Models of Time for Reductive Explanations in Experimental Biology

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Abstract

Although most analyses of reduction focus on spatial relationships among natural phenomena (e.g., part-whole relations), time is also an important aspect of reductive explanations in biology. Three different models of time can be distinguished: historical, iterated compositional, and causal process. After characterizing each of these, I show that the causal process model of time corresponds most closely to reductive explanations of ontogeny and explains the success of generalizations derived from the laboratory study of model organisms that differ compositionally. Philosophical preoccupation with synchronic, compositional relations has obscured this model of time in the practice of experimental biology. Additionally, focusing on the causal process model uncovers a new conceptual possibility: conflicting explanatory preferences between spatial and temporal variables in a reductive explanation. This possibility raises new questions about reductionism related to the diversity of temporal measures utilized by scientists.

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1. Space, Time, and Reduction

Spatial relations are the primary focus in reductive explanations, such as wholes being reducible to their parts or macroscale properties being reducible to microscale properties (Wimsatt 2007, ch. 9). The vertebrate heart's rhythmic contraction can be attributed to the activity of its component myocardial cells. The asymmetrical location of the heart within the body cavity (an anatomical feature at a higher spatial level of organization) can be explained by asymmetrical gene expression patterns (properties of a more fundamental spatial level) during ontogeny (Levin 2005). Reductionism focuses on these kinds of relations but there is little consensus about the associated reasoning patterns (e.g., Robert 2004; Rosenberg 2006), in part because of the diversity of biological disciplines (e.g., ecology, genetics, or physiology) and the heterogeneity of units that can be involved (e.g., theories, explanations, concepts, methods, or properties).

There are also temporal relations in reductive explanations, though they have received less explicit attention (Hüttemann and Love forthcoming). Intuitively, this seems appropriate since spatial relations are so central to reductionism. But it turns out to be incorrect, both in terms of past philosophical discussions of reductionism and in terms of fully comprehending reductive explanation in contemporary biology. The vertebrate heart's rhythmic contraction must be related to the activity of its component myocardial cells over period of time. Asymmetrical gene expression must occur earlier in ontogeny than the resulting asymmetrical location of the heart within the body cavity. In this paper I describe three different models of time for reductive explanations: historical, iterated compositional, and causal process. The first two of these are identifiable in philosophical literature

stemming from the work of Ernest Nagel (1961), but the causal process model of time corresponds most closely to reductive explanations found in 'experimental biology' (Weber 2005), illustrated here by developmental biology. In addition, the causal process model of time helps to explain the success of reductive generalizations about ontogeny that result from the study of model organisms. Philosophical preoccupation with synchronic, compositional relations has obscured this model of time in the practice of experimental biology. My analysis also uncovers a potential conflict between explanatory preferences related to spatial and temporal variables. This requires scrutinizing the diversity of temporal measures utilized by scientists (e.g., periodizations) and, as a consequence, a more complex space of possibilities for reductionism in biological science becomes available.

2. Three Models of Time for Reductive Explanation

2.1 Historical

Nagel's account of theory reduction in science explicitly recognized the need for a *historical* time index.

> The question of whether a given science is reducible to another cannot in the abstract be usefully raised without reference to some particular stage of development of the two disciplines. Questions about reducibility can be profitably discussed only if they are made definite by specifying the established content at a given date of the science under consideration (Nagel 1961, 361).

Commentators discerned that this bifurcated the issue of reductionism into the comparison of theory content between "different" sciences at a particular stage of development and the relation between the "same" science at different stages of development (e.g., Schaffner

1967; see Winther 2009). Subsequent discussion sharpened the distinction between issues of theoretical succession through history (temporal) and mereological (spatial) relations between different levels of organization in a reductive explanation (e.g., Wimsatt 2007, ch. 11). Thus, a *historical* model of time is needed to capture how an earlier theory reduces to a later theory, and is distinct from the spatial relations that involve reducing the behavior of a system to the behavior of its parts.

This division has been assimilated into the philosophical discussion of reduction and codified as a distinction between *synchronic* and *diachronic* reduction.

> The term *reduction* is often used to refer to the relation between a theory and its historical successor. …This is … diachronic reductionism. My concern, on the other hand, is solely with synchronic reductionism, … with the relations between coexisting theories addressed to different levels of organization (Dupré 1993, 94-5).

> Synchronic reduction is mereological explanation, in which the behavior of more composite items described in reduced theories is explained by derivation from the behavior of their components by the reducing theory. Thus, reduction is a form of explanation. Diachronic reduction usually involves the succession of more general theories which reduce less general ones, by showing them to be special cases which neglect some variables, fail to measure coefficients, or set parameters at restricted values (Rosenberg 2006, 28).

The distinction separates Nagelian theory reduction *sensu* succession ('diachronic') from part-whole explanatory reduction, which is interpreted as a relation between two different theories at a particular time ('synchronic').[1] Although the distinction is clear, the terminology (synchronic versus diachronic) is problematic because it intimates that the only

[1] There is an analogue of this in Nagel's distinction between emergence understood as irreducible hierarchical organization (i.e., the behavior of the whole cannot be explained by the behavior of the parts) and 'evolutionary emergence' understood as new, more complex entities arising from a historical process (Nagel 1961, 366ff). The former is synchronic and the latter is diachronic.

model of time relevant to reduction is historical. If reductive explanations are inherently synchronic, concerned primarily with compositional relations at a particular time, then temporality is only needed for discussing issues of theoretical succession. But this is implausible given that explanations of biological systems typically have explicit temporal components: "biological theories are usually given in the form of a series of temporal (and frequently causal) models. In physics, time is usually eliminated by making it implicit in differential equations, whereas in biology a temporal process, …is the rule" (Schaffner 1993, 83-4). In fact, "synchronic reduction" is a misnomer because it actually involves a different model of time.

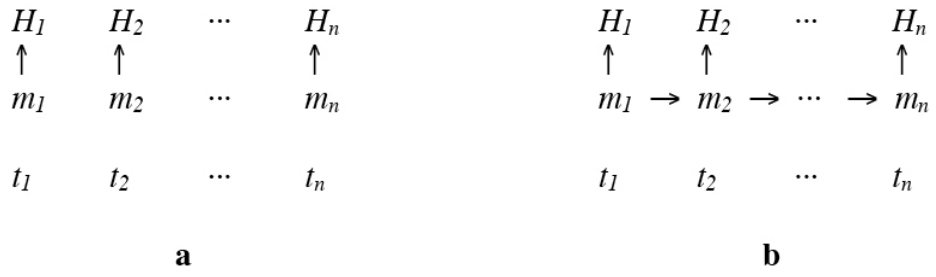
2.2. Iterated Compositional

Given that most biological explanations involve temporality, why is there such consensus that part-whole reduction labeled "synchronic"? One possibility is that the reductive explanation involves two distinct aspects: a reductive relation that is compositional and a causal relation that is non-hierarchical (i.e., does not involve relating two different levels of organization, however defined). Take, for example, reductive explanations of a beating heart. The heart's rhythmic contraction (*H*) is derived from the activity of its component myocardial cells (*m*) in a two-step fashion (Figure 1).[2] First, the part-whole spatial relations between the heart and its constituents are established for all relevant times ($t_1,...,t_n$). These compositional relations are reductive because an account of the behavior of the whole for any instant of time can be *derived* from an account of the behavior of the parts at that time (at least in principle). Thus, one step of the reductive explanation is synchronic

[2] This picture of the vertebrate heart's cellular composition is simplified for exegetical purposes. In addition to myocardial cells, the heart contains other cell types such as vascular smooth muscle cells.

