Real Patterns in Biological Explanation

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Abstract

In discussion of mechanisms, philosophers often debate about whether quantitative descriptions of generalizations or qualitative descriptions of operations are explanatorily fundamental. I argue that these debates have erred by conflating the explanatory roles of generalizations and *patterns*. Patterns are types of quantitative relationships that hold between quantities in a mechanism, over time and/or across conditions. While these patterns must often be represented in addition to descriptions of operations in order to explain a phenomenon, they are not equivalent to generalizations, because their explanatory role does not depend on any specific facts about their scope or domain of invariance.

Real Patterns in Biological Explanation

1. Introduction

Scientists often claim to have identified patterns in the world. In this paper, I will argue that these patterns are often explanatory in biology, and that their roles in explanation are distinct from the respective roles normally posited for *operations* and *generalizations* in discussion of mechanistic explanation. Operations are types of causal interactions between the parts of a mechanism, described qualitatively. Generalizations are quantitative descriptions of regularities, that normally are taken to involve (at least) two distinct properties in addition to the quantitative relationship. First is *scope*: applicability to a range of cases. Second is *domain of invariance*: insensitivity to manipulations of variables other than those named in the generalization (Woodward, 2010).

Theorists have almost universally equated patterns and regularities, and thus supposed that the explanatory roles of patterns are equivalent to those played by generalizations. For instance, Craver and Kaiser (2013) claim that regularities are "statistical patterns of dependence and independence among magnitudes," (p. 128) and that generalizations describe regularities. Dennett (1991), in his seminal discussion of patterns, calls them a "variety of regularity" (p. 40). Woodward (2010) says that causal relationships are "patterns of dependency" that are "stable or invariant" (p. 291). Most of the literature has followed a similar assumption.

I claim that the explanatory role of patterns is distinct from those of operations and generalizations, and thus that patterns should be considered their own explanatory category.

Patterns, for current purposes, are type-able variations within or between quantities. When biologists cite patterns, they say that a quantity of type X exhibits a particular type of quantitative variation, or that the variations of quantity X stand in a certain type of relation to variations of quantity Y.[1] I will mainly focus on inter-quantity relations here. Often it is important that these relationships occur *across conditions* and/or *over time*—examples include two variations being *proportional* to each other or *in phase* with one another.[1] I will discuss instances of explanation that employ these kinds of relationships, which I have elsewhere (Burnston, 2016) called "explanatory relations." The patterns cited in explaining with these relations are distinct from operations, since they consist in quantitative rather than qualitative types, and since knowledge of the patterns is not fully specified by knowledge of operations. But they are also explanatorily distinct from generalizations, since their explanatory role does not depend on any specific facts about the scope or domain of invariance of the relationships instantiating the pattern.

The initial payoff is simply descriptive adequacy: keeping distinct explanatory categories distinct. I also have a larger target in mind, however. There is currently a considerable amount of debate about whether operations or generalizations are explanatorily *fundamental*—i.e., does one explain the other, or vice versa. "Generalizationists" cite,

[1] While I mean this definition very liberally—the fact that a quantity "increases" in a certain condition is a pattern in this sense—it certainly won't exhaust all colloquial, or perhaps even scientific uses of the concept of a pattern. For instance, one might suggest that one's friend exhibits a negative pattern of behavior without trying to quantify it. Moreover, many patterns are simply statistical facts about a given sample (e.g., noise is "white" only when it has a constant spectral density). Finally, there may also be an infinite number of patterns that are not type-able *by us*. But I'm inclined to think that we need to type a pattern before it can be useful in science, and I will assume that here.

among other considerations, the need for regular quantitative relationships to hold before one can call something an operation (Leuridan, 2010). "Operationists" cite the need for qualitative descriptions of types of relationships in explaining why regularities hold (Andersen, 2011; Machamer, 2004). I think the fundamentality question is, in general, a bad one (cf. Tabery, 2004). In showing that patterns play a distinct role from either operations or generalizations, I hope to suggest that no category is fundamental. This results in a variety of contextualism about explanation.

