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Bowtie Structures, Pathway Diagrams, and Topological Explanation

Nicholaos Jones

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Abstract While mechanistic explanation and, to a lesser extent, nomological explanation are well-explored topics in the philosophy of biology, topological explanation is not. Nor is the role of diagrams in topological explanations. These explanations do not appeal to the operation of mechanisms or laws, and extant accounts of the role of diagrams in biological science explain neither why scientists might prefer diagrammatic representations of topological information to sentential equivalents nor how such representations might facilitate important processes of explanatory reasoning unavailable to scientists who restrict themselves to sentential representations. Accordingly, relying upon a case study about immune system vulnerability to attacks on CD4+ T-cells, I argue that diagrams group together information in a way that avoids repetition in representing topological structure, facilitate identification of specific topological properties of those structures, and make available to controlled processing explanatorily salient counterfactual information about topological structures, all in ways that sentential counterparts of diagrams do not.

1 Introductory Remarks

Inquiries into the nature of explanation in the biological sciences tend to focus upon either the nature of biological laws and their role in nomological explanation or the nature of mechanisms and their role in mechanistic explanation. (Examples of the former include Rosenberg 2001 and Press 2009; of the latter, Bechtel and Abrahamsen 2005 and Mc Manus 2012.) Recent work by Huneman (2010) focuses upon a third kind of explanation prevalent in the biological sciences: topological explanation. Rather than accounting for their explananda by showing them to be

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N. Jones (✉)
University of Alabama in Huntsville, 301 Sparkman Drive, Huntsville, AL 35899, USA
e-mail: nick.jones@uah.edu

outcomes of the operation of a mechanism or by subsuming them under biological laws, topological explanations show their explananda to be consequences of a system's topological properties.

Extant inquiries into the role of diagrams in biological science reflect this focus. Bechtel and Abrahamsen (2005: 427–429) argue that diagrams facilitate our understanding of mechanisms by offering relatively direct and iconic representational resources. Perini (2005) argues that diagrams facilitate functional explanation (a close cousin of mechanistic explanation) by virtue of being more concise than their sentential counterparts. Finally, Jones and Wolkenhauer (2012) argue that diagrams facilitate both mechanistic and nomological explanation in cell biology by virtue of being locality aids, grouping together information that is to be used together in a way that sentential representations do not. None of this literature, however, discusses the role of diagrams in topological explanations from the biological sciences. (While diagrams appear in Huneman's work, they do so only for illustrative purposes (2010: 235, 237). Huneman focuses, instead, on explicating the nature of topological explanation, distinguishing it from mechanistic explanation, and illustrating its pervasiveness.)

Bechtel and Abrahamsen suggest two questions appropriate to a philosophical investigation of diagrams in scientific practice (2005: 427):

- Why might scientists prefer diagrammatic representations of information rather than, or in addition to, sentential ones?
- Do diagrammatic representations facilitate important processes of explanatory reasoning unavailable to scientists who restrict themselves to sentential representations only?

I shall argue that extant philosophical accounts of diagrams in scientific practice provide incorrect or incomplete answers to these questions for diagrams associated with topological explanations. I shall argue, further, that scientists might prefer diagrammatic representations of information associated with topological explanations because such diagrams group together information in a way that avoids repetition in representing topological structures and facilitate identifying specific topological properties of those structures, and that diagrams make counterfactual information about topological structures available to controlled processing in a more direct manner than their sentential counterparts.

I begin by reviewing Kitano and Oda (2006) recent account of immune system vulnerability to attacks on CD4+ T-cells, an account which appeals to topological properties of the immune system cellular interaction pathway. Two subsequent sections address Bechtel and Abrahamsen's questions about the role of diagrams in scientific practice, offering support for my theses. Then, prior to some concluding remarks, I distinguish topological explanations from a certain kind of mechanistic explanation (so-called constitutive mechanistic explanations), and I explain why part of Bechtel and Abrahamsen's account does not apply to the diagram associated with Kitano and Oda's explanation.

While Kitano and Oda's account, and its associated pathway diagram, provide the evidential basis for the preceding theses, its choice as a case study is apt for other reasons as well. While Huneman focuses on the aptness of topological explanation for explaining robustness (2010: 229–239), this case focuses on the aptness of topological explanation for explaining fragility, the counterpart of robustness (Csete and Doyle 1999: 447). Moreover, because pathway diagrams are increasingly prominent in molecular systems biology (Cho and Wolkenhauer 2003: 1505), and because Huneman focuses his discussion on topological explanations in ecology (2010: 219–229), this case study reinforces Huneman's thesis about the pervasiveness of topological explanation in the biological sciences.