(Figure 1a). But since the very idea of rhythmically contracting involves reference to a temporally extended process, the compositional relations of parts to a whole must be *iterated* to achieve an adequate explanation. The behavior of the parts at earlier times (e.g., m_1) must be related to the behavior of parts at later times (e.g., m_2), i.e., a specification of 'part-dynamics' (Figure 1b). Although necessary to the explanation, this second step is not specifically reductive because it does not involve relating distinct hierarchical levels. Therefore, "synchronic reductionism" (*sensu* Dupré and Rosenberg) involves both synchronic compositional relations between wholes and parts, *and* 'diachronic' dynamical relations among the parts (or at a designated level of organization). The reductive explanation is not wholly synchronic because it involves iterating the compositional relations over time.

Figure 1



The two-step process involving both compositional and dynamical (or causal) relations corresponds to a distinction Nagel made between spatial and temporal modes of organization in biological explanations.

> [There is] a contrast between the *spatial* organization of anatomically distinguishable parts of an organ and the *temporal* (or spatiotemporal) organization of changes in those parts. What is investigated under each term of the contrasting pair is a mode of organization or a

> type of order. In the one case the organization is primarily if not exclusively a spatial one, and the object of the investigation is to ascertain the spatial distribution of organic parts and the modes of their linkage. In the other case the organization has a temporal dimension, and the aim of the inquiry is to discover sequential and simultaneous orders of change in the spatially ordered and linked parts of organic bodies (Nagel 1961, 426).

Although these modes can be pursued independently, reductive explanations using the iterated compositional (IC) model of time show how they can be coupled. The compositional relations are established synchronically and then changes over time are accounted for in terms of part-dynamics. It also upholds the intuition about the priority of spatial relations in reductive explanations, something Nagel explicitly acknowledged: "it is difficult to make sense of any supposition that a system of activities having a temporal organization is not also a system of spatially structured parts manifesting these activities" (426). What remains to be seen is whether the IC model of time, which yields a plausible preservation of the distinction between synchronic and diachronic reduction (*sensu* Dupré 1993 and Rosenberg 2006), is the only option for jointly incorporating spatial and temporal modes of organization in a reductive explanation. If more than one model can be isolated, then the question of deciding between them, and under what circumstances, arises.

The IC model of time comports well with interpretations of the metaphysical thesis of reductive physicalism. Arguments that rely on 'supervenience' (no change in a 'higher' level property without a change in a 'lower' level property) take a very similar form.

> Mental properties supervene on physical properties, in that necessarily, for any mental property *M*, if any thing has *M* <u>at time *t*</u>, there exists a physical base (or subvenient) property *P* <u>at *t*</u>, and necessarily anything that has *P* <u>at a time</u> has *M* <u>at that time</u>' (Kim 1998, 9, underline added).

Although these formulations emphasize synchronic compositional relations between 'levels' and usually ignore diachronic dynamics among parts, the inclusion of the latter does not seem conceptually prohibitive. Temporally extended instantiations of mental properties could be physically accounted for by iterating "in-principle" constitutional relations implied by supervenience while avoiding overdetermination worries and cross-level causal relations (cf. Kim 2005, ch. 4). But the widespread absence of the temporal iteration aspect of the explanation belies its seeming unimportance to questions of reduction.

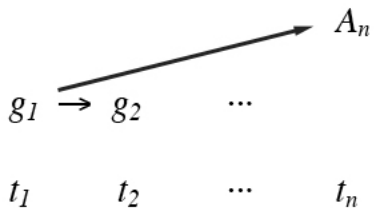
2.3 Causal Process

Although not explicit in Nagel's analysis of reduction, a third model of time can be developed through attention to his comments on special issues surrounding explanation in biology: "Teleological explanations focus attention on the culminations and products of specific processes, and in particular upon the contributions of various parts of a system to the maintenance of its global properties or modes of behavior" (Nagel 1961, 421-2). This juxtaposition of "culminations and products" alongside of relations between parts and system ("global") properties involves a different model of time. Part properties or activities at an earlier time causally contribute to or determine a property of the whole that is manifested at some later time via sequences of events (or processes). This *causal process* (CP) model of time differs from the IC model in how it combines the spatial and temporal modes of organization.

We can explicate the CP model of time with a reductive explanation of cardiac asymmetry in development. The asymmetrical location of the heart within the body cavity (*A*), a macroscale property of the system at time t_n in ontogeny, can be reductively explained

by asymmetrical gene expression (g_1) at an earlier developmental time (t_1), a microscale property of the system's parts (Figure 2). Although there is usually some attention to select aspects of the 'part-dynamics' (the arrow between g_1 and g_2), the CP model of time differs from the IC model in that part-dynamics are not fully specified.

Figure 2



The reductive explanation of the whole is largely accomplished by appeal to the system's parts at an earlier time, frequently ignoring intervals that include changing compositional relations and part-dynamics. The CP model of time does not require the articulation of compositional relations at all times because the explanatory reduction between higher and lower levels is temporally extended; i.e., it does not obtain at any particular time (i.e., it is not synchronic but diachronic). Reductive explanations in experimental biology often involve searching for actual *change* agents or 'difference makers' against a fixed background of contextual features (Waters 2007). Microscale difference makers operate at an earlier point in time, which is why intervention and manipulation of their behavior to ascertain the macroscale consequences at a later time is a standard mode of experimental reasoning. The CP model of time for reductive explanations corresponds primarily to causal relations between levels rather than compositional ones. Compositional relations are sometimes assumed (though not stated explicitly) and sometimes unavailable, as seen in

Figure 2 where higher levels of organization may be non-existent at earlier points in time. There is no heart to exhibit features of symmetry or asymmetry at t_1.