My strategy is as follows. I will first (section 2) discuss several cases in which biologists explain by representing patterns. In section 3.1, I will argue that this aspect of explanation is distinct from representing operations. I will then (section 3.2) take up a thread in the dialectic between operationists and generalizationists to show that patterns are distinct from generalizations. Some operationists have argued that generalizations are not fundamental for explanation, since we often want to explain in singular or statistically unlikely cases, which involve highly restricted scope and domain of invariance. I will argue that even in cases like these, biologists still need to represent patterns. Hence, operationists are wrong to exclude patterns on the grounds of rarity, and generalizationists are wrong to insist that patterns explain in virtue of having a particular scope or domain of invariance. In both cases, the error is due to equating the explanatory role of patterns and generalizations. I then close (section 4) by suggesting that which explanatory category is most important depends on explanatory context, and thus that there is no fundamentality between explanatory them. As should be clear, my focus is primarily on epistemic concerns. While

the debates about fundamentality discussed above often address both the metaphysics and epistemology of mechanisms, it is productive to keep analysis of these issues separate (Levy, 2013), as I will show below.

I draw my examples from mammalian chronobiology. Chronobiologists study circadian rhythms—roughly 24 hour, endogenously produced physiological rhythms which regulate a large number of processes in the body, ranging from sleep and cognitive abilities, to feeding behaviors, to gene expression. Many organisms have biological "clock" mechanisms within individual cells, which operate on the principle of negative feedback in gene regulation networks. In mammals, the intracellular clock consists in gene regulation between a "negative" loop consisting of the genes *Per* and *Cry* and their respective products (mRNAs and proteins), and a "positive loop" consisting of *Bmal1* and *Clock* and their respective products. In outline, it works as follows. Positive loop proteins bind to E-box promoters on the negative loop genes, activating their transcription. After translation outside of the nucleus, the negative loop proteins dimerize and are translocated back inside of the nucleus, where they bind to the positive loop genes on their own promoters, thus inhibiting their own transcription. As the negative loop proteins degrade, this inhibition is released and the cycle can begin again. With the right rates of transcription, translation, and degradation, these oscillations can occur over a roughly 24 hour period, hence providing a clock signal that can regulate other physiological processes. The clock mechanism is represented in the following diagram.

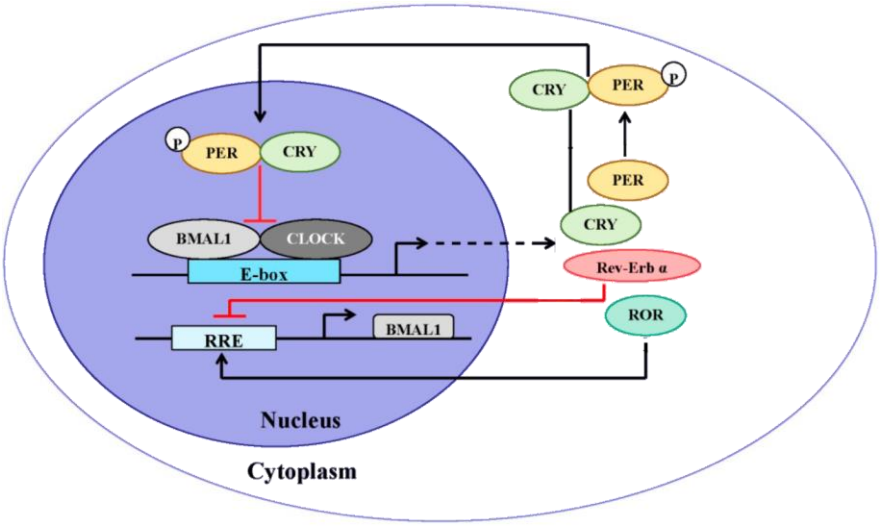

Figure 1. The mammalian intracellular clock mechanism. Modified from Wang, Zhang, Xu, and Tischkau (2014).