2 Case Study: Immune System Vulnerability to Attacks on CD4+ T-Cells

When human immunodeficiency virus (HIV) enters the body, it binds to CD4 receptor sites and either CCR5 or CXCR4 co-receptor proteins on the surface of infection-fighting CD4+ T-lymphocytes. After fusing with these lymphocytes and releasing its RNA into the cell bodies, the virus uses an enzyme, reverse transcriptase, to convert single-stranded HIV RNA into double-stranded HIV DNA. This DNA enters lymphocyte nuclei and remains inactive until, upon receiving an activation signal, the virus uses various enzymes in the lymphocyte nuclei to assemble new virus particles. These viral copies eventually leave their host cells, traveling throughout the host body to infect other CD4+ T-cells.

There is widespread agreement that untreated HIV infections in humans causes extensive depletion of CD4+ T-cells in host circulatory systems and bodily stores and that this depletion eventually leads to immune system failure in the chronic stages of HIV infection (Zeng et al. 2011: 998). Chronic active infections of Epstein-Barr virus (EBV, commonly known as mononucleosis) also seem to exhibit CD4+ T cell depletion (Carney et al. 1981; Wingate et al. 2009), and there is some evidence that this depletion abrogates the immune system's ability to control the proliferation of infected cells (Nikiforow et al. 2001). That CD4+ T-cell depletion compromises the human immune system in both untreated HIV and chronic active EBV infections suggests that the human immune system is generally vulnerable to attacks on CD4+ T-cells. Kitano and Oda (2006) take this vulnerability of the human immune system to be their explanandum. Their explanatory strategy is to characterize a biological pathway for the human adaptive immune system and infer their explanandum from claims about this pathway's architectural structure, thereby showing that "problems of host immune systems, such as autoimmunity and fragility against specific component failures, are deeply imbedded within the architectural features of the immune system" (2006: 6).

Generally, a biological pathway is a directed network of interactions or functional relationships between components of a biological system operating in concert to accomplish a biological function in response to environmental stimuli (see Saraiya et al. 2005: 191; Thagard 2003). Kitano and Oda suggest a pathway for the cellular interactions of the adaptive immune system: Environmental stimuli trigger cellular secretions of various cytokines, such as IFN-γ and IL-4. These cytokines activate dendritic cells, and signals from these dendritic cells and/or cytokines polarize naïve CD4+ T-cells into either Th1, Th2, or Tr1 cells. The result of naïve CD4+ T-cell polarization varies with different stimuli; for example, signals

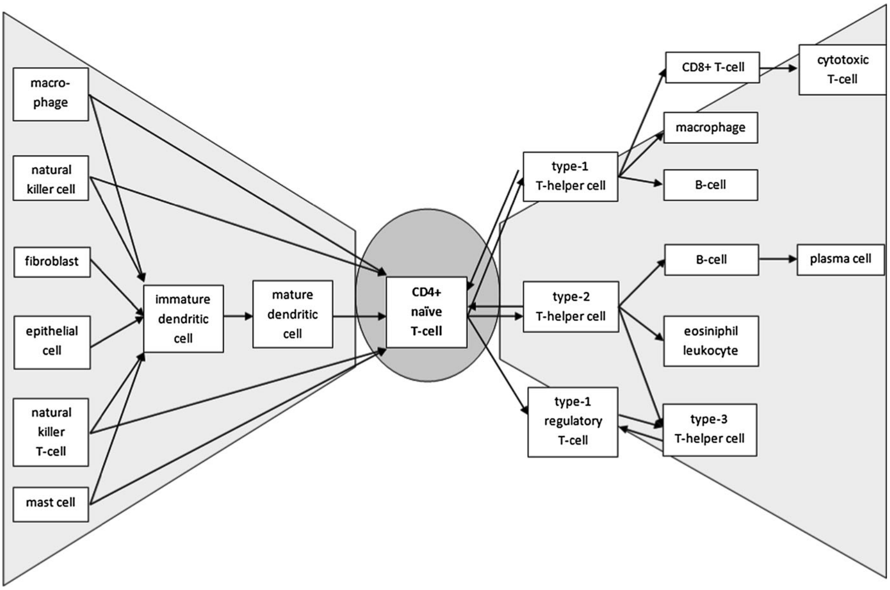

Fig. 1 Bowtie structure of immune system cellular interactions

from IFN-γ, IL-12, and IL-18 yield Th1 cells, while signals from IL-4 yield Th2 cells. Each kind of polarized CD4+ T-cell secretes different cytokines (e.g., Th1 cells secrete IFN-γ and IL-2, while Th2 cells secrete IL-4, IL-5, IL-10, and IL-13). These effector cytokines, in turn, activate responses from various cells directly involved in immunological responses, such as B cells, macrophages, and leukocytes (Kitano and Oda 2006: 3–4). Figure 1 provides a visual representation of the cellular interactions in this pathway. (Figure 1 is adapted from Kitano and Oda's visual representation of the pathway (2006: 3). There are two salient differences: first, I have rotated their representation 90 degrees counterclockwise, in order to emphasize the pathway's bowtie shape; second, I have deleted nodes which do not represent cells and edges which do not represent relationships among cells.)

