) famously claimed for the mechanistic and the finalistic understandings of living systems, complementary. That is to say, to obtain a full understanding of biological phenomena, the static and the dynamic modes of description were mutually exclusive, yet equally necessary. Therefore, choosing a dynamic medium of representation of development over a static one could not be interpreted as adopting a more 'realistic' perspective. Rather, opting for a processual mode of description of

development was also a kind of idealization, insofar as cell resolution was sacrificed for the sake of the dynamic visualization of development. And the opposite was also the case: the ascendancy of histological methods in the late nineteenth century was crucial to the success of a structure-based (as opposed to a process-based) approach to life (Landecker 2009). However, over the course of the twentieth century there have been three major advances in microscopy that have challenged the presumed inevitability of a trade-off between spatial and temporal **(p.273)** resolution, allowing researchers to combine in vivo high-resolution microscopy and time-lapse imaging. These are the introduction of the phase-contrast microscope in the 1930s, the invention of the laser scanning confocal microscope in 1986, and the cloning of the green fluorescent protein (GFP) of jellyfish in 1992 (Stramer and Dunn 2015: 12).

Having said this, time-lapse microscopy has been incapable, until very recently, of rendering 3D representations of development. Before the introduction of non-destructive 3D imaging, the only way of reconstructing the three-dimensionality of embryos was to physically slice the embryo into hundreds of sections and reconstruct the 3D morphology from these sections. At first, the series of sections, mounted on glass slides, was used to generate physical 3D models. With the digitalization of photography, sections were photographed and the digital images were virtually stacked together. In both cases, looking at processes was incompatible with appreciating the three-dimensionality of development. Embryos still needed to be frozen at different moments of their development in order for the researcher to ‘look’ inside them.

The major revolution in 3D imaging has come at the beginning of the present century, with the development of various non-destructive imaging modalities. These new microscopic techniques, such as optical, ultrasound, microcomputed tomography, as well as magnetic resonance imaging, allow us to obtain stacks of digital images of optical or virtual sections through a specimen. 3D visualization and the analysis of such massive data sets are performed with the aid of reconstruction software (Weninger et al. 2004). Thus, thanks to ‘virtual histology’ (Sharpe 2008), embryos can now not only be imaged in their natural environment, but also be manipulated without being destroyed. These new imaging modalities can be used to generate images from complex living embryos throughout embryonic development (Gregg and Butcher 2012), leading to time-lapse imaging in three dimensions, or 4D microscopy. Thus, whereas when choosing a microscopic technique there is always a compromise to make between spatial resolution and temporal sampling (Luengo-Oroz et al. 2011), 4D imaging finally makes it possible to acquire data that have high spatial context and which are longitudinal over time.

The ability of time-lapse imaging to characterize development at different levels of organization makes the resulting images the locus of integration of the different explanatory approaches in developmental biology. Thus Khaled Khairy

and Philipp Keller (2011: 488) set ‘the system-level understanding of developing organisms’ as the long-term goal of a descriptive model of embryogenesis that encompasses different levels of biological organization. According to Sean Megason and Scott Fraser (2007), this should also be the goal of developmental bioinformatics, namely the creation of a complete database with information on developmental processes at different levels of organization, including gene expression patterns, cell lineages, and cellular dynamics throughout the duration of development. This descriptive model ‘may allow the extraction of a fundamental set of mechanistic rules in a normalized morphogenetic scaffold and thus pave the way for a developmental computer model with truly predictive power’ (Khairy and Keller 2011: 488). Understanding how these new descriptive modelling strategies contribute to contemporary explanations of development will be the subject of the last section of this chapter.