It is critical to emphasize that the horizontal arrows in both Figures 1 and 2 are explanatory arrows (*epistemology*), not causal arrows (*metaphysics*). These are different ways to capture scientific reasoning about the spatial and temporal modes of organization in reductive explanations. No claim is being made about "interlevel" causes (cf. Craver and Bechtel 2007). A developmental biologist utilizing the CP model of time is not denying the existence of compositional relations for the macroscale property at an intervening time. The relevant issue in the present context is how well these different models of time correspond to the actual reductive *explanations* offered by biologists.

3. Reductive Explanation and Representation

3.1 Differences in Models of Time

If we compare these three models of time, the historical model's focus on relations between different instantiations of a theory suggests that it is not as pertinent to reductive explanation in contemporary biology (but see Wimsatt 2007, ch. 9, for a discussion of possible connections).[3] Reduction construed historically is concerned with theory succession and not always with the spatial relations between levels of organization associated with reductive explanation. The IC and CP models of time are more suitable to analyzing current practices in that both can be applied to existing reductive explanations. In

[3] On a deductive-nomological model of explanation these historical relations can still count as a reductive explanation, but it might be more productive to construe theoretical succession in terms of conceptual change or other categories. This is not so much a criticism of the historical model as a recognition of its proper domain of application.

order to discern if one is more appropriate for experimental biology than the other, we need to identify how the models differ.

One tactic for identifying differences between these two models is to look at how time is represented in reductive explanations, especially in experimental biology (e.g., molecular genetics and developmental biology). Natural phenomena must be symbolized, pictured, or designated through media such as equations, scale miniatures, or abstract diagrams. Every reductive explanation involves a representation of the systems or domains to be related by reduction. Sahotra Sarkar (1998, ch. 3) distinguishes three representational criteria for reductive explanations:

> (i) *fundamentalism*: the explanation of the phenomenon relies entirely on features from a more fundamental realm (usually microscale features)
>
> (ii) *abstract hierarchy*: the system is represented as a hierarchy (e.g., a directed graph), where features of the non-fundamental realm (usually macroscale features) are related to the more fundamental realm
>
> (iii) *spatial hierarchy*: the abstract hierarchy is rendered physical by the requirement that the entities on the fundamental level are (spatial) parts of the entities at the non-fundamental levels

The nature and strength of a reductive explanation can be evaluated on *how* these criteria are met (i.e., what representations are utilized, including the approximations involved) and *how many* of them are addressed (e.g., meeting all three criteria yields a stronger reduction than if only two are met).

Temporality can be added as a fourth representational criterion:

> (iv) *temporal hierarchy*: the abstract hierarchy is temporally indexed, requiring that the properties from the fundamental realm be prior to those at non-fundamental levels

This immediately adds new dimensions of complexity to how we understand reductive explanations. For example, we can consider cases where the temporal hierarchy criterion is met but the spatial hierarchy criterion is not (or *vice versa*), or ask about what approximations are involved in a particular temporal hierarchy while assuming that the other three criteria are met. In order to analyze the differences between IC and CP that might discern how well they fit the explanatory practices of experimental biology, I begin by briefly noting how the first three criteria are satisfied and then concentrate on how the issue of temporal hierarchy can be introduced using each model of time.

Consider again the heart's rhythmic contraction being attributed to the activity of its component myocardial cells. Consonant with an attempt at a reductive explanation, we meet the first criterion by taking the cellular realm as fundamental to the organ realm and trying to explain a feature of the organ realm (heart's rhythmic contraction) using only features of the cellular realm. An abstract hierarchy, the second criterion, is provided by a diagrammatic representation indicating that features of fundamental realm constituents are correlated with features at the non-fundamental realm. The third criterion, spatial hierarchy, is met by having fundamental realm constituents be spatial parts of the non-fundamental realm constituent of interest (e.g., myocardial cells are spatial parts of the heart).

Now the question is how to meet the temporal hierarchy criterion. If we use the IC model of time (Figure 1), then the reductive explanation of the heartbeat at time t_n is explained by appeal to properties of the fundamental realm constituents (m_n – myocardial cell ensemble) at time t_n, along with an account of the part-dynamics for all relevant time

slices (e.g., $m_{n-1} \rightarrow m_n$) *and* their compositional relations with the non-fundamental realm (e.g., between m_{n-1} and H_{n-1}). This places several burdens on the reductive explanation. First, if a representation of compositional relations is unavailable for any relevant period of time, then the explanation is incomplete. Second, if part-dynamics for any interval of two periods are missing, then the explanation does not go through. Third, it should never be the case that the dynamics represent a non-fundamental realm property at an earlier time making a difference in a fundamental realm property at a later time (e.g., the heart's rhythmic contraction at t_n should not be represented as making a difference in the properties of myocardial cells at t_{n+1}).

If we use the CP model of time (Figure 2), then the heartbeat at time t_n is explained by citing properties of fundamental realm constituents (myocardial cells) at an earlier time t_{n-1}. The reductive relations do not obtain within a particular period of time. Here the explanatory burdens are of a different nature. First, there have to be independent reasons to think that the non-fundamental realm property of interest (H_n at t_n) is related to the fundamental realm difference maker at an earlier time (m_1 at t_1). It is for this reason that select aspects of 'part-dynamics' become salient (e.g., the arrow between g_1 and g_2 in Figure 2). Second, researchers do not seek to provide all intervening compositional relations because the focus is on interlevel dynamics rather than synchronic relations of constitution. Third, time periods are unlikely to be instantaneous states or homogeneous partitions. When interlevel dynamics are in view for reductive explanations using the CP model of time, locating fundamental realm difference makers in a sequence of proximal and distal events is of more importance than isolating iterated time periods to document compositional relations and part-dynamics between them. Therefore, we would expect temporal representation to

variable in 'thickness' on a CP model of time, such as phases or stages of time rather than instantaneous states.

3.2 Models of Time in Experimental Biology

Having observed several differences between the IC and CP models of time with respect to the temporal hierarchy criterion, we are in a position to evaluate whether one better corresponds to reductive explanations in experimental biology. Recall the example of changes in the rhythmic contraction of the heart being explained by a rush of adrenaline evoked in a fear response. An adrenergic hormonal effect that reductively explains the increased tempo of the heartbeat is part of a temporally extended process whereby the relevant properties of the fundamental realm that bring about the non-fundamental realm property are obtaining at an earlier time. At first pass, this seems to fit better with the CP model. A case for preferring the CP model of time is even stronger in the example of cardiac asymmetry. Explaining the location of the heart within the body cavity or its asymmetrical chamber morphology by gene expression patterns at earlier times in development does not involve reductive relations at a particular time. The spatial features of heart asymmetry (macroscale properties) are reductively related to microscale properties (gene expression patterns) at earlier times, which are measured with temporal stages of varying duraion rather than instantaneous states.[4] Those investigating left/right asymmetry in cardiogenesis routinely pursue microscale features at much earlier times in order to *reductively* explain the asymmetry (Levin 2005). In both the physiological and

[4] "A stage defines more than an instant in time, it is merely a device for approximately locating a part of the continuum of development" (Kimmel et al. 1995, 254). Stages are different from the beginning and ending of the operation of mechanisms because different mechanisms can be studied using the same temporal stages.

developmental cases, reductive explanations appear to conform to the CP models of time rather than the IC model.