The explanatorily salient properties of this immune system pathway, according to Kitano and Oda, are its bowtie structure and the location of CD4+ T-cells within this structure. They write:

> The adaptive immune system displays a clear bow-tie structure at both the cellular interaction and signal transduction levels. … Owing to the structure of the intercellular interactions that form the bow-tie structure, with naïve CD4+ T-cells as the core of the network, the system is vulnerable to attack on CD4+ helper T-cells (Kitano and Oda 2006: 2).

The directionality of cellular interactions within the immune system pathway determines the pathway's bowtie structure: various stimuli activate pathways that converge to activate naïve CD4+ T-cells, which in turn activate a variety of responses. The naive CD4+ T-cells are the core of this bowtie, because all possible paths, from the initial interactions (environmental stimuli interacting with the body) to the terminal interactions, proceed through interactions that involve naive CD4+ T-cells. (These cells are also, trivially, non-redundant elements of this core, because they are the only elements in the core.) Kitano and Oda infer from these properties that the human immune system is vulnerable to attacks on CD4+ T-cells in general, because

> the bow-tie network in the immune system at both intracellular and intercellular levels is fragile against attacks on non-redundant elements within its core. Removal of such an element results in immunodeficiency (2006: 2).

(Kitano and Oda's focus on bowtie architecture is not unique. Csete and Doyle also claim that bowtie structures have "inherent fragilities," adding that "[b]ow-tie structures … are found throughout biology in parallel or convergent systems, as well as in homologous systems" (1999: 447). Tiere et al. identify bowtie architecture in the human Toll-Like Receptors and T-Cell Receptor systems (2010: 7)).

3 The Role of Kitano and Oda's Diagram in Representing and Identifying Architectural Features

Kitano and Oda's explanation for why the immune system is especially vulnerable to attacks on CD4+ T-cells appeals to architectural features of the immune system: its bowtie structure, the location of CD4+ T-cells in this structure, and the non-redundancy of the cells at this location. These features are what Huneman calls *topological properties*, because they concern "how parts of the system are located regarding one another, and whether those relations can still hold under some continuous deformations of the system (and which ones)" (2010: 214).[1] For instance, even if one "stretches" or "bends" the immune system pathway into a new shape, it continues to exhibit a bowtie structure with CD4+ T-cells at the core.

Their explanation, accordingly, is what Huneman calls a *topological explanation*: the explanantia are the facts that a system exhibits specific topological properties and the explanandum is a deductive consequence of these properties (Huneman 2010: 214, 216). (Although topological explanations resemble Hempel-style nomological explanations by virtue of being arguments, they do not appeal to natural laws.) Kitano and Oda's explanation, to be explicit, is that

1. The immune system cellular interaction pathway exhibits a bowtie structure.
2. CD4+ T-cells are located at the core of this bowtie structure.
3. CD4+ T-cells are non-redundant elements of this core.
4. Whenever a system exhibits a bowtie structure, the system is vulnerable to attacks on the non-redundant core elements of that structure.
5. Therefore, the immune system is vulnerable to attacks on CD4+ T-cells.

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[1] Specifically, given an abstract space E for representing relations among the parts of systems and a set of particular relations S′ in E representing the relations among the parts of a particular system S, the topological properties of S are the properties that are invariant under continuous transformations of S′ in E (Huneman 2010: 216).

The categorical claims in this explanans (premises 1–3) identify topological properties of the immune system cellular interaction pathway, and the hypothetical claim (premise 4) makes explicit why immune system vulnerability to attacks on CD4+ T-cells is a consequence of these properties. (The hypothetical claim is not a natural law because, if true, it is a necessary (mathematical) truth about the nature of bowtie structures rather than a contingent truth about biological pathways that realize bowtie structures.)

The pathway diagram of immune system cellular interactions is, in practice, an integral component of Kitano and Oda's explanation. This is for two reasons. First, the diagram groups together information in a way that its sentential counterpart does not, thereby avoiding repetition in representing the immune system pathway's global architectural structure and facilitating identification of specific architectural features of that structure.[2] Second, the diagram facilitates reasoning that supports the hypothetical explanans (premise 4) in a way that a sentential representation of the immune system pathway does not, by virtue of making apparent counterfactual features of the pathway's architectural structure in a way that the sentential representation of that structure does not. I focus on the second of these claims in the next section. In this section, I focus on the first, providing supporting evidence for the claim and arguing that, with respect to why scientists would prefer a diagram of the immune system pathway to a sentential representation, it provides an answer superior to ones provided by extant philosophical accounts of diagrams in biological practice.

