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ORIGINAL PAPER

"Organization" as Setting Boundaries of Individual Development

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Abstract "Development" suggests that there is something that is developing, or changing over time. We can ask about temporal boundaries of that developmental process, asking when development begins or ends and whether it has defined stages along the way, for example. We can ask about spatial boundaries as well: where does the developing object start and end? For this article, I ask about the boundary definition of the developing organism in particular. What is an individual organism, and what defines it as the same organism as it changes over time? In particular, how has this been answered historically: how have researchers described and explained what an individual developing organism is? This article explores ideas and approaches especially starting in the late 19th century, and in particular looks at the role of "organization."

Keywords Development · Embryo · Individual · Organism · Organization

What is it that developmental researchers have meant by "development"? It's one of the things that individual organisms do from their fertilization onward. They grow, cells differentiate, and organ systems arise through morphogenesis. They mature, senesce, and die, helping give rise to the next generation. Of course, there are questions about what causes development and about the boundaries of development in a number of senses, as discussed in the set of articles here. But there are also questions about what *constrains* and enables the development of an individual organism so that it is structurally and functionally integrated. What makes an individual developing organism something identifiable such that we can tell what it is that is developing?

One answer that was especially popular a century ago focused on "organization." It may no longer be clear how this even could be a scientifically satisfying answer to the questions at hand. Here, I will argue that taking this part of the history of biology seriously helps us see development in a new light and shows how organization of the regulatory whole can still be said to help us understand boundaries of development.

Generally, for sexually reproducing animals at least, biologists have thought that development, as distinct from inheritance, is what happens after the egg and sperm combine in fertilization. As Wilson (1896) recognized in the title of the first edition of his book, which is still considered a classic, biology is about *The Cell in Development and Inheritance* (1896). Within this context, development seems to involve the process of transforming that fertilized egg through the embryonic and fetal stages and on through morphogenesis, differentiation, growth, and so on. Development involves organization of material into an organism. This involves organism as a process (becoming organized) and as a result (being organized).

Today, we think we know that we are *organisms*, yes, and so are mice and frogs and chicks and worms and such. Furthermore, we seem to be spatially bounded in the sense that we can tell where our skin ends, for example. We feel like *individuals* and feel that we know what that means. Yet, we already realize that we can replace parts either naturally (cells and tissues die and are replaced at a rapid

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rate every hour, every day) or through engineering (organs, tissues, limbs, stem cells, even genes). The replacement can occur starting at the one-cell stage, with genetic replacement or enhancement, or at the two-cell stage when two cells from different eggs are combined. There is a kind of Aristotle's ship of Theseus problem here, in that so much is replaced that we end up with material that is quite different from what we started with. Yet, we feel that it is the same "ship," or the same organism just undergoing development.

We also know that the individual is a composite of many symbiotic and parasitic microorganisms that are part of us, aiding digestion and working away in our hearts and minds. Tumors are us, too, and even teratomas in which a mix of quite the wrong kinds of cells are developed in the wrong places at the wrong times. Each organism starts as a fertilized cell, but becomes a complex community system. Yet, we think of it as an organized, organic, individual whole organism. We know that these processes occur in mice and other species, and it seems probable that they either do or can occur in humans as well. Therefore, it is worth reflecting on how researchers have understood organization, and the way organization helps to define and reflect our understanding of organisms. The emphasis here is on historical interpretations of the whole developing organism, with many intersections with other philosophical analyses included in this collection.

Understanding Organization

Many thinkers over the past century and a quarter have discussed concepts of organization, what it means to be an organism, individuality of organisms, and relations of the developing organism to heredity and developmental processes. Here, I point to several approaches common at the beginning of the twentieth century, when the topic attracted lively debates and intense interest. Of course, we have made tremendous progress in understanding developmental biology since, but we have also continued to draw on the same basic strands of thinking introduced then. It is worth sorting out the different strands that come together today in new ways.