In the mechanism, the important parts include the genes and their assorted promoter regions, gene products, the nuclear membrane, etc. The key operations include the activation and inhibition of transcription via selective binding. There are a variety of more complex aspects to the clock mechanism. The products of the positive loop gene *Bmal1* also oscillate, due to a subsidiary feedback loop mediated by *Rev-erb* and *Ror* products. In addition, there are more gene products involved that play support roles, and more types of promoters. Particularly, D-box and RRE (Rev-erb response element) promoters serve as binding sites for a variety of proteins, and each of the promoters can regulate several different genes. Finally, several of the clock genes have *paralogs*—structurally similar genes that serve related functions in the clock.

While the canonical mechanism schema for the mammalian clock, including the parts and operations, has been largely agreed upon since the early 2000s (Zhang & Kay, 2010), investigation into the mechanism has continued—to a significant extent, investigators have turned towards discovering quantitative relationships within the mechanism. In the cases discussed below, I argue that the representation of quantitative patterns over time and across conditions is necessary for explaining certain circadian phenomena. In particular I will focus on temporal patterns regarding *phase* relationships and *proportional* responses in gene networks underlying compensation.

2. Patterns in Explanation

2.1. Phase relationships.

While the mechanistic picture given above is necessary for explaining rhythmicity, it is not sufficient. Several subsequent investigations have shown that it is not only that the mechanism operates according to the schema above that is important, but also that key quantities in the mechanisms bear particular temporal relationships to each other. Looking for these relationships involved measuring and conceptualizing data in certain ways not entailed just by knowing the mechanistic organization.

One such important relationship was discovered by Ueda et al. (2005), who decided to look at the temporal relationships between the activations of gene promoter types *as such*—meaning, regardless of the particular genes that they regulated. Since each type of promoter occurs on multiple distinct genes, analysis of promoters had generally taken a back seat to the study of the genes themselves. However, Ueda et al. showed that the particular

patterns of activity for each promoter type are important for explaining how an entire cell can oscillate in the quantities of its gene products. They first noticed that all of the different activators of a particular promoter type tended to hit their peak expression at similar times, and the same for its repressors. Moreover, for each promoter type—E-boxes, D-boxes, and RREs—there is a distinct phase relationship between their activators and inhibitors. This suggested to the researchers two ideas: (i) that each promoter of a given type is activated *in phase* with other promoters of the same type, even if they regulate different genes; and (ii) that each type of promoter should have a particular phase of peak activation. This is indeed what they found—E-boxes are most active in the morning, D-boxes during the day, and RREs in the evening.

Ueda et al. claimed a functional import for these relationships. Since the clock mechanism consists in a large number of interspersed gene relationships, the phasic regulation of particular promoters across all of the components can keep the many diverse gene interactions on a coherent schedule. For current purposes, however, the explanatory import of the patterns is most clear in a subsequent study by Ukai-Tadenuma et al. (2011). They showed that through very fine-grained manipulation of the *Cry1* D-box, they could manipulate the phase of *Cry1* expression, advancing or delaying it relative to normal D-box mediated expression. Only a phase of D-box-mediated transcription close to wild-type would produce normal cellular rhythms. So, the relative phases of the individual promoter types help to explain how the cell as a whole produces coherent wild-type rhythms.

Importantly, Ukai-Tadenuma did not manipulate the operation performed by the D-box—it still regulated *Cry1* just as normal. Instead, they manipulated the particular temporal pattern of its regulation. So, not only must the particular parts, operations, and causal organization of the mechanism be in place for it to work, but it must *also* have these elements coordinated according to the appropriate temporal patterns. Put simply, if the mechanism did not exhibit this particular set of temporal relations between its promoters, it would not oscillate, and learning this fact was an important addition to the explanation, overtop of the standard mechanism schema given in the clock model. What, then, is the explanatory role being played by the pattern? I suggest that it is adverbial (cf. Burnston, 2016). A mechanistic description shows *what* the operations are and shows the causal organization of their interactions. The representation of patterns shows *how* these interactions are coordinated in their levels and timing to produce quantitative phenomena like rhythmicity. The next example will further illustrate this role.

