Mechanistic Diagrams as Search Organizers

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Abstract

Many in cognitive science have noted the importance of external visualizations for reasoning and learning, and have suggested that such visualizations play a role in complex reasoning contexts such as scientific investigation. However, what cognitive role diagrams play in scientific reasoning is unclear. I suggest that mechanistic diagrams function as search organizers in active research projects. Diagrams aid in scientific reasoning by being uniquely positioned to coordinate cognitive search through multiple search spaces, both within an individual and within a field. I examine this role using a number of published diagrams from mammalian chronobiology.

Keywords: scientific diagrams; cognitive search; chronobiology.

Introduction

Diagrams are nearly ubiquitous in biological practice, in which the goal is often to construct an explanation of the mechanisms responsible for complicated phenomena. In journal articles, conference presentations, and whiteboard discussions, research scientists continually engage in the process of constructing, analyzing, and modifying diagrammatic representations. This ubiquity suggests that diagrams play an important role in reasoning about phenomena in biology. However, the specific role that diagrams play in reasoning is not established. Part of the difficulty is the sheer complexity of the reasoning processes involved. Scientists must coordinate a variety of representational resources in constructing mechanistic explanations, and diagrams are often involved in characterizing the phenomena of interest, organizing and presenting obtained data, and conveying the parts, operations, and organization of a proposed mechanism (Gooding, 2010; Sheredos, Burnston, Abrahamsen, & Bechtel, forthcoming).

The current literature on diagrams has focused largely on the meaning of diagrammatic elements and how they relate (Tversky, 2011), as well as on how diagrams might encode complete explanations (Perini, 2005), or function as learning tools for novices (Cheng, 2011). While these are important analyses, they leave a gap in understanding how diagrams might play a role, even for experts, in *constructing* explanations of complex phenomena. Pioneering historical studies of episodes of scientific discovery (Cheng, 1992; Nersessian, 2008) have focused on the use of visualizations in the efforts of individual scientists to explain mathematical or physical phenomena. The use of diagrams in an active field of contemporary science presents new challenges, as diagrams are used, discussed, and appropriated by numerous different researchers, each with different backgrounds, interests, and experimental skills.

In this paper I propose an account of how diagrams aid scientific reasoning in an active research field. The proposal draws upon several approaches in cognitive science, which construe reasoning as involving "cognitive search"—a process of selecting the right representations out of a space of possibilities in order to meet a cognitive goal. The search perspective on diagrams contends that diagrams facilitate scientists' cognitive search through the complex realm of possibilities that are relevant in explaining natural phenomena. Specifically, I contend that diagrams provide an external search space that allows for the coordination of both conceptual and experimental resources, both by individuals and by entire scientific communities.

I focus on diagrams of proposed mechanisms in biology. This type of diagram generally consists of proposed entities or events depicted by shapes and/or linguistic labels, organized in visual space, and related via arrows, lines, and enclosures to convey the structural, causal, functional, and/or conceptual (e.g., categorical) relations between them. Often, these diagrams occur at the beginning or end of a research article as a way of organizing the findings into a model of how physical components might interact to produce phenomena of interest. Moreover, these diagrams are often changed and expanded over a series of publications in order to incorporate new results.

While receiving relatively little attention in analyses of scientific practice, diagrams of this type can be extremely important, as even minor changes to diagrammatic form can have large effects on how the organization of a mechanism is interpreted. Sheredos et al. (forthcoming) have argued that these differences both constrain thought in particular ways and afford particular inferences that are useful for hypothesis construction. The search perspective expands on this viewpoint to further elucidate the use of mechanistic diagrams in a research field.

I will develop this perspective by analyzing the use of mechanistic diagrams in mammalian chronobiology. Chronobiologists study phenomena of circadian rhythms—daily, roughly 24 hour cycles in biological activity—in a variety of different organisms, at each of the behavioral, physiological, and molecular levels. Many biological processes exhibit circadian rhythms, including gene transcription, cell division, metabolism, and overt sleep and feeding behavior. Over the last 25 years, much progress has been made in understanding how these rhythms are

regulated by internal, molecular clocks that both keep time and entrain the organism to environmental timing cues such as light and temperature.