Compare Kitano and Oda's sentential and diagrammatic representations of the immune system cellular interaction pathway with respect to the way in which each conveys information about pathway elements, relationships, and global structure. Kitano and Oda provide a prose representation:

> Various stimuli from pathogens are transmitted to dendritic cells (DC) that polarize CD4+ T-cells. Stimuli trigger the differentiation of naïve CD4+ T-cells and effector cytokine releases to follow. The whole behavior of this subsystem is controlled by complex signal transductions, and the cytokine network has adapted to the pathogenic environment to which it was exposed during evolution. Upon recognition of appropriate peptide–MHC complex and/or cytokine stimuli, naïve CD4+ T-cells polarize into either Th1, Th2, or Tr1 cells depending upon the cytokine stimuli (…) that are provided by polarized DC and a variety of innate immune cells (…). Th1 cells are induced by IFN-γ, IL-12, and IL-18, and secrete IFN- γ and IL-2, whereas Th2 cells are induced by IL-4 and secrete IL-4, IL-5, IL-13, and IL-10 (…). Chromatin remodeling by GATA3 and T-bet is pivotal in Th1/Th2 polarization (…). Effector cytokines secreted from Th1 and Th2 cells affect various cells. For

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[2] According to Mach, the "goal which [physical science] has set itself is the *simplest* and *most economical* abstract expression of facts" (1895: 207; see also Duhem 1991: 21–24). Insofar as biological science aims for this economy of thought, there is an important sense in which Kitano and Oda's diagram marks scientific progress. For their diagram brings order to the facts about the immune system cellular interaction pathway, and it does so in a way superior to its sentential counterpart. I thank an anonymous referee for this observation.

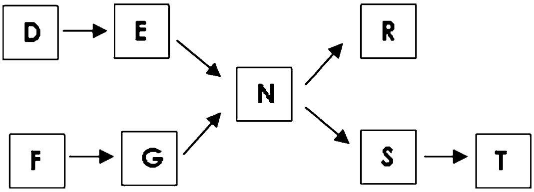
> example, IFN-γ activates B-cells to secrete IgG2a and IgG3, IL-2 activates cytotoxic T lymphocytes (CTL), and IL-4 and IFN-γ mutually inhibit the growth of Th1 and Th2 T-cells, respectively (…). Among these cytokines, IL-2 plays an important role in shaping the dynamics of T-cell response because it promotes growth and activation of CD4+ CD25+ regulatory T-cells (…), which suppress autoreactive T-cells whether Th1 or Th2 (…). The source of IL-2 involved in CD4+ CD25+ T-cell activation has yet to be fully determined, but DC (…) and autoreactive T-cells (…) are considered to be involved. CD4+ CD25+ regulatory T-cells are considered to interact with mature DC and suppress helper and effector T-cell activities by an as yet unidentified mechanism (…). Th3 and Tr1 are induced by IL-4 in the presence of TGF-γ and IL-10, respectively (…). Tr1 may also be induced by immature DC or IL-10-modulated DC under TGF-γ stimulation (…). Tr1 secretes IL-10 and TGF-γ in a CTLA-4-dependent manner (…) and Th3 secretes TGF-γ. Repeated stimulation of naïve T-cells in the presence of IL-10 induces Th1 T-cells, and a high dose of IL-10 suppresses the growth of both Th1 and Th2 cells (…). The mechanism of suppression of CD4+ CD25+ T-cells is actively being investigated, but is considered to involve TGF-γ release and binding of CTLA-4 to CD80 and CD86 on effector T-cells (…). The negative feedback loop is mediated by Tr1 and Th3, and CD4+ CD25+ regulatory T-cells constitute feedforward control via mature DC and negative feedback control via autoreactive T-cells that are critical in the proper control of adaptive immune response to prevent autoimmune diseases (2006: 3–4, references omitted).

Figure 1 represents similar information with a diagram.