(p.274) 4. Reconstructing and Explaining Developmental Processes

Philosophers of science have traditionally dismissed visual representations of natural phenomena either as data summaries or as purely illustrative tools of scientific theories. According to this view, descriptive models only become a legitimate part of scientific research when they are subordinated to explanatory models. Against this backdrop, recent studies of representation in scientific practice are deeply concerned with the role of visual representations in scientific explanation, from diagrams (Perini 2005) to 3D models (Chadarevian and Hopwood 2004). In particular, since the pioneering work of Nick Hopwood on the early history of representational practices in embryology (Hopwood 1999, 2005, 2007), the last few years have witnessed an increasing interest in the role of descriptive modelling strategies in the explanatory models of developmental biology and evo-devo (Griesemer 2002; Love 2010b; Fusco et al. 2014).

In the writings of the early cinema theorists and film-makers such as Sergey Eisenstein, Jean Epstein, or Béla Balázs, there was a recurring metaphorical connection between seeing life under a microscope and seeing it through a camera. In these writings, the movie shot was compared to the cell, the montage to the organism formed by cell division, and film-making to embryogenesis. Landecker (2005) has shown how the recurrence of this analogy illustrates the deep connection that tied cinema and biological research in the early twentieth century. I believe that these kinds of comparisons also point to another dimension of representation that reveals the connection between describing and explaining. In the same way in which watching a film is, in reality, an illusion that hides the fact that the spectator is actually viewing a succession of still pictures, not to mention all the editing that goes into making a movie, looking at development under a microscope or watching development on a screen is also artificial in other respects. Dynamic images of development are highly contrived representative or phenomenal models of development. Paradoxically, the most realistic images of development are also the most crafted reconstructions of it.

In the predigital age, reconstructions of development were derived from microscopical observations that relied on the visual inspection and manual analysis of drawings or photographs. Analyses of dynamic processes were particularly arduous. For instance, the only way to analyse cell movements was to print a series of individual frames at regular intervals and manually quantify the displacement of individual cells. Since the digitization of the video time-lapse in the mid-1990s and the increasing number of megapixels per image (Gordon 2009), computational tools for automated image processing and data analysis (from cell segmentation to cell-tracking algorithms) have become indispensable for achieving the reconstruction of developmental processes in space and time (Khairy and Keller 2011; Luengo-Oroz et al. 2011; Rittscher 2010). A major technological breakthrough of the digital revolution that has enabled the widespread diffusion of dynamic images of development has been the possibility to upload videos to online publishing platforms. In recent years, time-lapse movies both of microscopical recordings and of reconstructions have become more and more common in developmental biology (see e.g. Keller et al. 2008).

(p.275) The quantification of observation introduced by computer images has inverted the received view that developmental biologists had commonly assumed about descriptive modelling. While representative models of development have been traditionally assimilated to a qualitative understanding of ontogeny,[6] the main advantage of live imaging with regard to explanation is 'quantitation' (Pantazis and Supatto 2014). Indeed, the past two decades have seen a phenomenal increase in the number of tools for capturing quantitative data from living embryos, including new microscopy methods, the use of fluorescent molecules to probe gene function, and, above all, image analysis software. The combination of these new tools has turned microscopy into a quantitative methodology able to measure in great detail the spatio-temporal dynamics of developmental processes at the molecular, cellular, and tissue level (Oates et al. 2009). Some authors even claim that the quantitation of imaging is transforming developmental biology as a whole into 'a new interdisciplinary field where biologists' verbal descriptions are turned into more quantitative and formal descriptions amenable to automated quantitative analysis and comparison' (Luengo-Oroz et al. 2011: 630).

However, while the role of imaging in providing comprehensive and accurate descriptions of developmental processes is well appreciated, its role in the explanation of morphogenesis deserves more recognition. In a recent paper, Fengzhu Xiong and Sean Megason caution about the underestimation of the role of imaging in generating and testing models of development: 'imaging is often dismissively considered as "descriptive" at best whereas perturbation based approaches are automatically considered more "mechanistic"' (Xiong and Megason 2015: 632). Even among biologists who are explicitly sympathetic to a theoretical process-based approach to biological phenomena, the descriptive modelling of the dynamics of development, made possible by contemporary live

imaging technology, is regarded as a minor contribution by comparison to explanatory models. For example, after recognizing the ‘spectacular recent advances in live imaging technology’, Johannes Jaeger and Nick Monk caution that ‘it is important to keep in mind that they [the movies of developmental processes made possible by these new technologies] *only provide descriptions—not explanations*—of the phenomenally complex and orchestrated dynamic organization of cells and developing organisms’ (Jaeger and Monk 2015: 1067; emphasis added).