Due to its extensive use of diagrams in identifying and explaining complex phenomena, chronobiology is a fertile ground for inquiries about diagrammatic reasoning in active science. My aim is to offer a theoretical perspective that can guide further empirical research on scientific reasoning, diagrams, and cognitive search. I begin by discussing how the notion of search has been employed in understanding reasoning in cognitive science, and how it can be applied to diagrams, before turning to discuss particular examples from chronobiology.

Diagrams and Cognitive Search

One of the major challenges in science is the complexity of the reasoning processes that are required to grapple with natural phenomena. The notion of "search spaces" has been useful in trying to understand this challenge and how scientists proceed in meeting it. A "space," in this context, is simply a set of possibilities that are relevant to a reasoning task.

In a classic study, Klahr and Dunbar (Klahr & Dunbar, 1988) asked subjects to discover the function of a particular command in a robot's programming language. There were two relevant spaces in the task: the "hypothesis" space of possible functions for the command, and the "experimental" space of possible manipulations to test given hypotheses. In the study, these spaces were artificially constrained via the experimenters—they chose what to tell subjects about the command, thus limiting the hypothesis space, and they set up the language of the robot, thus limiting what manipulations could be performed. They used this limited space to analyze subjects' reasoning, which allowed them to characterize the difficulty of the task and the (sometimes different) reasoning strategies that individuals used to solve it.

The search perspective has been used in a variety of other investigations into scientific reasoning (Schunn & Klahr, 1996; Thagard, 1998), and experimental work in non-scientific contexts has begun to elucidate the cognitive and neural mechanisms that underlie search through the space of semantic memory (Hills, Todd, & Goldstone, 2008). I here apply the search perspective as a way of understanding contributions of diagrams to reasoning in active scientific research.

While different numbers of search spaces have been proposed, for simplicity's sake I begin with two spaces, a conceptual space and an experimental space. The conceptual space consists of a scientist's or group of scientists' knowledge or beliefs about a system—including the particular entities that produce phenomena, their properties, and the kinds of interactions in which they can be involved. So, when a scientist approaches a phenomenon, they do so with an understanding of the entities involved in producing that phenomenon. This knowledge provides a set of resources for reasoning about the system in question, which is continually modified and updated as investigation proceeds. In constructing and testing explanatory hypotheses, scientists consider this realm of possibilities in a flexible way—coming up with a good hypothesis involves "finding" the right system knowledge to account for the phenomenon of interest.

Experimental space consists of the possible manipulations that can be performed on the system in question given the practical strategies and limitations available to a field at a given time. This knowledge is often "embodied" in the sense that it involves practical know-how about successful manipulations, but it also can involve a theory of the instrument that licenses inferences to be drawn from particular results. To these I add a third, diagrammatic space, which plays the role of flexibly indexing and guiding search through the other two spaces. In employing the notion of search space, I make no claims about the format of the internal representations involved, or about the nature of the search algorithm. So long as such conceptual and experimental knowledge exists, my claim is that diagrams provide a way of indexing those bodies of knowledge.

One of the differences between reasoning tasks posed in psychology experiments and those undertaken by scientists "in the wild" is that in science the search task is often ill-defined. That is, there are not clearly constrained solution options for a given reasoning task. Search through diagrammatic space, I propose, allows for flexible constraints on conceptual and experimental search, which allows both for productive investigation within specific models and continual questioning and reconceptualization of those models. Diagrams contain elements which provide directions of search *through the diagram*—arrows, enclosures, etc. This external search can then serve as a guide to the difficult work of employing one's conceptual space in reasoning about the system, and in using one's experimental space to devise tests of that reasoning. This external search space can be manipulated with relatively little cognitive demand. Moreover, diagrammatic space can be shared in common amongst individuals whose conceptual and experimental spaces differ, thus guiding a *field's* investigations into phenomena and mechanisms. I will discuss each of these points, with examples from mammalian chronobiology. My discussion will be illustrative. Importantly, I do not claim that *all* such reasoning *must* occur through diagrams. I only attempt to characterize the resources that diagrams *can* provide in active research, and I contend that this can help account for their importance and ubiquity in biology.