One might suppose that scientists would prefer a diagram of the immune system pathway to a sentential representation for reasons of relative conciseness (see Cook et al. 2001: 8; Perini 2005: 266). For while Kitano and Oda use both diagrammatic and prose representations of the immune system pathway to convey similar information, their diagram uses fewer symbols than their prose. However, this apparent difference is largely an artifact of notational choice. From a graph-theoretical perspective, the immune system pathway is an ordered pair (V, A) of sets, where the elements of V are the nodes (or vertices) of the pathway and the elements of A are ordered pairs of nodes called arcs (directed lines), such that the first member of each such pair is the tail of the arc and the second member is the head of the arc. This perspective facilitates a mathematical sentential representation of the immune system pathway that involves approximately the same number of symbols as the diagram: (*Fibroblast*, *Immature DC*), (*Mast Cell*, *Immature DC*), (*Immature DC*, *CD4+ T-cell*), (*CD4+ T-cell*, *Th1*), (*CD4+ T-cell*, *Th2*), and so on. (This representation is sentential because, like Kitano and Oda's lengthier prose representation, the elements of its data structure appear in a single sequence. Data structures for diagrammatic representations, in contrast, index information by two-dimensional location (Koedinger 1992: 151)).

One might, instead, suppose that scientists would prefer a diagram of the immune system pathway to its sentential counterparts because "diagrams offer

Fig. 2 Toy pathway diagram



relatively direct, iconic resources for representation" (Bechtel and Abrahamsen 2005: 428). Diagrams offer more direct representations than their sentential counterparts—that is, they make relationships among system components more directly apparent to us than their sentential counterparts—because diagrams simultaneously represent the components of a system, spatial relations among those components, and (in some cases) temporal relations among the operations of the components (Bechtel and Abrahamsen 2005: 428; see also Perini 2005: 266). Moreover, diagrams are more iconic, because the shapes and colors of icons and arrows can highlight distinctions among system parts or operations (Bechtel and Abrahamsen 2005: 428).

These claims are true of Kitano and Oda's diagram immune system pathway diagram. Certainly it is a colorful diagram, with several different icon shapes (such as ovals, thick arrows, thin arrows, and daggers). But since not all diagrammatic representations of the immune system pathway contain this variety (see, for example, Figs. 2 and 4 below, as well as the reconstruction of Kitano and Oda's diagram in Fig. 1), perhaps Kitano and Oda's diagram need not contain this variety in order to be preferable to its sentential counterpart. Moreover, more can be said regarding why the relative directness of Kitano and Oda's diagram (and perhaps other pathway diagrams) might be advantageous.

The relative directness of Kitano and Oda's pathway diagram makes it a locality aid, so that it groups together information about the global position of pathway elements to an extent that its sentential counterparts do not. Rather than illustrate this point with Kitano and Oda's massive diagram, consider the toy pathway diagram in Fig. 2 as a stand-in. (The toy diagram may be thought of as a drastic simplification in detail of Kitano and Oda's diagram.)

This diagram simultaneously groups together the relations of nodes *E*, *G*, *N*, and *S* within the entire pathway. A sentential representation of the same pathway, however, simultaneously groups together at most three of these node-pathway relations. For example, using graph theory notation, we can write:

$$(\mathrm{D,E}), (\mathrm{E,N}), (\mathrm{G,N}), (\mathrm{N,R}), (\mathrm{N,S}), (\mathrm{S,T}).$$

The first two elements in this sequence group together the relations of *E* within the pathway; the center four, the relations of *N* within the pathway; and the last two, the relations of *S* within the pathway. The cost of this arrangement is that grouping together the relations of *G* within the pathway requires repeating the element (G,N) from the sequence: (F,G), (G,N). There is a way to avoid repetition of this element, namely, by writing:

$$(\mathrm{F,G}), (\mathrm{G,N}), (\mathrm{E,N}), (\mathrm{N,R}), (\mathrm{N,S}), (\mathrm{S,T}).$$

But now grouping together the relations of *E* within the pathway requires repeating the element (E,N) from the sequence. For larger pathways, such as the immune system interaction pathway, grouping together the relations of nodes to entire pathways requires more repetition. Pathway diagrams avoid this repetition by simultaneously representing all such node-pathway relations, and thereby represent information about architectural structure more directly than their sentential counterparts. (Jones and Wolkenhauer (2012: 712–714) discuss a similar difference between diagrammatic and sentential representations of mechanisms; Merico et al. (2009: 923) briefly mention the ability of network diagrams to represent global system-level relationships.) Hence, the relative directness of Kitano and Oda's diagram is advantageous, in part, because it allows them to avoid repetition when representing global architectural structure.