In 1976, in her *Crystals, Fabrics, and Fields*, Donna Haraway pointed to three approaches by looking at three intriguing individuals. Ross Granville Harrison, Joseph Needham, and Paul Weiss adopted different approaches in what Haraway saw as a move away from an older framework that addressed disputes about preformation versus epigenesis and vitalism versus mechanism to a more wholistic view based in organicism. Haraway's interpretation of the metaphors they used and the changing understanding of developing embryos introduced some of the possible approaches. I refer readers to Haraway's discussions, especially of Needham and Weiss, as deserving more attention.

Here, however, I take a historical approach to survey the larger range of approaches for explaining the organization that clearly exists or emerges over time. This is just an introduction to a complex of views, which sometimes overlapped as a researcher held more than one position, even while emphasizing one more than others. Nonetheless, the approaches fall roughly into distinct groups that emphasize the:

Structural The egg itself is organized in some way by the end of the fertilization process. This may happen in the cytoplasm, through *cytoplasmic localization*. Or in the nucleus, through some process of *nuclear determinism.* Or through an interaction of cytoplasmic and nuclear factors.

Physiological/Metabolic It is the functional interactions rather than the structure itself that causes the organization and developmental processes. This includes the idea that the metabolic processes are driven by primarily *physical* forces or fields that exert influence and lead to organization. Or alternatively, they are driven by *chemical* differences.

Wholistic Regulatory Interaction From the beginning, the whole egg-becoming-organism experiences an interactive, regulatory action of the whole such that the "wholeness" shapes the responses to internal and external environmental changes.

Now let us look historically at the emergence and interplay of these points of view starting at the end of the nineteenth century.

Roux and Driesch: Structural or Wholistic Embryos?

It is worth a reminder of what the apparent disagreements between the familiar cases of Wilhelm Roux and Hans Driesch were really about. On the face of it, this was a debate about Roux's preformation versus Driesch's epigenesis. Later, it was presented as a debate about Roux's materialism versus Driesch's vitalism. Somewhere along the line, it actually became a disagreement about the relative importance of experimental biological or metaphysical approaches to understanding life, on one hand, and on the other hand about the relative determinism or regulatory capacities of organic development. Some of this is familiar ground, but we can look at it in new ways.

In 1888, Roux was studying frog eggs. He had come to the conviction that the first egg contains all the inherited material for subsequent development, and that with each cell division, the material was distributed differentially into the different cells. The result was, as he put it, a mosaic of different cells. He hypothesized that if he could kill one of the first two cells after division, the result would be development of one-half of a frog. In his enthusiasm for experimental embryology, or *Entwicklungsmechanik*, he carried out the analytical experiment. He stuck one of the two cells with a hot needle to kill it, to determine the extent to which each cell undergoes "self-differentiation—to determine whether, and if so how far, the fertilized egg is able to develop independently as a whole and in its individual parts." The alternative was that "normal development can take place only through direct formative influences of the environment on the fertilized egg or through the differentiating interactions of the parts of the egg separated from one another by cleavage" (Roux 1888, p. 133).

Roux predicted half frogs, and that is what he saw. In fact, his method involved leaving the one apparently dead cell attached to the other because he had not figured out how to remove the rather strong protective membrane that surrounds frog eggs. The result was one cell that looked like half the normal embryo and one that looked like inert matter that was not undergoing further development. Cells, it seemed to Roux, are very much self-differentiating. They are guided by inheritance, but then run forward on developmental processes. He concluded that his earlier ideas were confirmed and that,

> … developmental processes may not be considered a result of the interaction of all parts, or indeed even of all the nuclear parts of the egg. We have, instead of such differentiating interactions, the self-differentiation of the first blastomeres and of the complex of their derivatives into a definite part of the embryo. (Roux 1888, pp. 25–26)

Driesch agreed that this seemed likely. He took up the same experimental idea, only with the sea urchins that he had readily nearby during his studies at the Naples Stazione Zoologica. Driesch knew from earlier study that it was possible with sea urchins to shake the two cells apart, and he felt that this would be a cleaner experiment than Roux's in which the inert material remained attached. He reported that he shook the cells apart, then fully expected that by the next morning, he would find two half urchin larvae. Instead, he found two smaller sized complete pluteus larval forms (Driesch 1891–1892).