One reason for the appropriateness of a CP model of time in reductive explanations of ontogeny is that compositional relations between fundamental and non-fundamental domains are unavailable at all stages of a developmental sequence. Levels of organization progressively emerge during ontogeny.[5] At the earlier time when the gene expression pattern is identified (*explanans*), the heart morphology (*explanandum*) is nonexistent. An appeal to a microscale difference maker at an earlier time to explain the subsequent emergence of a macroscale feature recognizes this phenomenology. A second reason for the appropriateness of the CP model is that compositional relations between fundamental and non-fundamental domains change over time. Populations of cells involved in the difference making gene expression at t_1 may undergo apoptosis (programmed cell death) and be absent at a later time t_n when the *explanandum* feature is manifested. Another reason why the CP model is more appropriate is that biologists routinely represent non-fundamental realm properties at earlier times making a difference in fundamental realm properties at later times within the context of a reductive explanation. This is a direct violation of the explanatory burdens associated with the IC model of time. It is best seen in a more detailed example.

In a recent study, researchers offered a reductive explanation of the developmental origin of aortic arch asymmetry using gene expression at an earlier point in ontogeny (Yashiro, Shiratori, and Hamada 2007; Figure 3). The explanation involves a sequence where fundamental level properties (gene expression) change non-fundamental level

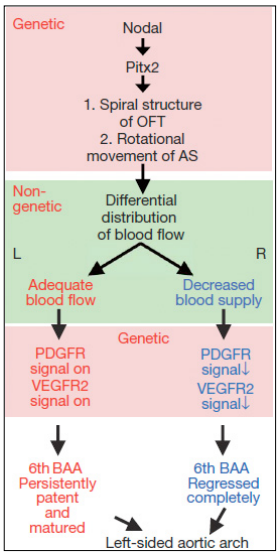
[5] Nagel made a similar observation in the context of hierarchical relations in biology: "it should be noted that in embryological development the spatial hierarchy changes, since in this process new spatial parts are elaborated" (Nagel 1961, 439).

properties (arterial structure), thereby altering blood flow dynamics, which induces a change in other fundamental level properties (gene expression) that produce the non-fundamental property of interest, aortic arch asymmetry.

Figure 3

Schematic Representation of a Reductive Explanation of Ontogeny

(Yashiro et al. 2007)



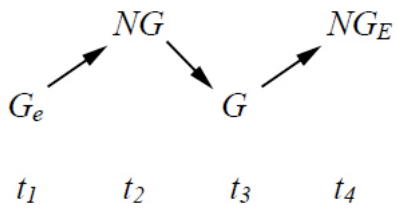
Legend: Gene expression (Nodal/Pitx2) at an earlier time reductively explains the origin of an asymmetric (left-sided) aortic arch at a later time. This schematic representation of the explanation is incongruent with the IC model of time because compositional relations are largely ignored, part-dynamics for significant intervals are ignored, and a non-fundamental realm property (blood flow) at an earlier time makes a difference in a fundamental realm property at a later time (regulation of PDGFR or VEGFR2). It is congruent with the CP model because there are independent reasons to link the non-fundamental realm property of interest (left-sided aortic arch) with the fundamental realm difference maker at an earlier time (Nodal/Pitx2), there is only a partial representation of part-dynamics, intervening compositional relations are largely ignored or implicit, and time is represented in terms of proximal and distal periods rather than as instantaneous states. **Abbreviations**: Nodal, Pitx2, PDGFR, VEGFR2 (gene names); OFT = outflow tract; AS = aortic sac; BAA = branchial arch artery.

This pattern of reasoning is common in developmental biology (e.g., Auman et al. 2007; Hove et al. 2003) and has been previously noted (though not analyzed).[6] Distal gene expression is represented as bringing about changes in a higher-level feature, which in turn is depicted as modifying subsequent patterns of gene expression. These include phenomena such as the mechanical loading of muscle in shaping the form of bones or the physical compression of cells modulating gene expression (Brouzés and Farge 2004). Although this representation may not be transparent, we can reconstruct it in a more simplistic fashion to make the point explicit (Figure 4). A fundamental realm (genetic) is distinguished from a

[6] "Because developmental processes are complex and because changes in the timing of embryological events may produce a cascade of effects at several different levels, one sometimes uses descriptions at higher levels to explain what goes on at a more fundamental level" (Kitcher 1984, 371).

non-fundamental realm (non-genetic), four time periods are considered, and the specific details of the genes and morphology are compressed into simple variables (G – genetic; NG – non-genetic; *e – explanans*; *E – explanandum*).

Figure 4



An immediate objection to the purported fit between reductive explanatory practices in developmental biology and the CP model of time is that the case can be described differently. For example, *Nodal* gene expression and the blood flow occur within the region the heart will occupy eventually and therefore compositional relations are present in principle, even if they are not highlighted. There are two problems with this objection. First, it is not always the case that the relevant gene expression occurs within the embryonic field of interest. Gene expression from other embryonic regions, such as the forelimb, can be a part of reductively explaining aspects of heart morphology (Waxman et al. 2008). Second, an alternate description cannot eliminate problematic features, such as the appeal to non-fundamental level properties as difference makers for subsequent fundamental level properties, without intentionally departing from the reasoning offered by the scientists.

A related but distinct objection is that one can always reconstruct the CP model of time in terms of the IC model for reductive explanations in experimental biology. Even though biologists appeal to asymmetrical gene expression at earlier times to reductively explain cardiac asymmetry at later times, we could intentionally diverge from the reasoning

offered by the biologist and (in principle) recast it by giving an account of the compositional relations and part-dynamics along with a translation of the periods or stages into homogenous states. There are two ways to respond to this. First, it might be possible to translate the actual scientific reasoning that uses a CP model into something using the IC model for the sake of arguing for (or against) some other thesis (e.g., reductive physicalism). But this will not illuminate the scientific reasoning involved. The primary aim of this paper is to comprehend reductive explanation as it appears in biological research; it is neutral with respect to reconstructions of this reasoning *for other philosophical aims*. Second, if the claim is that the IC model of time is a better fit for the reductive explanations offered in experimental biology then it is simply incorrect.[7] Researchers do not give their reductive explanations in terms of synchronous compositional relations or focus on detailing part-dynamics across all relevant periods. They seek microscale difference makers at earlier times, which are mediated via fundamental and non-fundamental level processes, to account for macroscale properties at later times. Part of this explanatory practice includes representations of macroscale properties altering microscale properties within these temporally extended sequences. These reductive explanations are not promissory notes for the future delineation of compositional relations at all relevant time periods as expected for the IC model of time. The explanations sought by developmental biologists are unencumbered by these demands and instead correspond with the burdens of the CP model.