But there is another, stronger reason that the relative directness of Kitano and Oda's diagram is advantageous. More direct representation of information about architectural structure facilitates identifying specific architectural features, especially when those features are ill-defined. For example, it is likely that Kitano and Oda rely upon their diagram of the immune system pathway to identify the pathway's architectural features and thereby support the categorical claims in their explanans. Those claims, that the immune system pathway exhibits a bowtie structure and that CD4+ T-cells are non-redundant core elements of this structure, appeal to the notions of *bowtie structure*, *bowtie core*, and *non-redundant element of a core*. There are, at present, several proposals for how to define these notions in a precise, mathematical manner. For example, Supper et al. (2009) introduce the notion of a bowtie score, defining the bowtie core as the set of graphical elements with the maximal bowtie score; Yang et al. (2011) define the notion of a bowtie decomposition of a graph with respect to a strongly connected component of that graph; and Polouliakh et al. (2009), denying that a bowtie structure requires a strongly connected component, define a bowtie network to consist of "sub-networks with diverse inputs converting into a conserved core sub-network (an input wing), another conserved core sub-network (a bowtie core), and an output sub-network that enables diverse responses to the input stimuli (an output wing)." None of these definitions would have been available to Kitano and Oda in 2006, however. For, as Yang et al. note, while "the bow-tie structure is frequently cited in the literature, it is generally described in words or by an illustration and has never been precisely defined" (2011). Hence, Kitano and Oda likely justify their categorical claims in a less formal and rigorous manner.

The classic source for the notions of *bowtie structure* and *bowtie core* is Broder et al. (2000), who attempt to characterize the topology of the world wide web. Representing the network architecture of the world wide web as a graph, they discover a strongly connected component (SCC) of 56 million nodes, such that each node is reachable from every other; a set of 44 million IN nodes, each of which can reach every node in the SCC via some directed path; another set of 44 million OUT nodes, each of which is reachable from any node in the SCC via some directed path; and 44 million tendril nodes, which can neither reach nor be reached from any node

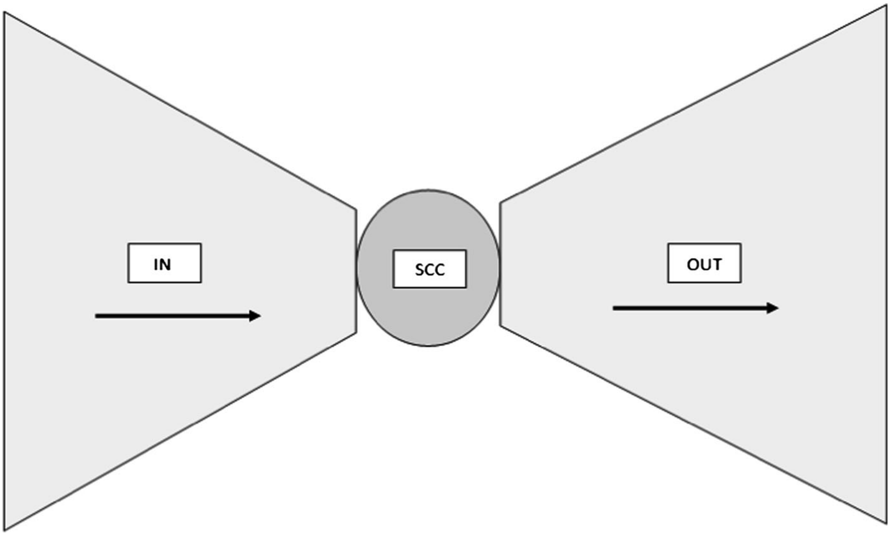


Fig. 3 Bowtie structure of the web (adapted from Broder et al. 2000: 318)

in the SCC.[3] Figure 3 provides a visual representation of this network structure (without the tendril nodes).

Based upon its visual resemblance to a bowtie, this network architecture comes to be known as a *bowtie structure* and the SCC component comes to be known as the *core* or *knot* of the bowtie. Ma and Zeng (2003) subsequently identify a similar structure in the metabolic pathway for *E. coli*, representing metabolites as nodes and reactions as arcs. The basis for this identification seems to be, at least in part, similarities to the network architecture of the world wide web: because both the metabolic pathway for *E. coli* and the network architecture of the world wide web contain a strongly connected component surrounded by a set of IN nodes and a set of OUT nodes, Ma and Zeng infer that the metabolic pathway for *E. coli* exhibits a bowtie structure.

Given this history, presumably Kitano and Oda likewise determine, on the basis of similarities between the world wide web pathway (or other system pathways accepted as exhibiting a bowtie structure) and the immune system pathway, that the immune system pathway exhibits a bowtie structure with CD4+ T-cells at the core. (Nelson et al. (2011: 11–15) seem to follow a similar procedure.) This kind of analogical reasoning involves identifying the elements (nodes) of the immune system pathway, the directed relationships (arcs) between those elements, and a strongly connected component surrounded by appropriate sets of IN and OUT nodes. Because each element of a pathway, considered by itself, is a strongly

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[3] The *strongly connected components of a graph* are its strongly connected subgraphs; a subgraph is *strongly connected* just in case each of its nodes is reachable from every other node; and a node w is *reachable* from a node v just in case there is a path from v to w, where a *path from* v *to* w is a sequence of nodes $v = v_o, v_1, \ldots, v_n = w$ (distinct except for the possibility that $v = w$) such that, for each $i = 0, 1, \ldots, n$, (v_i, v_{i+1}) is an arc (Yang et al. 2011).