2.2. Proportionality and compensation.

Baggs et al. sought to study an important phenomenon related to molecular clocks, namely that of *compensation*. In noisy molecular networks, shifts above and below normal quantities of key components are common, but can also be problematic—as shown above, for instance, the clock requires precise temporal coordination of gene product levels in the mechanism. Baggs et al. (2009) showed that compensation in clock mechanisms relies both on their particular mechanistic organization *and* on the particular patterns of change in quantities of gene products as other gene products vary. Their manipulations consisted in

insertion of small interfering RNA (siRNA) into cells in vitro, targeted to specific mRNAs. SiRNA knocks down its targeted mRNAs in a dose dependent fashion, thus allowing for the comparison of responses in varying levels of knockdown. They represented their results in a variety of bar graphs, taken to show the types of responses that were important in implementing compensation. Two are shown below.

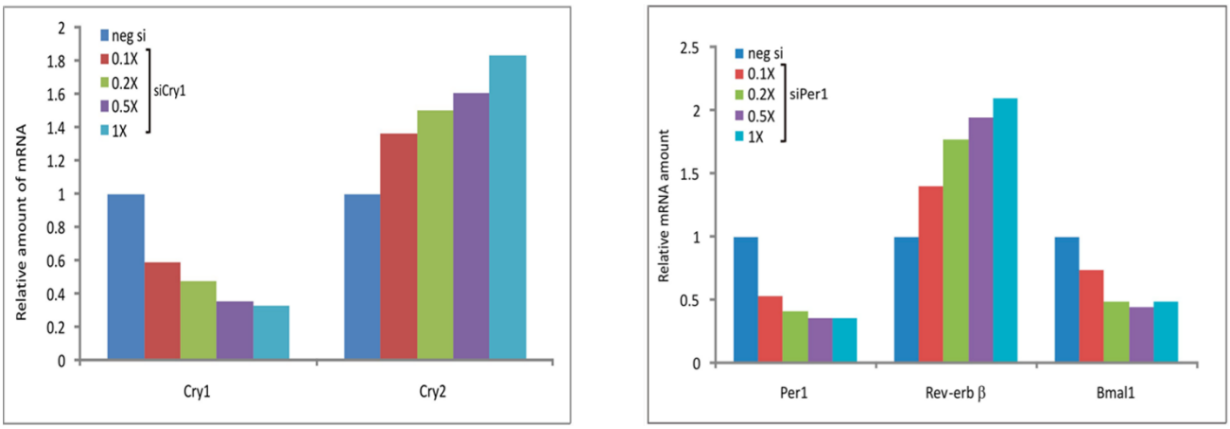

Figure 2. Proportionality patterns in knockdown conditions. From Baggs et al. (2009).

The left panel of figure 2 shows that, with increasing levels of knockdown for *Cry1* mRNA, *Cry2* mRNA *increases*. But not only does it increase, it does so *proportionally*—the greater the knockdown of mCry1, the greater the increase of mCry2. Since *Cry2* is the paralog of *Cry1*, it performs similar operations at similar targets. So, as mCry1 is depleted, the rising mCry2 level results in the overall level of *Cry* influence at its targets remaining the same, thus allowing for the cell's overall pattern of rhythmic gene interactions to continue. Proportional responses are also important in non-paralogous compensation. The right panel shows the effect of mPer1 knockdown on mRev-erbß and mBmal1. *Rev-erbß* is activated by *Per* proteins, and the proteins it codes for inhibit *Bmal1*. When mPer1 levels go down,

mRev-erbß levels go up proportionally. This in turn produces a proportional decrease in mBmal1. The fact that knockdown of mPer1 should cause mRev-erb levels to go up, and that increasing mRev-erb levels should subsequently cause *Bmal1* transcription to decrease, makes sense given the known operations performed by each part: mPer inhibits *Rev-erb*, whose products in turn inhibit *Bmal1*. However, the discovery that each relationship is *proportional* is presented by Baggs et al. as an important further fact in explaining compensation.