Mechanistic Diagrams in Biological Research

As Klahr and Dunbar (1998) pointed out, one of the ways to constrain a space is to convey an abstract structure. Diagrams, given their particular elements and arrangements, do this exceedingly well. Consider Figure 1, a diagram

from a relatively early period in the history of mammalian circadian research. The diagram depicts a series of events

Figure 1: Three-stage model of the relationship between the endogenous clock and activity onset; from Welsh, Engle, Richardson, and Dement (1986).

that occurs at the beginning of an organism's "subjective day" (the part of the day during which the animal is active—dawn for diurnal organisms, dusk for nocturnal ones). The organism's internal clock functions to *anticipate* the external light schedule, and sends a signal to the mechanisms in the organism that govern waking and activity onset.

The diagrammatic space in the figure consists of the enclosed shapes and the arrows connecting them. Importantly, there are two distinct shapes, providing a visible, categorical distinction between the referent of the circle and those of the rectangles. The arrows imply an ordering of some sort between these referents, where this ordering has a *directionality* (i.e., it goes from the circle to the squares and not vice-versa) and is sensitive to the variables *w* and *a*. This exhausts the *purely visual* set of constraints present in the diagram, which provide suggested patterns of search through the diagram. However, even these very minimal constraints manage to convey a great deal of abstract structure. It is abstract in that *any* entities and relations referred to must fit this pattern, if the diagram is taken as correct.

The connections to conceptual and experimental space are provided by the linguistic labels, as well as the instructions for how to interpret the figure. The denotation of the circle as a 'clock signal' indexes researchers' conceptual space regarding the nature of the clock and its relation to observable behavior. At this point, behavioral studies addressing rhythmicity had already established that the clock was *endogenous*—i.e., that it is an internal mechanism that can run without external input. Lesion studies had also suggested that the central clock in mammals has a particular brain locus in the suprachiasmatic nucleus (which was later conclusively confirmed), but little to nothing was known about the detailed mechanisms. Thus, the abstract model encoded in the diagram suggested that the 'clock signal', presumed to be coming from this central mechanism (whatever its detailed nature), must be related by an unknown process to the observable behavioral events under its control—in this case, waking and activity onset. The distinction between the circle and the rectangles denotes this categorical difference between the presumed mechanism and observable states. The caption, in addition, instructs that *w* and *a* should be interpreted as the *time lag* involved in the transmission of the signal that cues wake processes, and the time lag between waking and activity onset, respectively.

Thus, the abstract structure conveyed in the diagram, along with its indexing of conceptual space and interpretational instructions, expresses a *three-stage* model of activity onset rhythms, in which a clock signal precedes waking, which precedes activity onset. As Welsh et al. stress, there is also an implied *causal* order in the diagram—that is, since the timing of activity onset is dependent on both the timing of the clock signal and that of the waking onset, it is suggested that the causal process leading to activity runs through these events.

In addition, the model's structure indexes the experimental space available to researchers. Two important experimental procedures in chronobiology are (i) the statistical analysis of variation in the phase of particular circadian events and (ii) external manipulation of the environmental factors involved in generating rhythms. Welsh et al. kept mice on a constant light schedule (ii), and analyzed the resulting phases of each stage (i) to test the model above. They discovered that there were no significant differences in phase between activity onsets over a period of days, while there were significant differences in wake onset.

Welsh et al. explicitly interpret this result with reference to the diagram in Figure 1. This result, initially, seems to be incompatible with the model, since variation across multiple time lags should produce greater variation at the end of the signaling chain. However, Welsh et al. argue that it is not incompatible, so long as the two signals are anti-correlated, with one becoming longer whenever the other is shorter. They then consider a number of possible mechanisms. The first proposes that a longer lag in *w* allows the organism to be better prepared to begin activity, and thus leads to shorter *a*. The second, more radical proposal, argues that the *timing* of these events depends on a direct relationship between activity and the clock signal, with waking being indirectly regulated.