This led him to conclude that there was a regulatory process, what he eventually called a "harmonious equipotential system"—which emphasized the system and harmonious whole. Driesch saw this system as maintained by an Aristotelian-inspired "entelechy," which certainly had vitalistic overtones, and he felt that mere materialistic mechanisms could not—based on what anybody knew at the time—explain how the whole remains an organized whole. What is perhaps most important about Driesch's view, however, is his emphasis on regulation and his demand that the regulatory abilities of the whole have to be explained to achieve an adequate understanding of development.

Cytoplasmic Localization

This was a hot topic in the 1890s, at times dominating discussion at the Marine Biological Laboratory (MBL) in Woods Hole, Massachusetts, and the Stazione Zoologica in Naples. The MBL Director Charles Otis Whitman (1894) noted that organization does not come from nothing, magically, but rather,

> The indubitable fact on which we now build is no bit of inorganic homogeneity, into which organization is to be sprung by a coagulating principle, or cooked in by a *calidum innatum*, or wrought out by a spinning archaeus, but the *ready-formed living germ, with an organization cut directly from a preexisting, parental organization of the same kind.* [That is,] there is some primary organization that underlies every anatomical organ. (Whitman 1894, pp. 212–213)

Whitman did not, in fact, explain further but he actively recruited others to take up the question of how organization is established.

Wilson was one of those who did take up the question. In his *Cell*, which was so widely read and carefully studied by generations of students that it is worth taking it here as the entry point for the diversity of views, Wilson provided an excellent summary of those, including those drawing on interpretations of cytoplasmic localization. Some researchers such as Edwin Grant Conklin or Oscar Hertwig had found examples of what seemed to be highly structured eggs from the very earliest stages, while others found considerable homogeneity at that point. The structured examples seemed in some cases to involve different sorts of cytoplasmic localizations, with various degrees of determinism with respect to subsequent development. Others denied that the cytoplasm was localized at all, or at least not in ways that mattered for development.

Wilson concluded that it was possible to reconcile the apparent differences,

> … with the hypothesis of cytoplasmic isotropy. Primarily the egg-cytoplasm is isotropic in the sense that its various regions stand in no fixed and necessary relations with the parts to which they respectively give rise. Secondarily, however, it may undergo differentiations through which it acquires a definite regional predetermination which becomes ever more

> firmly established as development advances. (Wilson 1896, p. 320)

It is possible to have a balance of cytoplasmic localization and responsiveness to conditions. Furthermore, "the process, does not, however, begin at the same time, or proceed at the same rate in all eggs" (p. 320). Eggs might have structure, and they might even be organized from the beginning. They might even, as Jacques Loeb put it (1916, pp. 151, 39), serve as "an embryo in the rough." Yet, they seem most often to be able to respond to the changing environmental conditions during the developmental process, and the localization is therefore not deterministic. This was Wilson's view.

Nuclear Determinism

Wilson also took up the question whether it is the nucleus instead of the cytoplasm that determines what happens in development. Again, he concluded that the nucleus contributes, but that it is not decisive. Theodor Boveri was clearly the most important contributor to understanding the nature and role of the nucleus. Though Boveri's definitive study came later, already in 1896 Wilson saw the significance of his approach.