By contrast, advocates of imaging techniques in developmental biology have adopted an explanatory approach to development that opposes the traditional explanatory approach of developmental genetics (e.g. Lippincott-Schwartz 2011; Xiong and Megason 2015). Developmental genetics conceives of development as a spatio-temporal sequence of gene expressions, a linear approach to causality that allows developmental genetics to explain ontogeny. This *interventionist approach* begins with an induced mutation and a discrete phenotypic consequence, and then establishes a perturbation-to-consequence chain of events in which the mutant gene is taken to be the cause of the developmental process under study (von Dassow and Munro 1999). These causal sequences, visually represented **(p.276)** by gene regulatory networks, are further completed with other genes that intervene in the generation of a particular organ. The interventionist mode of explanation assumed in developmental genetics seems to fit well with contemporary mechanistic accounts of how phenomenal and explanatory models relate in scientific research. Carl Craver (2006: 356) characterizes purely phenomenal models as those representations ‘that scientists construct as more or less abstract descriptions of a real system’. By contrast, explanatory models are meant to account not merely for how the system behaves, but also for ‘how it will behave under a variety of interventions’ (ibid., 358). The explanatory models of developmental genetics abstract away genes and gene interactions on the basis of the effects of their manipulation. The details recorded in the phenomenal model (e.g. the mechanical properties of the cells, the geometry of tissues) are assumed to be irrelevant for explanation, insofar as they are seen as somehow encoded by the causal (genetic) factors identified in the explanatory model.

The major handicap of the interventionist approach is that, while it allows identification of some of the causal factors (the genes and their products) that participate in a given developmental process, it cannot unravel the dynamics leading to the final outcomes of development (Xiong and Megason 2015). In other words, the interventionist approach cannot articulate the genotype–phenotype map (von Dassow and Munro 1999). Many developmental biologists hold an alternative view, which does not reduce development to a problem of gene expression. In what can be called the *morphogenetic view* of development, genes do not make structures in an autonomous way; instead they confer certain properties to cells, which self-organize in the construction of organs and

structures in accordance with physico-chemical laws (Alberch 1991). The properties resulting from the interactions at the molecular, cellular, and tissue levels (e.g. the physical properties of biological materials, the self-organizing capacities of cell aggregates, the geometry of tissues) are not codified in the genome but emerge from the dynamics of developmental systems (Oster et al. 1988).

The morphogenetic view of development implies a very different approach to the non-trivial relation between merely phenomenal and genuinely explanatory models in developmental biology. As recognized by Wilhelm His—one of the founders of experimental embryology and the inventor of the microtome—organismal form is not a self-evident problem awaiting mechanical explanation. Rather, if embryologists aim to understand morphogenesis, they should actively engage in reconstructing the embryo by reproducing the causal relationships they want to understand (Hopwood 1999). Whereas in His' case the 3D reconstructions of development were intimately tied to his topological explanations of morphogenesis, contemporary developmental biologists converge in claiming that the current level of technological progress associated with processual phenomenal models allows a switch from the perturbation approach to 'explanation in terms of dynamical formulation and behavior' (von Dassow and Munro 1999: 310).

In this view, the explanations of developmental genetics are seen as qualitative in nature, whereas the progress in quantitative imaging of dynamic phenotypes is considered as paving the way towards the quantitative explanation of development (Oates et al. 2009). Thus, in a recent review, Jennifer Lippincott-Schwartz identifies two approaches to development. She describes the molecular explanation of **(p.277)** development as instantiating a 'structure approach' to the developing organism, insofar as it attempts to obtain the blueprint of normal development from knowledge of the epigenomic state of the organism. In contrast, those explanations of development that aim to characterize the cells' relationships with their cellular and tissue environment during development are seen as instantiating a 'process approach', insofar as they need to characterize cell behaviours throughout the entire duration of development. The 'imaging approach' appears as the bridge between the two explanatory approaches, owing to the ability of imaging to provide quantitative descriptions of spatio-temporal relationships among genes and the associated cell and tissue outputs (Lippincott-Schwartz 2011).