3.3 Model Systems and Generalizing Reductive Explanations

In addition to the CP model's conformity to the reductive explanations offered by

[7] The relevant model of time outside of experimental biology is another question.

developmental biologists, further insights can be gleaned about the use of model organisms and counterfactual supporting generalizations. If compositional relations are critical for reductive explanations involving iterated sequences, as one would expect for the IC model of time, then a paradox emerges about model systems in developmental biology (and elsewhere). Heart ontogeny is reductively investigated in fruit fly, zebrafish, and mouse models where the compositional relations vary dramatically. Unlike vertebrates, *Drosophila* has only one cardiac cell type, an open vascular system, no atrial or ventricular chamber morphology, and no neural crest cells (Kirby 1999). And yet reductive explanations of heart development are routinely generalized across these different model systems (Gajewski and Schulz 2002). For example, cardiogenesis in all invertebrates and vertebrates investigated thus far depends essentially on the expression of the homeobox gene *Nkx2.5* (aka *tinman*).[8] Because the compositional relations are radically divergent in the model organisms studied to yield this generalization, the demand for an articulation of the compositional relations at all (or even many) intervening states would make these generalizations destabilize over time, changing robust reductive explanations across model organisms into less stable and narrower scope explanations within a model organism ('death by a thousand compositional specifications'). This contrasts with the practices of biologists where these generalizations are treated as robust reductive explanations as expected on the CP model of time, and not placeholders to be filled out with descriptions of compositional relations.

Not only does the CP model of time shed light on how reductive explanations generalize (i.e., *because of* the absence of compositional relations at all relevant periods), it also helps to show how generalizations can be established via increased abstraction (cf.

[8] The point also applies to other organ systems, such as the control of cell proliferation and differentiation in the *Drosophila* hindgut and mammalian intestine (Takashima et al. 2008).

Mitchell 2000). If one seeks to generalize a reductive explanation for left/right asymmetry to other morphological features (i.e., abstracting away from the heart alone), then the appeal to *Nodal* and *Pitx* is stable as long as compositional relations are *increasingly* ignored. For example, sea urchin embryos establish left/right axial asymmetry with *Nodal* and *Pitx* (Duboc et al. 2005), and snail shell chirality is explained similarly (Grande and Patel 2009). This yields a heuristic reasoning strategy for reductive explanations: *abstract away from compositional relation details for increased generalization*.[9] The strategy of scientists is exactly the opposite of what one would expect if the IC model of time operated in reductive explanations. Instead of seeking to fill in atemporal, compositional relations, dynamic interlevel relations are preserved and extended by repeated abstraction from material constitution. Contrary to many philosophical analyses, whether focused on theory reduction or mechanisms, compositional relations are not sought in the explanation. This is not to say that developmental biologists always abstract away from compositional relations. There may be good reasons to decrease the level of abstraction, and thereby decrease the scope of generalization. For example, a reductive explanation of particular asymmetric features of the heart, such as ventricle morphology, involves *dHAND* gene expression (Brand 2003). But the absence of those features in *Drosophila* (no chamber morphology) means that a reductive explanation of ventricle formation in terms of *dHAND* will not generalize, even though an orthologue of *dHAND* is expressed during *Drosophila* cardiogenesis. Thus, the heuristic for generalizing reductive explanations comes at a cost – decreased specificity – which also may be of explanatory interest (cf. Waters 2007).

[9] This is related to another reductionistic heuristic, 'abstractive reification': "Observe or model only those things that are common to all cases; don't record individuating circumstances" (Wimsatt 2007, 349).

4. Time and Reductive Explanation: New Questions

4.1 Temporal fundamentality

Nagel's contrast between spatial and temporal aspects of biological explanation was aimed at ongoing research. In particular, he perceived methodological value in varying what period of time is viewed when investigating causes. "It is nevertheless intellectually profitable in causal inquiries to focus attention on certain earlier stages in the development of a process rather than on later ones" (Nagel 1961, 424). This is exactly what is salient for the CP model of time in reductive explanations. How might this transform our views of reductive explanation? One approach to this question is to treat the first representational criterion, fundamentality, as bearing on more than spatial relations. Previously we assumed that parts operating at a lower level of organization were more fundamental than the behavior of the whole at a higher level of organization. We met the temporal hierarchy criterion on representation for a reductive explanation subsequent to meeting the spatial hierarchy criterion. But what if we satisfied the fundamentality criterion *with respect to time* before making a judgment about fundamentality with respect to space?

We can formulate an answer by distinguishing proximal and distal temporal features in an explanation. Return to the case of vertebrate cardiac asymmetry. If there is a preference for distal gene expression as more explanatory than proximal cellular interaction, then we take distal temporal events as more fundamental than proximal ones. But this example mixes preferences about spatial and temporal fundamentality because the distal explanatory preference is also a microscale preference. If we neutralize the question of microscale versus macroscale and simply ask whether we prefer proximal or distal gene expression, it is not obvious how we should answer. We can adopt as a starting point the

preference for more proximal features because distal features are less likely to be causally specific than proximal features to changes in subsequent events (*ceteris paribus*).[10]

Following an earlier discussion (Jackson and Petit 1992), call the preference for microscale rather than macroscale properties a 'small-grain' (spatial) explanatory norm (pursue difference makers at lower levels - SGN), and a preference for proximal rather than distal properties a 'close-grain' (temporal) explanatory norm (pursue difference makers at more intermediate steps - CGN). An explanation of cardiac asymmetry using distal gene expression rather than proximal cellular interaction would conform to SGN while violating CGN. An explanation using proximal cellular interaction instead of distal gene expression would conform to CGN but violate SGN. An explanation using proximal gene expression would conform to both simultaneously. Therefore, choices of fundamentality with respect to space and time can be complementary or conflicting.