"The conclusion is irresistible," Wilson wrote,

> that the specific character of the cell is in the last analysis determined by that of the nucleus, that is by the chromatin, and that in the equal distribution of paternal and maternal chromatin to all the cells of the offspring we find the physiological explanation of the fact that every part of the latter may show the characteristics of either or both parents. (Wilson 1896, p. 258)

The nucleus matters; chromosomes matter. Furthermore, this was not just conjecture. Rather, Boveri "has attempted to test this conclusion by a most ingenious and beautiful experiment; and although his conclusions do not rest on absolutely certain ground, they at least open the way to a decisive test" (Wilson 1896, p. 258). Boveri had already embarked on what became a magnificent series of experiment with fragments of sea urchin eggs, drawing on the same techniques that Driesch had used in shaking apart cells and in this case even shaking cells into fragments. His evidence already showed that it made a difference whether the whole chromosome or only part, and which chromosomes, ended up in which fragment. Their developmental capacities were clearly directed by the particular nuclear components (see Laubichler and Davidson 2008).

As Wilson fully recognized, this did not mean that only nuclear determination is at work. His view was that nuclear and cytoplasmic structural influences work together. He summarized Driesch's theory and explained why he felt it was substantially correct, while pointing to work by Thomas Hunt Morgan and others as providing important experimental confirmation: we start with cells that have essentially equivalent nuclei, with the same chromosomal material distributed through mitotic division. Then,

> Through the influence of this idioplasm the cytoplasm of the egg, or of the blastomeres derived from it, undergoes specific and progressive changes, each change reacting upon the nucleus and inciting a new change. These changes differ in different regions of the egg because of pre-existing differences, chemical and physical, in the cytoplasmic structure; and these form the conditions ("Formbildungsfaktoren") under which the idioplasm operates. (Wilson 1896, p. 317)

We do not know how these processes work, Wilson acknowledged, and that is just fine. Indeed, "the progress of science is retarded rather than advanced by a premature attack upon its ultimate problems" (Wilson 1896, p. 330). Wilson's explication of that ultimate problem of development and organization did much for grounding the discussion that followed. Morgan agreed that the important thing for science was to take up questions that could be answered. Thus, "If our analysis of the problem of development leads us to the idea of an organization existing in the egg, our next problem is to discover how it acts during development" (Morgan 1901, p. 258). Twentieth-century researchers took up the challenge of explaining those unknown factors driving development about which Wilson felt it would be premature to speculate.

Metabolic Dynamic Factors

One bit of evidence that organization was considered an important topic for discussion still lies in the MBL collection in Woods Hole. The old card catalog, with its hand-typed entries and subject labels assigned by MBL librarians, sits outside the Archives and Rare Books Room. One of the subject headings is "Organization," and it consists of several dozen entries from Charles Manning Child's 1915a study of gradients to Conrad H. Waddington's 1957 edited symposium volume. This period brought different interpretations.

Child rejected cytoplasmic localization, vitalism, and other ideas that he considered as merely hypothetical ideas of organization. He wanted a materialistic, mechanistic explanation of organization. For Child, the embryo was organized into gradients that were set up progressively from the earliest developmental stages. The gradients set up linear, axial paths of differential "influence" and were dynamic and metabolic rather than strictly chemical or physical. In *Individuality in Organisms*, he provided evidence that such gradients exist, what they are, and how they work through dynamical interactions along the axes of dominance. He was convinced that these gradients are established very early, even in the egg before embryonic development begins (Child 1915a, p. 199), a point that others including Wilson had questioned.

That Child was committed to a dynamic metabolic view and was highly critical of structural or morphological views is clear from his concluding comments that,

> Being entirely unable to find any degree of intellectual satisfaction in those static conceptions of the organisms which seem to have no relation to anything else in the world and which raise many questions but answer none, and being forced by my own experimental investigations to conclusions very different from these, I have attempted to apply dynamic conceptions to certain biological problems, with the results which have been considered in the preceding pages. (Child 1915a, pp. 207–208)

He continued with an emphasis on the usefulness of such an approach for addressing central challenges in biology. This is because,

> whatever other value the dynamic viewpoint may possess, it serves as a basis for the synthesis and ordering of many facts in various fields which heretofore have seemed to have little or nothing in common, and I think we may say that it aids in bringing certain aspects of biology at least within hailing-distance of physic–chemical conceptions. (Child 1915a, pp. 207–208)

Child’s *Senescence and Rejuvenescence* (1915b), another very long book, reinforces the themes and makes the claim that development continues throughout all stages of an individual’s life.