It might be argued that the phenomenal models of development provided by current live imaging techniques are closer to explanations in the morphogenetic approach than to explanations in the interventionist approach. In the intreventionist approach of developmental genetics, phenomenal models of development are 'detached' from the explanatory models, being mere illustrations of the effect of genes in development. In contrast, in the

morphogenetic approach, phenomenal models act as a kind of scaffolding for the explanatory models of developmental processes. Xiong and Megason (2015) highlight two ways in which this interaction between imaging and modelling (or between phenomenal and explanatory models, in my terminology) takes place. First, a detailed observation of the phenomena to be explained allows formulation and testing of explanatory models. Thus cell migratory tracks, cell division patterns, and lineage trees can be tested against biophysical models of cell behaviour and cell mechanics. Here quantitation plays an essential role, since mathematical modelling requires precise numbers to use the data for modelling. In this way, explanatory models of a given developmental process can only become testable once the process is translated into quantitative descriptions. Second, since the morphogenetic approach aims to provide quantitative explanations of the dynamics of development, modelling demands imaging to have the highest possible temporal amplitude. It is in the context of specific, testable models that perturbation can become a truly powerful tool for explanation.

An illustrative example of how imaging can play a crucial role in formulating morphogenetic explanations of development is the unravelling of the physical forces that intervene in the epiboly process in zebrafish embryos (Xiong and Megason 2015). In zebrafish epiboly, the enveloping cell layer (EVL) surface epithelium at the animal pole spreads over the yolk cell, dragging deep cells along via adhesion. According to the prevalent model, the force-generating mechanism driving the spreading is the contraction exercised by a contracting ring of actomyosin on the frontier of the EVL. However, imaging of epiboly at high resolution at the marching frontier has allowed us to identify friction-resistant actomyosin flows as an equally important force-generating mechanism driving the spreading of the EVL.

5. Conclusions

A processual view of biological entities might be said to be congenial to embryologists. Throughout the history of embryology, philosophers and naturalists have denounced the artificiality of the static, purely morphological characterization of **(p.278)** development, blaming the anatomists' bent for forms frozen in time. However, the intractability and speed of developmental processes progressively led to an epistemological abandonment of processes in favour of discretizing ontogenies in arrays of patterns. Very recently, however, new microscopic, video, and bioinformatic techniques for visualizing and analysing developmental processes are finally making it possible to bring processes back from the noumenal darkness, so that they may be treated as proper objects of research in their own right. Since the early years of the new millennium, films of 'digital embryos' built from in vivo microscopy not only have started to replace the static series of normal stages as the standard

representations of development, but also are contributing to a processual understanding of development.

In this chapter I have shown that the introduction of time-lapse imaging in developmental biology has opened the door to a whole new realm of processual phenomena and has cast well-known developmental processes under a radically new dynamic light. I have also discussed how imaging technologies are important actors in the current return of organicism in developmental biology, being essential tools for capturing both the holistic and the hierarchical dimensions of morphogenesis. Moreover, I have examined how, in overcoming the methodological trade-off between spatial and temporal resolution, 4D imaging has simultaneously shortened the theoretical distance between processual and structural approaches to development. Finally, I have argued that the quantitative information encoded in contemporary images of development transcends the traditional role associated with visual models as mere illustrations of causal theories. In fact, in morphogenetic approaches to development, the construction of phenomenal models appears to take on a crucial role in the process of formulating and testing explanatory models.

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References

Bibliography references:

Alberch, P. (1991). From Genes to Phenotype: Dynamical Systems and Evolvability. *Genetica* 84 (1): 5–11.