Interpreting these possibilities in light of the model further provides suggestions for experimental manipulation via method (ii)—namely, manipulating the availability of activity by controlling access to the running wheel. Several of the authors performed a separate study in which limiting wheel-running to specific times of day was shown to shift the phase of the central clock signal (Edgar, Martin, & Dement, 1991). This in turn prompted the idea that there is a *feedback* signal from mechanisms controlling activity to the central clock, which was subsequently widely adopted. The picture that emerges is one in which continual consultation and interpretation of the figure allows for iterative episodes of indexing conceptual and experimental spaces, where the constraints present in the model guide subsequent investigation. Even if the model is eventually expanded (e.g., through the incorporation of a feedback

arrow running from the box on the right to the circle on the left) or overturned, this in no way lessens the potential importance of the figure for reasoning about the system in question. This analysis is at least broadly in tension with views of diagrams as *conveyors* or *communicators* of explanations—diagrams can aid cognitive search even if they are not taken as correct or complete explanations of phenomena. If this analysis is right, even extremely simple diagrams can be important reasoning tools. I now go on to discuss how this kind of analysis can be applied to more complex diagrams, which aid search in the construction of explanations involving complex mechanisms with many interacting parts.

Discovering Parts and Operations: The Function of CRY Proteins

The central clock mechanism, in many organisms, consists of a "core" molecular clock, which operates via the interaction of multiple feedback processes. In this mechanism, the expression of a "positive" element causes, via DNA binding, the expression of a "negative" element, which in turn inhibits both its own transcription and that of the positive element. After the negative element is degraded, inhibition on the positive element is released and the cycle begins again—the period of the cycle is determined by the time course of the interactions between the relevant components. In the 1990s, several of the key genes involved in these feedback processes were discovered through research on fruit flies and rodents. Figure 2, from Dunlap (1999), represents the state of understanding of the mammalian core clock at the end of the decade.

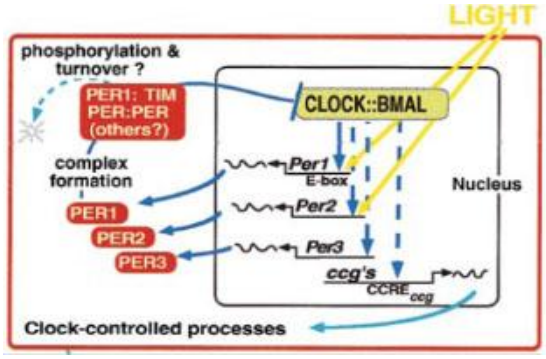

Figure 2: Diagram of a model of the mammalian core clock, circa the late 1990s; from Dunlap (1999).

The positive elements of the core clock are the protein products of the genes *Clock* and *Bmal*, and the negative elements are transcripts of the various paralogs of the *Period* (*Per*) gene. The diagram depicts the positive element proteins binding to the promoter region (E-box) of the *Per* genes, whose transcribed mRNAs move outside of the nucleus and are translated into proteins. The proteins then form complexes of an unknown kind, and then inhibit their own transcription by binding to the CLOCK::BMAL complex. External light, denoted with yellow arrows, is presumed to affect the clock by interacting with the negative loop.