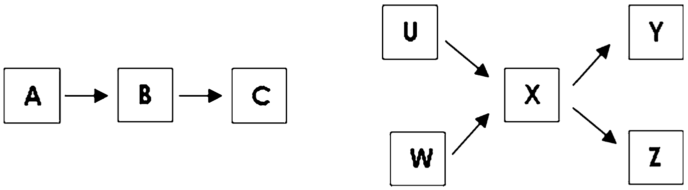

Fig. 4 Two simple pathways

connected component of the pathway, the principal challenge is finding a core element—a (perhaps single-membered) strongly connected component that is reachable from relatively many elements and from which many other elements are reachable. (Although Kitano characterizes a bowtie structure as “a large, highly connected core cluster [that] is interfaced with less connected in- and out-clusters” (2004: 831), Kitano and Oda (2006) seem to downplay the size requirement on the core cluster in the case of the immune system pathway. A likely reason for this is that the scale of the world wide web is much larger than that of the immune system.) For example, even though both pathways in Fig. 4 contain a strongly connected component surrounded by a set of IN nodes and a set of OUT nodes, only the rightmost one exhibits a bowtie structure.

The relative directness with which Kitano and Oda’s immune system pathway diagram represents the architectural structure of the immune system pathway allows them to more easily solve the challenge of finding a core element in that pathway: visually inspecting the diagram suffices. (This advantage would remain were rigorous and precise definitions of *bowtie structure* and *bowtie core* available, by virtue of minimizing the amount of search required to extract, from their pathway representation, information sufficient for identifying a core element. For a similar idea, see Jones and Wolkenhauer 2012: 712–714.)

4 The Role of Kitano and Oda’s Diagram in Explanatory Reasoning

The ability of Kitano and Oda’s diagram to group together information about the global positions of pathway elements suggests two reasons that scientists might prefer their diagrammatic representation of the immune system pathway rather than its sentential counterpart: the diagram avoids repetition in representing global architectural structure, and it facilitates identifying specific architectural features in that structure. This ability also allows Kitano and Oda’s diagram to facilitate inferences about the consequences of the immune system’s architectural structure in a way that logical inferences based upon the diagram’s sentential counterparts do not. I shall focus on the hypothetical explanans in Kitano and Oda’s topological explanation to support this claim.

Recall that, according to Kitano and Oda, whenever a system exhibits a bowtie structure, the system is vulnerable to attacks on the non-redundant core elements of that structure. Because there is no standard graph-theoretical definition of *bowtie structure* available to Kitano and Oda prior to publication of their paper, they cannot establish this conditional claim through mathematical derivation. Resources available to them are notions of *bowtie structure* and *bowtie core* based upon analogies with claims in other publications; a fairly formal notion of *node redundancy* according to which a node in a network is redundant iff for any path to a node that involves the node in question, there is an alternative path to the same node that does not involve the node in question; and an informal notion of *vulnerability to attack* according to which a network is vulnerable to attack on a node if there would be no path from certain initial nodes of the network to certain final nodes of the network were the node in question (and its associated arcs) eliminated (see Palumbo et al. 2005: 4642). (Kitano and Oda themselves do not formulate any application conditions for these notions; this is an attempt at a reconstruction.)

If the cores of all bowtie structures were strongly connected, the following *apriori* argument would be available for the conditional claim in Kitano and Oda's explanation. Suppose a pathway exhibits a bowtie structure. Then every path from an arbitrary $x \in$ IN to an arbitrary $y \in$ OUT involves some node in the bowtie core. Since (by assumption) the bowtie core is strongly connected, there is a path from any node in the bowtie core to every other node in that core. Hence, if there is a path from $x \in$ IN to $y \in$ OUT that involves some node in the bowtie core, then for each node in the bowtie core, there is a path from an arbitrary $x \in$ IN to an arbitrary $y \in$ OUT that involves that node. Accordingly, if there is a non-redundant element z of the bowtie core, there is some $n \in$ OUT such that every path to n involves z. Thus, if z (and its associated arcs) were eliminated, there would be no path from any $x \in$ IN to that node n. Therefore, the pathway is vulnerable to attack on z. Hence, pathways exhibiting bowtie structures are vulnerable to attack on their non-redundant core elements.