Even more interesting are cases of conflict that arise when the SGN is considered across a temporal sequence. The CP model of time reveals the possibility of cases where there is a conflict with respect to SGN *at different times*. Depending on which earlier time period is utilized to explain a non-fundamental feature at a later time, SGN may not be satisfiable for both. When explaining aortic arch asymmetry, an appeal to the distal gene expression fulfills SGN but an appeal to the more proximal blood flow dynamics due to changes in arterial structure violates SGN (Figures 3, 4). Therefore, the CP model of time reveals possible conflicts between different reductive explanations regardless of any commitments to CGN. The question is not just whether the explanation is reductive but

[10] Perspectives differ here. For example, Waters (2007) emphasizes specificity in a way that bolsters preferring proximal features but an emphasis on 'explaining more' can go in the opposite direction: "In a causal chain from *A* to *B* to *C*, *B* is a proximal cause of *C*, while *A* is a more distal cause of *C*. In a sense, *A* explains more than *B* does since *A* explains both *B* and *C*, while *B* explains just *C*" (Sober 2000, 8).

whether it appeals to the fundamental realm at earlier or later periods of time—the CP model of time uncovers complexity in reductive explanations that was previously unrecognized. These diverse possibilities can be depicted in an abstract possibility space for the minimum number of variables: two spatial 'levels' (micro vs. macro) and three temporal partitions in order to produce a proximate versus distal contrast (Figure 5). Although the scenarios represent logical possibilities, our examples have shown them to be biologically relevant.[11] They also draw attention to questions about how temporal stages are first established.

4.2 Periodization

If simply paying attention to the SGN across a temporally extended sequence yields consequences for reductive explanation, then a natural follow-up question concerns how stages of a sequence can be represented. On the CP model of time we expect temporal partitions to vary in thickness, which is observable in developmental biology. The changes that occur in ontogeny are all physically continuous so decisions must be made about how to represent time, especially since 'chronological age' is of little use. Developmental events exhibit variability despite homogeneous environments so that the 'same' stage in a model organism under identical control conditions is reached at different 'ages.'

Researchers make several distinctions about partitioning time (Reiss 2003). The first is between sequence and duration. Sequence concerns event ordering, such as gastrulation occurring prior to organogenesis, whereas duration concerns a succession of defined intervals, which may or may not map onto sequences of events. For any sequence we can

[11] One possible objection is that it is the entire temporal sequence that should be considered explanatory. But this worry cannot address why there is such a focus on the initiating difference makers and final outcomes (as seen in generalizations across model organisms), or why some features (including those at the fundamental level) are ignored at numerous junctures in the temporal sequence.

ask about the relative duration of the events (for interval definition *d*, event *A* to event *B* occurs over 3*d* in one species whereas in another species it occurs over 4*d*), and whether they exhibit reliable transformation ordinality (event *B* always precedes event *C* or event *B* usually precedes event *C*).

Scenario	Periodization						Explanatory Norm	
	Stage 1		*Stage 2*		*Stage 3*		*Small Grain*	*Close Grain*
α_1	A_{micro}	→	B_{micro}	→	C_{micro}		– / –	Y
α_2	A_{micro}	→	B_{micro}	→	C_{micro}		– / –	N
β_1	A_{micro}	→	B_{micro}	→	C_{macro}		– / Y	Y
β_2	A_{micro}	→	B_{micro}	→	C_{macro}		– / Y	N
γ_1	A_{micro}	→	B_{macro}	→	C_{micro}		Y / N	Y
γ_2	A_{micro}	→	B_{macro}	→	C_{micro}		Y / N	N
δ_1	A_{micro}	→	B_{macro}	→	C_{macro}		Y / –	Y
δ_2	A_{micro}	→	B_{macro}	→	C_{macro}		Y / –	N
ε_1	A_{macro}	→	B_{micro}	→	C_{micro}		N / –	Y
ε_2	A_{macro}	→	B_{micro}	→	C_{micro}		N / –	N
ζ_1	A_{macro}	→	B_{micro}	→	C_{macro}		N / Y	Y
ζ_2	A_{macro}	→	B_{micro}	→	C_{macro}		N / Y	N
η_1	A_{macro}	→	B_{macro}	→	C_{micro}		– / N	Y
η_2	A_{macro}	→	B_{macro}	→	C_{micro}		– / N	N
θ_1	A_{macro}	→	B_{macro}	→	C_{macro}		– / –	Y
θ_2	A_{macro}	→	B_{macro}	→	C_{macro}		– / –	N

Figure 5
Space of possibilities for interactions between different explanatory norms

Legend: Assuming that the *explanandum* is the feature in Stage 3, this figure documents the possible interactions between the small grain norm (SGN) and close grain norm (CGN) for the minimum number of variables: two spatial 'levels' (micro vs. macro) and a periodization of three temporal stages in order to produce one proximal vs. distal contrast per scenario genus (designated with a Greek alphabet letter; e.g., α). The shaded boxes with arrows indicate whether proximal or distal dependency relations are in view for each scenario type. The SGN is evaluated twice for each scenario species (e.g., α_1), but yields identical results for both species of a scenario genus (e.g., α_1 and α_2). Choices of fundamentality with respect to space and time can be complementary, conflicting, or orthogonal. Eight scenario species where CGN is assessed are orthogonal because there is no commitment ('–') for or against SGN (α_1, α_2, δ_1, δ_2, ε_1, ε_2, θ_1, θ_2). These are not reductive because they only concern relations within a particular 'level' at earlier and later times. Four of the scenario species are complementary: SGN and CGN are either simultaneously met (β_1, ζ_1) or not (γ_2, η_2). Thus, one can adhere to both norms simultaneously. Four of the scenario species exhibit conflict: either SGN is instantiated and CGN is violated (β_2, ζ_2), or CGN is instantiated and SGN is violated (γ_1, η_1). Therefore, in some cases, one cannot adhere to both norms. In four scenario species, SGN is instantiated at one interval and violated at another (γ_1, γ_2, ζ_1, ζ_2). Adhering to SGN requires specifying which stages are in view, regardless of CGN commitments, in order to assess the success or failure of reductive explanations.

Relative timing of one set of sequences to another can also be assessed using an intrinsic interval definition. For two event sequences ($A \rightarrow B \rightarrow C$; $D \rightarrow E \rightarrow F$), the timing of $D \rightarrow E \rightarrow F$ can be measured with respect to the interval occurrences defined by $A \rightarrow B \rightarrow C$. Alternatively, one or more event sequences or intervals can be measured according to extrinsic time measures, such as with common units using a timepiece ('the transition from event *A* to event *B* occurs in 2.5 hours').

These diverse conceptions of time generate distinct periodizations of developmental processes (Minelli 2003, ch. 4), which suggest further questions for reductive explanation (assuming the CP model of time). For example, does a reductive explanation in a model organism that stages ontogeny according to sequences generalize if ontogeny is staged according to durations of an extrinsic interval (e.g., hours)? More abstractly, how do reductive explanations hold up when different temporal partitions are utilized. Answering this question involves determining whether proximal/distal relations are preserved (i.e., isomorphic) across different measures of time. This is directly parallel to the question of whether different decompositions of complex systems into parts have spatially coincident boundaries (Wimsatt 2007, ch. 9).