It is important for compensation for the following reason: the clock relies on precise interacting levels of inhibition and excitation between the positive and negative loops. Having the levels of one abnormally higher than the levels of the other would wreak havoc on the necessary interplay of inhibition and excitation. As is evident in the right panel, the combined proportional interactions result in a *balance* between the levels of mBmal1 (positive loop) and mPer1 (negative loop), hence keeping the interaction between loops functioning as normal. Knockdowns of other components are compensated for according to similar principles, inducing no loss of rhythmicity elsewhere in the clock.

Proportional relationships, as revealed in the bar graphs, are inherently *patterns of quantitative responses* across knockdown conditions. And, as with the case above, one must represent these patterns in addition to the mechanistic organization to understand how compensation comes about. As Baggs et al. summarize: "the clock network combines these activator and repressor modules with various forms of proportionality to construct relays that generate complex gene expression responses to single gene perturbations" (2009, p. 0570).

So, it is not only the types of causal interactions that occur ("activator and repressor modules"), but also the particular quantitative patterns in which they interact ("forms of proportionality") that explain compensation. This in turn helps explain how functioning rhythms at the cellular level can be maintained despite noisy conditions.

3. Patterns as Their Own Category

3.1. Patterns are distinct from operations.

A category is explanatory when representing it shows, perhaps in part, how the phenomenon of interest comes about. In previous work(Burnston, 2016), I argue in detail that the explanatory role played by representations of patterns is *dissociable* from that played by representations of operations (e.g., in a mechanism diagram). I will only summarize these arguments here, before moving on to discuss the relationship between patterns and generalizations. The key point to note is that in each of the studies above, the parts, operations, and causal organization of the mechanism were already known—neither study extends, revises, or modifies the known mechanistic organization. In each case, however, the researchers discovered and represented a set of relationships between quantities in the system at specific times and/or across specific conditions. As such, knowing the relevant facts about parts and operations *constrains, but does not determine,* all of the relevant facts about the patterns. For instance, in discussing the Baggs et al. case I only focused on linear proportional patterns of responses, but these are not the only possible ones. Baggs et al. also explore several other types, including proportional relationships with fractional coefficients and non-linear responses, which play roles in compensation for other knockdowns. The

point is this: these distinct patterns of relationships are all (epistemically) possible *even given the known operations* performed by each part and the targets they perform them on. So, specifying the parts and operations does not give us all of the information we need to explain. We must also represent quantitative patterns.

3.2. Patterns are distinct from generalizations.

Those who are inspired to consider generalizations as fundamental in explanation often note that mechanisms comprise causal relations, but causal relations of a certain sort, namely ones that are "stable" or "robust" (Leuridan, 2010; Woodward, 2010). A mechanism, the intuition runs, is one that exhibits a stable organization that can produce "regular changes" (Machamer, Darden, & Craver, 2000) in its environment. Hence, mechanisms depend on generalizations instantiated amongst their parts. Those who consider operations fundamental often point to the shortcomings of generalizations for explaining causal relationships *between particulars.* It is the activities of particulars, the intuition goes, that have effects on other particulars, not whether they instantiate some generalization. These relationships can hold even in statistically unlikely or rare cases—in extreme cases, we could want to explain *singular events*, which only happen once. Bogen (2005) and Craver and Kaiser (2013) take this argument to show that explanations do not depend on relationships with a significant domain of invariance or scope, and thus that generalizations only play subsidiary epistemic roles, which help us to access the operations that actually explain.

Patterns of the type I have described, however, are explanatorily distinct from generalizations. The argument involves two claims, one against the generalizationists and

one against the operationists. Against the operationists: representing patterns is necessary for explanation even in cases of minimal scope or domain of invariance. Against the generalizationists: it is the specific pattern in the relationship, not any specific facts about its domain of invariance or scope, which is important for explanation. Presumably, if it were really the case that the explanatory role of a pattern depended on its status as a generalization, then that role would be closely related to how wide a scope the pattern has or how broad its domain of invariance is. The following two simple thought experiments show this not to be the case. The first assesses domain of invariance, and the second assesses scope.