Baedke, J. (2013). The Epigenetic Landscape in the Course of Time: Conrad Hal Waddington’s Methodological Impact on the Life Sciences. *Studies in History and Philosophy of Biological and Biomedical Sciences* 44 (4): 756–73.

Bergson, H. (1911). *Creative Evolution*. New York: Henry Holt and Company.

Boehm, B., Rautschka, M., Quintana, L., Raspopovic, J., Jan, Z., and Sharpe, J. (2011). A Landmark-Free Morphometric Staging System for the Mouse Limb Bud. *Development* 138 (6): 1227–34.

Bohr, N. (1933). Light and life. *Nature* 133: 421–3 and 457–9.

(p.279) Bonner, J. T. (2015). *Life Cycles: Reflections of an Evolutionary Biologist*. Princeton: Princeton University Press.

Brainered, E. L. and Hale, M. E. (2006). In vivo and Functional Imaging in Developmental Physiology. In S. Warburton and W. Burggren (eds), *Comparative Developmental Physiology* (pp. 21–40). New York: Oxford University Press.

Brigandt, I. (2003). Homology in Comparative, Molecular, and Evolutionary Developmental Biology: The Radiation of a Concept. *Journal of Experimental Zoology* 299 (1): 9–17.

Brigandt, I. (2015). Evolutionary Developmental Biology and the Limits of Philosophical Accounts of Mechanistic Explanation. In P.-A. Braillard and C. Malaterre (eds), *Explanation in Biology* (pp. 135–73). Berlin: Springer.

Chadarevian, S. and Hopwood, N. (2004). *Models: The Third Dimension of Science*. Stanford: Stanford University Press.

Craver, C. F. (2006). When Mechanistic Models Explain. *Synthese* 153: 355–76.

Davidson, D. and Baldock, R. (2001). Bioinformatics beyond Sequence: Mapping Gene Function in the Embryo. *Nature Reviews Genetics* 2 (6): 409–17.

De Beer, G. (1958). *Embryos and Ancestors*. Oxford: Oxford University Press.

Fusco, G., Carrer, R., and Serrelli, E. (2014). The Landscape Metaphor in Development. In A. Minelli and T. Pradeu (eds), *Towards a Theory of Development* (pp. 114–28). Oxford: Oxford University Press.

Gaycken, O. (2012). The Secret Life of Plants: Visualizing Vegetative Movement, 1880–1903. *Early Popular Visual Culture* 10 (1): 51–69.

Gilbert, S. (2000). Diachronic Biology Meets Evo-Devo: C. H. Waddington's Approach to Evolutionary Developmental Biology. *American Zoologist* 40: 729–37.

Gilbert, S. and Sarkar, S. (2000). Embracing Complexity: Organicism for the 21st Century. *Developmental Dynamics* 219 (1): 1–9.

Gordon, R. (2009). Google Embryo for Building Quantitative Understanding of an Embryo as It Builds Itself. II: Progress toward an Embryo Surface Microscope. *Biological Theory* 4 (4): 396–412.

Gregg, C. L. and Butcher, J. T. (2012). Quantitative in vivo Imaging of Embryonic Development: Opportunities and Challenges. *Differentiation; Research in Biological Diversity* 84 (1): 149–62.

Griesemer, J. R. (2000). Reproduction and the Reduction of Genetics. In P. J. Beurton, R. Falk, and H.-J. Rheinberger (eds), *The Concept of the Gene in Development and Evolution: Historical and Epistemological Perspectives* (pp. 240–85). New York: Cambridge University Press.

Griesemer, J. R. (2002). Time: Temporality and Attention in Iconographies of the Living. In H. Schmidgen (ed.), *Experimental Arcades: The Materiality of Time Relations in Life Sciences, Art, and Technology (1830–1930)* (pp. 45–57). Berlin: Max Plank Institut für Wissenschaftsgeschichte.

Griesemer, J. R. (2007). Tracking Organic Processes: Representations and Research Styles in Classical Embryology and Genetics. In M. D. Laubichler and J. Maienhein (eds), *From Embryology to Evo-Devo* (pp. 375–433). Cambridge, MA: MIT Press.