Assessing whether or not proximal/distal relations are preserved is difficult because the ontogeny of model organisms is not staged using a single measure of time. Instead of a periodization based on a consistent principle of temporal decomposition, 'normal' stages for embryogenesis are hybrid periodizations.[12] For example, the developmental stages

[12] "Anatomical, physiological, developmental, and biochemical criteria … all interact … in analyzing organisms into functional [temporal] systems and subsystems. This borrowing of criteria of individuation of

established for zebrafish use a combination of diverse event sequences that are correlated with absolute duration (Kimmel et al 1995; Figure 6). One reason for a hybrid periodization is that the distinctness of the stages generated facilitates more precise explanations within developmental biology (cf. Griesemer 1996). But it also raises questions about whether these stages encourages particular kinds of process individuations or are systematically biased against seeing specific phenomena (Love 2010). Trade offs of this nature (more precise explanations but skewed in a particular direction) are what we expect from reductionist reasoning methods (Wimsatt 2007, ch. 5).

Figure 6

Period	**Blastula**									**Gastrula**					
Stage	128-cell	256-cell	512-cell	1k-cell	High	Oblong	Sphere	Dome	30% Epiboly	50% Epiboly	Germ-ring	Shield	75% Epiboly	90% Epiboly	Bud
Absolute Duration Correlate (hours)	2.25	2.5	2.75	3	3.33	3.67	4	4.33	4.67	5.25	5.67	6	8	9	10

A second new question concerns how well reductive explanations generalize from one model system with a particular periodization scheme (*Drosophila*) to another model system that is represented differently (zebrafish)? Are reductive explanations relative to the choice of periodization? Answering these questions is all the more difficult because hybrid periodizations often involve events that are present in one model organism and not another. Unlike zebrafish, morphogenesis related to gastrulation in *Drosophila* does not involve epiboly and the embryo never exhibits a tail bud. Our brief canvassing of successful generalizations via removal of compositional information in Section 3.3 would seem to indicate that no caution is needed. But since periodizations are heuristics, and heuristics have characteristic biases, their success may not be due to a robustness of the reductive

parts from different and diverse theoretical perspectives is one factor that can make functional organization in general and biology in particular a conceptual morass at times" (Wimsatt 2007, 184).

explanation but rather to shared assumptions or 'pseudo-robustness' (Wimsatt 2007, ch. 4). How sensitive are reductive explanations to alternative representations of time (e.g., sequence versus event)? It has been noted previously that alternative periodizations can be utilized as a methodological tool across disciplinary approaches (Griesemer 1996), but it has not been observed that alternative periodizations may be of value for assessing robustness within a particular discipline. These and other questions that bear on reductive explanation in biology require further investigation.

5. Conclusion

Philosophical preoccupation with synchronic, compositional relations has obscured model of times in the explanatory practices of experimental biology that concentrate on causal relations across different levels or between parts and wholes (Hüttemann and Love forthcoming). By implication, time is considered irrelevant to questions of reduction and part-whole explanations are described as "synchronic." Are there any other reasons that account for why models of time have not received more attention in discussions of reductive explanation in biology and elsewhere? A few possibilities can be noted. First, part-whole reductive explanations in physical science are often atemporal (Hüttemann 2005; Love and Hüttemann in press) and tend to ignore temporality.[13] Furthermore, many explanations in physics focus on isolated systems and presume that compositional relations remain constant, which does not hold in the case of developing organisms. The degree to which models of explanatory reduction are imported from physics into biology is the degree to which

[13] "The general methodology of physics is marked by synchrony: the pursuit of understanding in terms of the properties of instantaneous states. …Physics considers that we know everything relevant about a system if we know everything about it at one point in time" (Kellert 1993, 93).

temporality is ignored. Second, the distinction between synchronic and diachronic reduction encourages a model of time that only pertains to theory succession rather than part-whole relations found in contemporary reductive explanations. Since authors who otherwise disagree hold the distinction, it signals a blindspot in discussions of reductive explanation.[14] The foregrounding of temporality in biological reasoning often travels with a commitment to set aside issues of reduction completely (cf. Craver 2005). The narrowness of reductionism discussions, including the predominant focus on compositional relations and consequent overlooking of temporality, follows a pattern—many interesting but neglected philosophical issues are contained in Nagel's *nonformal* conditions on theory reduction (Nagel 1961, 358-361; cf. Sarkar 1998; Waters 1990). For example, the second of Nagel's nonformal criteria is the presence of surprising connections between seemingly unrelated processes. Few biologists thought that flies, fish, and frogs would build their eyes, guts, and hearts with the same genetic factors. The fulfillment of this criterion in reductive explanations of ontogeny remains mysterious unless the CP model of time is invoked, thereby giving an explicit license to abstract away from the dramatic compositional heterogeneity across these different model organisms.

A third reason for the relative neglect of models of time is the use of concepts that are primarily atemporal, such as identity, supervenience, and realization (cf. Kim 1998, 2005). This constrains reductive relations to obtain strictly within a narrow and homogeneous period of time (often a time 'slice'). CP models of time appear irrelevant from this perspective, especially if they are interpreted metaphysically (though they need not be – see Craver and Bechtel 2007). Rosenberg (2006) has claimed that reductionism

[14] "The debate over reductionism has taken a somewhat narrow direction, in spite of the broad range of epistemological and ontological issues that are connected to reductionism" (Weber 2005, 18)

disputes in biology are essentially metaphysical. But developmental biologists offer reductive explanations of ontogeny that intentionally leave out compositional details to purchase generalizations with wide scope from model organisms, and not just as promissory notes for a future, completed biology or because we are cognitively handicapped. The availability of different models of time, which parallels the availability of different representations of spatial relations, implies that the core issues are epistemological. As a result, a forced choice between reductionism and antireductionism is foreign to analyses that concentrate on reductive explanations in scientific reasoning because they display multiple aspects of success and failure (Hüttemann and Love forthcoming; Sarkar 1998).

In summary, three models of time relevant to reductive explanations can be distinguished: historical, iterated compositional (IC), and causal process (CP). The latter corresponds closely to the reasoning found in reductive explanations of ontogeny. A CP model of time helps to explain why generalizations of reductive explanations from model organisms are stable under radical compositional differences. It also directs our attention to an array of new questions surrounding periodization and reductive explanation that were not visible previously. None of this entails "that the use of such explanations in biology…requires a radically different logic of inquiry" (Nagel 1961, 428), but it does suggest that many facets of reductive explanations in biological science remain unexplored when philosophical attention is fixated on synchronic, compositional relations.

References

Auman, Heidi J., Hope Coleman, Heather E. Riley, Felix Olale, Huai-Jen Tsai, and Deborah Yelon (2007), "Functional modulation of cardiac form through regionally confined cell shape changes", *PLoS Biology* 5:e53.

Brand, Thomas (2003), "Heart development: molecular insights into cardiac specification", *Developmental Biology* 258:1-19.