The fragile oscillator. Suppose that we have a system that exhibits the patterns of phase relationships shown in the Ueda et al. study, and thus oscillations amongst the gene products in its molecular clock. But it is highly fragile, meaning that there is an *extremely specific* set of conditions that has to hold in order for it to oscillate. Perhaps the constituent proteins are easily broken apart, or the environment is highly volatile, so that even slight variations in (say) temperature or PH will modify transcription and degradation rates, interrupting the needed patterns and preventing oscillation within the system. One could dress up the example until arriving at a case where the patterns have a *minimum* domain of invariance—that is, in which there is only one set of conditions in which the mechanism will oscillate. In this case wiggling *any* variable other than the ones mentioned in the pattern will prevent the pattern from occurring. If the explanatory role of patterns were based on their having some specific domain of invariance, then they should play a lesser or different

explanatory role in this case than in a case where their domain of invariance is broader. This, I submit, is not the case. When we go to explain how this system works, we will need to mention both its mechanistic organization and the phase relationships between promoters, just as Ueda et al. see fit to do. But if the explanatory role played by representations of the phase relationships is the same in either case, then that role doesn't depend on its domain of invariance.

The lonely compensator. It is important to emphasize here that domain of invariance is distinct from scope. Even if the conditions needed were maximally specific, they could occur in many different instances. To address scope specifically, imagine an opposite case from that above, namely an oscillator that was *so* stable, and existed in *such* an amenable environment, that there were virtually no instances where its gene product quantities varied significantly from their normal (oscillating) values. Now suppose that some cosmically unlikely event occurred, whose only effect was to knock *Per* mRNA quantities away from their normal level. As a matter of historical fact, this has only occurred once, but when it did the system compensated, according to the explanation given by Baggs et al. When giving the explanation for what occurred in this system, if Baggs et al. are right, we will need to posit proportional patterns of the type I described above (along of course, with the standard mechanism schema). Here, ex hypothesi, we have a phenomenon that occurs only once, thus having minimal scope, and yet we still need the representation of patterns in the same explanatory role as in our world where compensation is common. So, the explanatory import of patterns does not depend on facts about their scope.

Both generalizationists and operationists have erred in conflating patterns and generalizations. Against the generalizationists, the explanatory role of patterns does not depend on their having scope or domain of invariance. Against the operationists, they must be represented even in highly specific or unlikely cases. There are likely to be objections from each side. First, generalizationists might insist that, in the thought experiments I've discussed, the patterns *do* have a domain of invariance and a scope; it's just that these are at the theoretical minimum. Hence, they are still generalizations. Operationists, for their part, are likely to suggest that these patterns only "specify key quantities" (to use Bogen's phrase) and that since they do not themselves describe the causal relationships at work, they rely on more fundamental descriptions of operations.

The response to each of these objections is the same: they may make sense as metaphysical claims, but don't tell against the epistemic thesis I am advocating here. I have argued for a particular *explanatory* role for patterns. The cases above show that this explanatory role of patterns remains *the same* regardless of any specific facts about scope or domain of invariance. If a generalizationist wishes to insist that any pattern *must* be a regularity on metaphysical grounds, and is willing to bite the bullet of calling the relationships discussed in the thought experiments regularities, this does nothing to undermine an explanatory distinction between patterns and generalizations. As for the operationist's response, the discussion in section 2 showed that knowing the relevant facts about parts and operations simply doesn't exhaust the explanation. There is a particular role to be played in representing patterns, and this role must be pursued in addition to listing the

parts, operations, and organization. If the explanatory roles are distinct and both necessary, then there is no in principle *epistemic* priority between them (Burnston, 2016). If operationists wish to pursue the fundamentality claim as a metaphysical one, I have no quarrel with them, so long as distinct explanatory roles are kept distinct.