Hall, B. (2003). Unlocking the Black Box between Genotype and Phenotype: Cell Condensations as Morphogenetic (modular) Units. *Biology & Philosophy* 18 (2): 219–24.

Hopwood, N. (1999). 'Giving Body' to Embryos: Modeling, Mechanism, and the Microtome in Late Nineteenth-Century Anatomy. *Isis* 90 (3): 462–96.

Hopwood, N. (2005). Visual Standards and Disciplinary Change: Normal Plates, Tables and Stages in Embryology. *History of Science* 43: 239–303.

(p.280) Hopwood, N. (2007). A History of Normal Plates, Tables and Stages in Vertebrate Embryology. *The International Journal of Developmental Biology* 51 (1): 1–26.

Jaeger, J. and Monk, N. (2015). Everything Flows: A Process Perspective on Life. *EMBO Reports* 16 (9): 1064–7.

Jamniczky, H. A., Boughner, J. C., Rolian, C., Gonzalez, P. N., Powell, C. D., Schmidt, E. J., et al. (2010). Rediscovering Waddington in the Post-Genomic Age. *Bioessays* 32 (7): 553–58.

Keller, P. J., Schmidt, A. D., Wittbrodt, J., and Stelzer, E. H. K. (2008). Reconstruction of Zebrafish Early Embryonic Development by Scanned Light Sheet Microscopy. *Science* 322 (5904): 1065–9.

Kelty, C. and Landecker, H. (2004). A Theory of Animation: Cells, L-Systems, and Film. *Grey Room* 17: 30–63.

Khairy, K. and Keller, P. J. (2011). Reconstructing Embryonic Development. *Genesis* 49 (7): 488–513.

Kirschner, M., Gerhart, J., and Mitchison, T. (2000). Molecular ‘Vitalism’. *Cell* 100 (1): 79–88.

Landecker, H. (2005). Cellular Features: Microcinematography and Film Theory. *Critical Inquiry* 31 (4): 903–37.

Landecker, H. (2006). Microcinematography and the History of Science and Film. *Isis* 97 (1): 121–32.

Landecker, H. (2009). Seeing Things: From Microcinematography to Live Cell Imaging. *Nature Methods* 6 (10): 707–9.

Landecker, H. (2012). The Life of Movement: From Microcinematography to Live-Cell Imaging. *Journal of Visual Culture* 11 (3): 378–99.

Laubichler, M. D. and Wagner, G. P. (2001). How Molecular Is Molecular Developmental Biology? A Reply to Alex Rosenberg’s Reductionism Redux: Computing the Embryo. *Biology & Philosophy* 16 (1): 53–68.

Lippincott-Schwartz, J. (2011). Bridging Structure and Process in Developmental Biology through New Imaging Technologies. *Developmental Cell* 21 (1): 5–10.

Love, A. C. (2010a). Idealization in Evolutionary Developmental Investigation: A Tension between Phenotypic Plasticity and Normal Stages. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences* 365 (1540): 679–90.

Love, A. C. (2010b). Rethinking the Structure of Evolutionary Theory for an Extended Synthesis. In M. Pigliucci and G. B. Müller (eds), *Evolution: The Extended Synthesis* (pp. 403–41). Cambridge, MA: MIT Press.

Luengo-Oroz, M. A., Ledesma-Carbayo, M. J., Peyriéras, N., and Santos, A. (2011). Image Analysis for Understanding Embryo Development: A Bridge from Microscopy to Biological Insights. *Current Opinion in Genetics and Development* 21 (5): 630–7.

Maienschein, J. (1991). Epistemic Styles in German and American Embryology. *Science in Context* 4 (2): 407–27.

Megason, S. G. and Fraser, S. E. (2007). Imaging in Systems Biology. *Cell* 130 (5): 784–95.