Dunlap's diagram also included a question mark in the red box at the upper left, to indicate that there were likely other dimeric partners involved in the negative loop. At the same time, it was known that mammalian cells contained the gene *Cryptochrome* (*Cry*), a homolog of the *Cry* gene in drosophila, which serves as a photoreceptor for the light signaling pathway in flies. However, the function of *Cry* in the mammalian clock was unclear, as manipulation did not have any effect on entrainment to external light. Thus, it was left out of Dunlap's diagram. Further evidence against *Cry* as part of the entrainment mechanism appeared in the same year; Van der Horst et al. (1999) showed that individual knockouts of the *Cry1* and *Cry2* paralogs had effects on circadian period, and that double knockouts eliminated rhythmicity completely. Kume et al. (1999), while citing Dunlap at several places, immediately proposed that CRY proteins might fit into the model at the point where, in the red box in the upper left, Dunlap had left a question mark—it might replace TIM as the proposed dimeric partner for PER. They performed a variety of manipulations on CRY, showing: (i) that CRY protein quantities are dependent on the functioning of *Clock*, (ii) that CRY can stop activation due to CLOCK::BMAL, and (iii) that CRY and PER dimerize and are transmitted to the nucleus together. It seems clear that Kume et al. were working from the model encoded in Dunlap's figure.

In this case, a change in conceptual space—the idea that *Cry* might be involved in the core clock—interacts with the model represented in the diagrammatic space to suggest experiments that can establish whether this new role is correct. Constraints for these experiments are present in the diagram—e.g., by guiding search for interactions with the proposed PER dimer—and its further indexing of the other elements of conceptual space. Once again we can see the potential cognitive benefits of encoding a model in diagrammatic space, and how this further relates to the interaction of conceptual and experimental space.

Diagrams for a Field: Coordinating Multiple Conceptual and Experimental Spaces

In my final example, I show how diagrams can be shared search spaces for researchers with different theoretical and experimental backgrounds. The results of Kume et al., among others, are expressed in Figure 3, from Lowrey and Takahashi (2004). The basic organization from the Dunlap diagram is still present (although flipped left to right), and a few further elements have been added, including the additional support loop formed by the *Rev-erb* gene, which acts as a positive regulator of *Bmal* transcription. Ye, Selby, Ozturk, Annayev, and Sancar (2011) decided to test a core assumption of this model—that the PER::CRY dimer

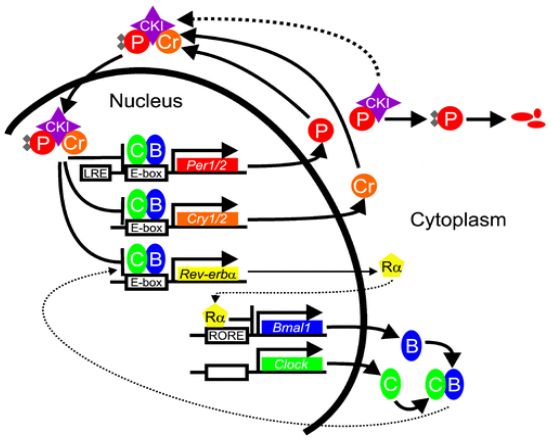

Figure 3: Diagram of a model of the mammalian core clock, circa the mid-2000s; from Lowrey and Takahashi (2004).

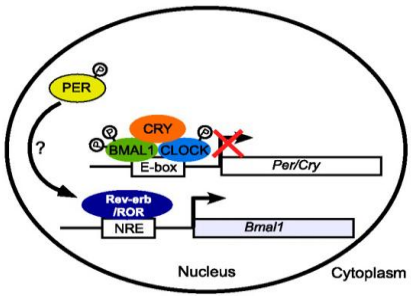

Figure 4: Diagram of the results of Ye et al. (2011), suggesting a revised role for the PER protein in the core mammalian clock; from Ye et al. (2011).

inhibits transcription of *Per* and *Cry* by binding to the CLOCK::BMAL complex while it is on the E-box—via sophisticated biochemical analysis. They employed chromatin immunoprecipitation (ChIP), a technique that allows for the isolating of particular DNA/protein complexes in the nucleus, and the determination of what proteins bind to particular sections of DNA. Importantly, this technique allows for a different trajectory through experimental space than the techniques used to develop the core model, which did not allow for precise localization and analysis of binding within the nucleus. While ChIP had existed in other fields of biology, it began to be used frequently in chronobiology only in the mid-2000s.