Finally, generalizationists are likely to note that I have leaned on counterfactual reasoning in discussing the role of patterns—i.e., if the patterns *weren't* instantiated, then the phenomenon would not come about. While generalizations are often thought of as grounding counterfactuals, this is different from saying that the explanatory role of a pattern *depends* on its status as a generalization. As the above has shown, we could make the same counterfactual claim regardless of any facts about scope or domain of invariance. For instance, the very same counterfactual holds for proportional relationships in the lonely compensator case as holds in the real world where the scope of proportional relationships is much greater. Again, so long as we are talking about the epistemology of explanation, the role of patterns should be kept distinct.

4. Conclusion: Contextualism and Explanation

I think that the right lesson to draw from the foregoing is that we should distinguish between (i) describing the mechanistic organization of a system, (ii) explaining how a phenomenon comes about, and (iii) generalizing either (i) or (ii). In science, each of these projects is pursued and they are often pursued in tandem; hence they are often run together.[2]

[2] Craver and Kaiser (2013) clearly distinguish between (i) and (iii), but not between (i) and (ii); this is because they miss the distinction between patterns and generalizations, and the important explanatory role played by the

Keeping them distinct, however, allows us to overcome the question of fundamentality by describing the relative roles of operations, patterns, and generalizations in explanation. Aspect (i), obviously, involves discovery and representation of parts and operations. Aspect (ii) often involves aspect (i) *plus* the representation of key quantitative patterns. The thought experiments above show that while aspects (i) and (ii) *can* be extended to ask questions about generalization, they needn't be.

When we *do* turn to generalization, we do so with specific goals and questions in mind. For instance, how widespread phylogenetically is the set of parts, operations, and patterns that implements oscillation? Are other organizations and patterns exhibited elsewhere? At least in terms of mechanistic organization, interacting positive and negative feedback loops between genes is extremely common (although the particular components differ) across a wide range of phyla. This fact about scope is an extremely interesting generalization, since it clues us in to the central importance of circadian timekeeping for all organisms. Equally important, however, is learning the *limits* of these generalizations. One of the major discoveries in chronobiology in the last 15 years is that molecular clocks in cyanobacteria operate on a post-translational mechanism, rather than on interlocking feedback loops of gene regulation (Masato et al., 2005), and hence that the scope of the dual-loop model is limited. Similarly, we could want to know about domain of invariance. For instance, what are the conditions for having a well-functioning clock, and how are they

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former overtop of describing the relevant parts and operations. Some of what I say about generalization in this section is compatible with Craver and Kaiser's discussion of the distinction between (i) and (iii).

compromised in shift-work disorder, familial advanced sleep phase syndrome, jet lag, and other circadian interruptions? One hypothesis is that jet lag is due to disrupted phase relationships between cellular clocks in two parts of the mammalian suprachiasmatic nucleus (Davidson et al., 2009); hence, in odd lighting conditions the normal phase patterns break down and cannot instantiate wild type behavioral rhythms. These are inherently questions that rely on the generalizations surrounding circadian mechanisms, but the importance of these questions doesn't support the fundamentality of any particular category in giving explanations.

What I want to suggest is that there are simply distinct explanatory contexts, and which category comes to the forefront depends upon the kinds of questions we are asking. For instance, if we are asking what *type* of causal relationship we are analyzing—what parts interact, whether they do so directly, what the results of those interactions are, , etc.—this this predisposes the explanation to invoke operations. When we are interested in how phenomena arise from the operations of a mechanism, attention turns to the interplay of quantities in the mechanism, and thus to patterns and explanatory relations. If we are interested in the robustness of relationships, then scope and domain of invariance, and hence generalizations, come to the fore. This is a distant cousin of contextualisms about explanation that have been advanced before (Van Fraassen, 1983), and while it is not currently a popular way of thinking, I suggest that contextualism is the best way to make sense of the relationship between distinct categories and their relative explanatory roles.

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