Meijering, E., Smal, I., Dzyubachyk, O., and Olivo-Marin, J. C. (2008). Time-Lapse Imaging. In Q. Wu, F. A. Merchant, and K. R. Castleman (eds), *Microscope Image Processing* (pp. 401–40). Amsterdam: Elsevier Academic Press.

Minelli, A. (2003). *The Development of Animal Form: Ontogeny, Morphology, and Evolution*. Cambridge: Cambridge University Press.

Nicholson, D. J. and Gawne, R. (2015). Neither Logical Empiricism nor Vitalism, but Organicism: What the Philosophy of Biology Was. *History and Philosophy of the Life Sciences* 37 (4): 345–81.

Nuño de la Rosa, L. (2010). Becoming Organisms: The Organisation of Development and the Development of Organisation. *History and Philosophy of the Life Sciences* 32 (2–3): 289–315.

(p.281) Nuño de la Rosa, L. and Etxeberria, A. (2012). Pattern and Process in Evo-Devo: Descriptions and Explanations. In H. de Regt, S. Hartmann, and S. Okasa (eds), *EPSA Philosophy of Science: Amsterdam 2009*, vol. 1 (pp. 263–74). Amsterdam: Springer.

Oates, A. C., Gorfinkiel, N., Gonzalez-Gaitan, M., and Heisenberg, C.-P. (2009). Quantitative Approaches in Developmental Biology. *Nature Reviews Genetics* 10 (8): 517–30.

Oster, G. F., Shubin, N., Murray, J., and Alberch, P. (1988). Evolution and Morphogenetic Rules: The Shape of the Vertebrate Limb in Ontogeny and Phylogeny. *Evolution* 42 (5): 862–84.

Pantazis, P. and Supatto, W. (2014). Advances in Whole-Embryo Imaging: A Quantitative Transition Is Underway. *Nature Reviews Molecular Cell Biology* 15 (5): 327–39.

Perini, L. (2005). Explanation in Two Dimensions: Diagrams and Biological Explanation. *Biology & Philosophy* 20 (2): 257–69.

Peterson, E. L. (2011). The Excluded Philosophy of Evo-Devo? Revisiting C. H. Waddington's Failed Attempt to Embed Alfred North Whitehead's 'Organicism' in Evolutionary Biology. *History and Philosophy of the Life Sciences* 33 (3): 301–20.

Richardson, M. K. (1995). Heterochrony and the Phylotypic Period. *Developmental Biology* 172 (2): 412–21.

Rieppel, O. (2006). 'Type' in Morphology and Phylogeny. *Journal of Morphology* 267 (5): 528–35.

Rittscher, J. (2010). Characterization of Biological Processes through Automated Image Analysis. *Annual Review of Biomedical Engineering* 12 (1): 315–44.

Salazar-Ciudad, I. and Jernvall, J. (2004). How Different Types of Pattern Formation Mechanisms Affect the Evolution of Form and Development. *Evolution and Development* 6 (1): 6–16.

Sharpe, J. (2008). Optical Projection Tomography. In C. W. Sensen and B. Hallgrimsson (eds), *Advanced Imaging in Biology and Medicine: Technology, Software Environments, Applications* (pp. 199–224). Berlin: Springer.

Stramer, B. M. and Dunn, G. A. (2015). Cells on Film: The Past and Future of Cinemicroscopy. *Journal of Cell Science* 128 (1): 9–13.

Tomer, R., Khairy, K., Amat, F., and Keller, P. (2012). Quantitative High-Speed Imaging of Entire Developing Embryos with Simultaneous Multiview Light-Sheet Microscopy. *Nature Methods* 9 (7): 755–63.

Totaro, D. (2001). Time, Bergson, and the Cinematographic Mechanism: Henri Bergson on the Philosophical Properties of Cinema. *Offscreen* 5 (1). http://offscreen.com/view/bergson1.

Vienne, F. (2015). Seeking the Constant in What Is Transient: Karl Ernst von Baer's Vision of Organic Formation. *History and Philosophy of the Life Sciences* 37 (1): 34–49.