Joseph Needham’s three-volume *Chemical Embryology* (1931) and *Biochemistry and Morphogenesis* (1942) provide another, later, approach to metabolic understanding of development. He begins the first volume with a wonderful philosophical and historical perspective on the problems of understanding development, which leads him to his chemical approach. “Chemical embryology is not indeed at a critical point in its history,” Needham proclaimed. Rather, it links with the morphological approach of classical embryology and the experimental approach of *Entwicklungsmechanik*, while also linking with genetics, “a science which is every day becoming more physiological and which will more and more seek for the effects of its factors in the biochemistry of development” (Needham 1931, p. 37). As Haraway explains, however, Needham’s point of view was not immediately adopted. Other alternative views also commanded attention.

Transplantation and Organization: Wholistic Regulatory Interactions

One of the most celebrated approaches was built on techniques of transplantation. Researchers in the 1890s began using frogs to transplant bits of frog embryos from one individual to another, asking what would happen and assessing what the result meant in terms of development. Harrison (1937) and Spemann (1938) became the dominant figures in this field. Since they each also acquired leadership positions in biology and trained many students, in the US and Germany, respectively, they played an important role in shaping interpretations of development.

Harrison’s best-known work, which raised new questions, was his transplantation of neuroblast cells out of the frog and into an external culture medium. He carried out the experiment to discover whether the neuroblast cells would be able to extend their fibers in a normal way or whether the nerve fibers needed the surrounding organism to organize and direct differentiation and growth. The fibers did grow, and Harrison concluded that much of what directs development comes from within the cells. This was the first tissue culture experiment and also the first stem cell experiment (Harrison 1910; Maienschein 1991).

Spemann also transplanted pieces of frog embryos, from one frog to another. His best-known study began with his student Hilde (Pröscholdt) Mangold and involved transplanting a piece from the dorsal lip of the blastopore stage of one frog to the interior of another embryo. The result was the “induction” of a second whole embryo attached to the first. The piece of tissue had seemingly “organized” the second embryo, and was therefore labeled an “organizer.” Spemann undertook a series of experiments to discover the nature of the organizer, and even (according to his scientific biographer Viktor Hamburger) considered vitalistic interpretations of this powerful organizing factor (Hamburger 1988; Spemann 1938).

In the conclusion of the 1938 volume that summarized his study, and which was delivered initially as a set of Silliman Lectures at Yale University at the invitation of Harrison, Spemann concluded that the experimental biologist must work very carefully. He must be “like the archeologist who pieces together the fragments of a lovely thing which are alone left to him. As he proceeds, fragment by fragment, he is guided by a conviction that these fragments are parts of a whole which, however, he does not yet know.” To understand the whole, he must work as an artist and not rush to conclusions or he cannot “ultimately achieve a true restoration of the master’s creation” (Spemann 1938, pp. 367–368). Making such true restorations of developmental processes is the challenge for developmental biologists.

Spemann clearly thought that the organizer material has to be alive, but Johannes Holtfreter showed that this is not so and that killed tissue or even inert material can produce the same effects (Holtfreter 1991). This, and other trends in the field, led Harrison to proclaim that the "state of the nation" of embryology was experiencing "a Tower of Babel" and needed much further clarification of the processes of organization and development (Harrison 1937).