Brouzés, Eric, and Emmanuel Farge (2004), "Interplay of mechanical deformation and patterned gene expression in developing embryos", *Current Opinion in Genetics & Development* 14:367-374.

Craver, Carl F. (2005), "Beyond reduction: mechanisms, multifield integration and the unity of neuroscience", *Studies in the History and Philosophy of Biological and Biomedical Sciences* 36:373-395.

Craver, Carl F., and William Bechtel (2007), "Top-down causation without top-down causes", *Biology and Philosophy* 22:547-563.

Duboc, Véronique, Eric Röttinger, François Lapraz, Lydia Besnardeau, and Thierry Lepage (2005), "Left-right asymmetry in the sea urchin embryo is regulated by Nodal signaling on the right side", *Developmental Cell* 9:147-158.

Dupré, John (1993), *The Disorder of Things: Metaphysical Foundations of the Disunity of Science*. Cambridge, MA: Harvard University Press.

Gajewski, Kathleen, and Robert A. Schulz (2002), "Comparative Genetics of Heart Development: Conserved Cardiogenic Factors in *Drosophila* and Vertebrates", in B. Ostadal, M. Nagano and N.S. Dhalla (eds.), *Cardiac Development*, Boston: Kluwer Academic Publishers, 1-23.

Grande, Cristina, and Nipam H. Patel (2009), "Nodal signalling is involved in left-right asymmetry in snails", *Nature* 457:1007-1011.

Griesemer, James R. (1996), "Periodization and models in historical biology", in M.T. Ghiselin and G. Pinna (eds.), *New Perspectives on the History of Life*, San Francisco: California Academy of Sciences, 19-30.

Hove, Jay R., Reinhard W. Köster, Arian S. Forouhar, Gabriel Acevedo-Bolton, Scott E. Fraser, and Morteza Gharib (2003), "Intracardiac fluid forces are an essential epigenetic factor for embryonic cardiogenesis", *Nature* 421:172-177.

Hüttemann, Andreas (2005), "Explanation, emergence, and quantum entanglement", *Philosophy of Science* 72:114-127.

Hüttemann, Andreas and Alan C. Love (forthcoming), "Aspects of reductive explanation in biological science: fundamentality, intrinsicality, and temporality", *The British Journal for Philosophy of Science*.

Jackson, Frank, and Philip Petit (1992), "In defense of explanatory ecumenism", *Economics and Philosophy* 8:1-21.

Kellert, Stephen H. (1993), *In the Wake of Chaos: Unpredictable Order in Dynamical Systems*. Chicago: University of Chicago Press.

Kim, Jaegwon (1998), *Mind in a Physical World*. Cambridge, MA: MIT Press.

——— (2005), *Physicalism, or something near enough*. Princeton: Princeton University Press.

Kimmel, Charles B., William W. Ballard, Seth R. Kimmel, Bonnie Ullmann, and Thomas F. Schilling (1995), "Stages of embryonic development of the zebrafish", *Developmental Dynamics* 203:253-310.

Kitcher, Philip (1984), "1953 and all that: a tale of two sciences ", *Philosophical Review* 93:335-373.

Kirby, Margaret L. (1999), "Contribution of neural crest to heart and vessel morphology", in R.P. Harvey and N. Rosenthal (eds.), *Heart Development*, San Diego, CA: Academic Publishers, 179-193.

Levin, Michael (2005), "Left-right asymmetry in embryonic development: a comprehensive review", *Mechanisms of Development* 122:3-25.

Love, Alan C. (2010), "Idealization in evolutionary developmental investigation: a tension between phenotypic plasticity and normal stages", *Philosophical Transactions of the Royal Society B: Biological Sciences* 365:679-690.

Love, Alan C. and Andreas Hüttemann (in press) "Comparing part-whole reductive explanations in biology and physics," in D. Dieks, J.G. Wenceslao, S. Hartmann, T. Uebel and M. Weber (eds.), *Explanation, Prediction, and Confirmation. New Trends and Old Ones Reconsidered*, Dordrecht: Springer.

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

Mitchell, Sandra D. (2000), "Dimensions of Scientific Law", *Philosophy of Science* 67:242-265.

Nagel, Ernest (1961), *The Structure of Science: Problems in the Logic of Scientific Explanation*. New York: Harcourt, Brace & World, Inc.

Reiss, John O. (2003), "Time", in B.K. Hall and W.M. Olson (eds.), *Keywords and Concepts in Evolutionary Developmental Biology*, Cambridge, MA: Harvard University Press, 359-368.

Robert, Jason Scott (2004), *Embryology, Epigenesis, and Evolution: Taking Development Seriously*. New York: Cambridge University Press.

Rosenberg, Alexander (2006), *Darwinian Reductionism: Or, How to Stop Worrying and Love Molecular Biology*. Chicago: University of Chicago Press.

Sarkar, Sahotra (1998), *Genetics and Reductionism*. New York: Cambridge University Press.

Schaffner, Kenneth F. (1967), "Approaches to reduction", *Philosophy of Science* 34:137-147.

——— (1993), *Discovery and Explanation in Biology and Medicine*. Chicago: University of Chicago Press.

Sober, Elliott (2000), *Philosophy of Biology*. 2nd ed. Boulder, CO: Westview Press.

Takashima, Shigeo, Marianna Mkrtchyan, Amelia Younossi-Hartenstein, John R. Merriam, and Volker Hartenstein (2008), "The behaviour of *Drosophila* adult hindgut stem cells is controlled by Wnt and Hh signalling", *Nature* 454:651-655.

Waters, C. Kenneth (1990), "Why the antireductionist consensus won't survive the case of classical Mendelian genetics", in A. Fine, M. Forbes and L. Wessells (eds.), *Proceedings of the Philosophy of Science Association, 1990*, Vol. 1 (Contributed Papers), East Lansing, MI, 125-139.

——— (2007), "Causes that make a difference", *Journal of Philosophy* 104:551-579.

Waxman, Joshua S., Brian R. Keegan, Richard W. Roberts, Kenneth D. Poss, and Deborah Yelon (2008), "Hoxb5b acts downstream of retinoic acid signaling in the forelimb field to restrict heart field potential in zebrafish", *Developmental Cell* 15:923-934.

Weber, Marcel (2005), *Philosophy of Experimental Biology*. New York: Cambridge University Press.

Wimsatt, William C. (2007), *Re-Engineering Philosophy for Limited Beings: Piecewise Approximations to Reality*. Cambridge, MA: Harvard University Press.

Winther, Rasmus G. (2009), "Schaffner's Model of Theory Reduction: Critique and Reconstruction", *Philosophy of Science* 76:119-142.

Yashiro, Kenta, Hidetaka Shiratori, and Hiroshi Hamada (2007), "Haemodynamics determined by a genetic programme govern asymmetric development of the aortic arch", *Nature* 450:285-288.