Ye et al. found, contrary to the standard model, that only CRY, and not the PER::CRY dimer, bind to the CLOCK::BMAL dimer while it is on the E-box. Moreover, the presence of PER actually *inhibits* this process of binding. If correct, this forces a relatively major revision of the model. Ye et al. represent a possible revision in Figure 4. This re-coding has significant conceptual ramifications for anyone familiar with the core clock, as it forces revision of the standard assumption about the causal process in the negative loop.

As the diagram suggests, and Ye et al. elucidate, new functional posits are needed to understand the role of PER in the clock mechanism. What does the diagram contribute? First, it emphasizes the difference between the previous model and the current results. Second it provides a functional posit for PER, as being potentially involved inmodulating the *Rev-erb* loop. This diagram suggests a new course through experimental space—inquiry into the potential binding of PER to the elements of this loop at different times during the circadian day. Moreover, those familiar with the standard model must now adjust their representation of the place of PER in the core loop (this suggests "replacing the top part of Figure 3 with the type of representation given in Figure 4). Despite revisions such as this, the standard diagrams still provide structural and functional indices that constrain conceptual search for new roles of PER, as we saw in the discussion of Figure 2. We can expect that, should these results gain widespread acceptance, future review articles will incorporate these changes to the standard model.

This example shows a broader role for diagrams than in the reasoning of individuals. The standard model is explicitly targeted by Ye et al. as the source of their analysis—and they cite the Lowrey and Takahashi paper, among others. This suggests that diagrams play the role of organizing different methodological approaches around the same phenomenon and proposed mechanism. As Ye et al. mention, a variety of methods were used in constructing the standard model; however, emerging methods of analyzing protein interactions using biochemistry have the potential to fill in gaps or question particular aspects of models that are standard in the field. Crucially, not all scientists studying a phenomenon possess the same methodological expertise—that is, their experimental spaces differ. Equally important, once the results regarding the PER::CRY dimer have been obtained, they are re-encoded into a diagrammatic form that is common to those across different experimental backgrounds.

Based on these analyses, I propose that a primary function of mechanistic diagrams is to provide an external search space that coordinates search in conceptual and experimental spaces, across both personal and interpersonal contexts.

Conclusion

The ubiquity of diagrams, and their seemingly important resources for aiding reasoning about complex systems, resist the interpretation that they are eliminable—i.e., that *all* of the actual thinking done by scientists is purely internal. To treat diagrams as themselves sufficient to convey scientific theories or explanations, however, seems equally unrealistic, as it fails to account for the vast amounts of detailed conceptual knowledge and experimental expertise that individual scientists, as well as research fields, bring to understanding any particular diagram.

I have argued that a search perspective on diagrams can make sense of their role in active research, and used this perspective to construct a sense-making narrative of important epochs of research in mammalian chronobiology. While the success of the narrative is not proof of the theory, the view I have proposed has a number of potential benefits for experimental studies of scientific reasoning. First, it can relate the search for scientific solutions to the more general literature on cognitive search. Much progress has already been made in understanding how subjects search through a visible space in relation to a task. Do these principles carry over to search in scientific diagrams? Stieff, Hegarty, and Deslongchamps (2011) have conducted an eye tracking study showing that individuals' eye movement patterns while using multiple visualizations (a mechanism diagram, a graph, and an equation) in a problem solving task are related to their particular educational experience. Mechanistic diagrams, on the search perspective, are ripe for this kind of study.

Finally, the search perspective can aid discussions and experimentation on both scientific reasoning and diagrams in general. Diagrammatic form can be used in a variety of tasks, and can help model discovery situations when individuals' conceptual and experimental spaces are shaped by the experimental setup. As shown by Sheredos et al. (forthcoming), changes in diagrammatic form affect interpretation, and thus the experimental manipulation of diagrams across reasoning tasks can shed light on the nature of individuals' search strategies. Taking the search perspective on mechanistic diagrams, then, has promise for helping to overcome the difficult methodological gap between standard psychology experiments and creative scientific reasoning.

Acknowledgements

This material is based upon work supported by the National Science Foundation under Grant No. 1127640. I would like to thank the members of the WORGODS (WORking Group on Diagrams in Science) research group for valuable feedback.

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