Harrison was right. By the 1940s, embryology involved a lot of different approaches, with a lot of different underlying assumptions, and a lot of different methodologies involved to pursue them. World War II slowed research down for a while, and the 1950s brought a turn to incorporating genetics and to asking less about organization of the whole than about the underlying internal causes of developmental effects, especially effects of differentiation. This is not the place to survey that literature, which turned "embryology" into "developmental biology." But it is worth noting that researchers are today beginning to pick up many of the threads of embryological research that were left behind or that were not yet ready for productive scientific exploration. Let us look at studies of the embryo today and at ways in which the idea of its "organization" have become more complicated—and yet perhaps also more comprehensible.

Reorganizing Regulatory Interactions and Conclusions

Not all embryos are naturally organized autonomous things. Harrison showed that he could transplant cells and culture tissues outside the body. Spemann showed that moving small pieces of tissue could significantly change development. Their research built on the experimental studies of Roux and Driesch in assuming that experimentation can provide useful ways to enlighten us about what occurs in normal development.

In the 1960s, the plot thickened. In one line of research, Beatrice Mintz showed in mice that she would take cells from different lineages and stick them together. They would combine and produce perfectly normal looking and normal acting mice, even though they were chimeras drawn from two (or more) different individuals. The remarkable result was that the cells could reorganize and develop perfectly well. The resulting embryo was something she had constructed out of pieces of other embryos. She had caused a new organization, new individual, and new organism to emerge (Mintz 1962).

In other research, Leroy Stevens had discovered a strain of mice that develop teratomas. Typically in the testicles, the mice would develop mixtures of hair, tooth, and other cells that were definitely not following the normal organizational pattern. Stevens named them "pluripotent stem cells" and concluded that they retain their pluripotency much later than normal cells and end up not responding properly to the surrounding conditions as they developed. The apparently finely honed organization does not always work, particularly for those cells that are not "programmed" (as we call it now) in the "right" way (Stevens 1970). In this case, the organization of the parts within the whole was not quite right, and these parts were extras that did not fit.

Genetic engineering has shown the capacity for cells to receive altered genetic material and still develop "normally" or abnormally in interesting ways. Cloning and induced pluripotent stem cell technologies reveal the tremendous regulatory plasticity of developmental processes. Research in developmental evolution, including Eric Davidson's work in understanding gene regulatory networks (GRNs) has taken us far toward seeing the organized individual organisms as reflective of not only heredity and development but also evolution—another theme that Wilson recognized but noted that science was not ready to address effectively. All this study strongly indicates that the individual organized embryonic organism is a highly complex product of heredity, development, evolution, and modification through the action of experimental and environmental conditions. It is also responsive to changing conditions both within and outside the organism itself. The organization can, in fact, be reorganized. Autonomy, individuality, and the organismal organization can all be changed. As a result, we have new questions to add to the traditional ones about organization and the boundaries of developing individuals.

We are developing new and more sophisticated understandings of the boundaries of development in many ways. Understanding draws on the traditions for interpretation laid down starting 125 years ago. And recognition that organisms are not so well defined or bounded as we once thought surely raises new questions and offers intriguing new directions for philosophical as well as scientific exploration (see Pradeu 2011, this issue).

As one example, take stem cell research. Stem cells are defined as becoming certain types of cells because of their structure. They are valued because they function in particular ways and take up defined roles in the metabolic/physiological system. And they both develop and develop into something that we value as potentially clinically useful because of the regulatory capacities of the whole organism. They become valuable when they take up roles as part of an organized whole (on stem cells and development, see Laplane 2011, this issue). Therefore, we see that reflecting on how developmental researchers have thought about development in the three different ways outlined here can inform current understanding of the developmental processes and results. Wilson, after cautioning that, "the progress of science is retarded rather than advanced by a premature attack upon its ultimate problems," continued: He noted in 1896 that "the splendid achievements of cell research in the past 20 years stand as the promise of its possibilities for the future" (Wilson 1896, pp. 330). Perhaps with respect to understanding organization, we are at least developing effective tools to make real progress.

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