Von Dassow, G. and Munro, E. (1999). Modularity in Animal Development and Evolution: Elements of a Conceptual Framework for EvoDevo. *Journal of Experimental Zoology* 285 (4): 307–25.

Waddington, C. H. (1957). *The Strategy of the Genes*. London: Allen & Unwin.

Webb, A. B. and Oates, A. C. (2015). Timing by Rhythms: Daily Clocks and Developmental Rulers. *Development, Growth and Differentiation* 58 (1): 43–58.

Wellmann, J. (2015). Folding into Being: Early Embryology and the Epistemology of Rhythm. *History and Philosophy of the Life Sciences* 37 (1): 17–33.

Weninger, W. J., Tassy, O., Darras, S., Geyer, S. H., and Thieffry, D. (2004). From Experimental Imaging Techniques to Virtual Embryology. *History and Philosophy of the Life Sciences* 26 (3–4): 355–75.

Winslow, B. B., Takimoto-Kimura, R., and Burke, A. (2007). Global Patterning of the Vertebrate Mesoderm. *Developmental Dynamics* 236 (9): 2371–81.

Wolkenhauer, O. and Ullah, M. (2007). All Models Are Wrong. In F. Boogerd, F. J. Bruggeman, J.-H. Hofmeyr, and H. V. Westerhoff (eds), *Systems Biology: Philosophical Foundations* (pp. 163–79). Amsterdam: Elsevier Academic Press.

(p.282) Wong, C. C., Chen, A. A., Behr, B., and Shen, S. (2013). Time-Lapse Microscopy and Image Analysis in Basic and Clinical Embryo Development Research. *Reproductive BioMedicine Online* 26 (2): 120–9.

Wong, M. D., Eede, M. C. van, Spring, S., Jevtic, S., Boughner, J., Lerch, J., and Henkelman, R. M. (2015). 4D Atlas of the Mouse Embryo for Precise Morphological Staging. *Development* 142 (20): 3583–91.

Wong, C. C., Loewke, K. E., Bossert, N. L., Behr, B., De Jonge, C. J., Baer, T. M., and Reijo Pera, R. A. (2010). Non-Invasive Imaging of Human Embryos before Embryonic Genome Activation Predicts Development to the Blastocyst Stage. *Nature Biotechnology* 28 (10): 1115–21.

Woodger, J. H. (1929). *Biological Principles: A Critical Study*. London: Kegan Paul.

Xiong, F. and Megason, S. G. (2015). Abstracting the Principles of Development Using Imaging and Modeling. *Integrative Biology: Quantitative Biosciences from Nano to Macro* 7 (6): 633–42.

Notes:

([1]) On this conception of development, see also chapter 11.

([2]) Organicist conceptions of the organism are examined in chapters 1 and 7.

([3]) It has been argued that Waddington's commitment to Whitehead's process metaphysics was one of the reasons for his lack of impact on the evolutionary biology of his time (Peterson 2011). For detailed discussions of Waddington's processual views, see chapters 11 and 12.

([4]) Curiously enough, Henri Bergson—one of the most passionate advocates of a process metaphysics—did not show any enthusiasm for the film camera as an enhancer of temporal perception (Totaro 2001). On the contrary, in his *Creative Evolution*, he argued that the cinematographer was an instrument analogous to the human intellect, insofar as it acted as a mechanism to spatialize time (Bergson 1911). According to Bergson, the intellect is by nature a spatializing mechanism that can only acquire knowledge by expressing movement, the essence of reality, in static and discontinuous terms. In the same way, the camera breaks down real movement into a series of still frames and then re-creates (through projection) an illusion of movement. The cinema, just like our intellect, is incapable of capturing what Bergson calls 'duration', a process where past, present, and future overlap.

([5]) For a review of the current state of the art in time-lapse microscopy imaging, see Meijering et al. 2008.

([6]) In particular, when they were introduced in cell biology in the early twentieth century, dynamic modes of imaging were criticized as unscientific on account of their qualitative nature (Landecker 2009).