This argument is problematic in two ways. First, the argument is unsound, because some cores of bowtie structures are not strongly connected (Polouliakh et al. 2009). If a pathway exhibits a bowtie structure with a core that is *not* strongly connected, it is possible for a core element of a bowtie structure to be non-redundant even though, for any path to a node in OUT that involves the non-redundant node, there is an alternative path not involving that node. For instance, if there is a node A in a bowtie core that is not strongly connected such that A is only reachable from some other core node B, B is non-redundant; but if, for every path from A to a node C in OUT, there is another pathway not involving A, eliminating B would not thereby eliminate all paths to C.

Second, even disregarding the problematic assumption that all bowtie cores are strongly connected, it is not clear that a pathway which exhibits a bowtie structure is vulnerable to attack on non-redundant elements of its core just because eliminating that node would remove all paths to *at least one* node in the set of OUT nodes. Being vulnerable to attack on a node seems to connote that eliminating the node would remove paths to *many* nodes in OUT or *especially important* nodes in OUT. Unfortunately, the informal notion of *vulnerability to attack* is too imprecise to capture this connotation. (Lemke et al.'s (2004) notion of *damage*, which characterizes the effect of deleting a node from a network, and Pržulj et al.'s (2004) notion of *bottle-neck node*, which characterizes a particular kind of topological connectivity of a node within a network, both offer promising approaches to formalizing the notion of *vulnerability to attack*. It is not clear whether the conditional claim in Kitano and Oda's explanation remains valid when interpreted with these alternative notions. Since Kitano and Oda (2006) do not discuss the issue, it might be appropriate to view their account as an explanatory scheme which awaits more precise details.)

The first of these problems can be avoided by adapting the unsound argument into a sound argument for a slightly different conditional, namely: whenever a system exhibits a bowtie structure *and the core elements of that structure are strongly connected*, the system is vulnerable to attacks on the non-redundant elements of the core. Whether there are sound arguments for weaker conclusions, with less restrictive conditions in their antecedents, is an open question. But this revised conclusion suffices for Kitano and Oda's explanation, because the core elements of the immune system pathway are strongly connected. (There is only one element in that core (*CD4+ T-cells*). Since every element is reachable from itself, this element is reachable from itself, and so the core elements are strongly connected.) The second problem can be avoided by formulating a more precise notion of *vulnerability to attack*. Whether the revised conditional remains true given this precisification will then depend upon the details of the precisification, and in particular upon whether an attack on a non-redundant element of a strongly connected bowtie core eliminates not merely some OUT elements, but many or especially important ones.

But these qualifications and speculations are idle. They do not appear in Kitano and Oda's paper. Nor do they appear in other papers which address similar issues. (Consult the bibliography for examples.) Yet reasoning about the consequences of the bowtie structure, with respect not only to fragility but also to robustness under perturbation, continues apace. One potential explanation for this practice is that the biologists are incautious, driven to make premature inferences for the sake of securing grant funding, earning tenure, or advancing their career prospects. However, even if these aims play some motivating role, there is a better explanation available, namely, that there is no need for mathematical rigor and formal precision because diagrams facilitate the required inferences in the absence of rigor and precision.

Consider again Kitano and Oda's diagram of the immune system pathway (Fig. 1). The diagram makes apparent that the pathway exhibits a bowtie structure, that CD4+ T-cells are non-redundant elements at the core of this structure, that this core is strongly connected, and that eliminating CD4+ T-cells from the pathway thereby removes *all* paths from the initial elements of the pathway (*Environmental Stimuli*) to the final elements (*Perforin*, *Plasma Cell*, *TGF-β*, and so on). This consequence of eliminating CD4+ T-cells is strictly stronger than the consequence supported by the preceding formal argument (namely, that eliminating CD4+ T-cells from the pathway thereby removes *at least one* path from the initial elements of the pathway to the final elements). It is also apparent despite the absence of precise and rigorous definitions of key terms. The reason for this (or, at least, one reason) is that Kitano and Oda's pathway diagram groups together information about the global positions of pathway elements in a way that facilitates ready apprehension of constraints influencing the outcomes of qualitative "what if" experiments regarding what would happen if certain elements of the pathway were disabled or removed.

This inferential advantage of Kitano and Oda's diagram is a general advantage of diagrammatic representations over their sentential counterparts with respect to topological explanation. Lewis (1991) discusses a similar advantage in the context of the Blocks Problem. The problem is to determine, from a particular configuration of irregularly stacked blocks, which blocks need to be moved, and the order in which they need to be moved, in order to uncover a buried block in a way that permits its removal from the stack. Lewis provides informationally equivalent diagrammatic and sentential representations of a particular configuration (1991: 554–555). The diagram shows a series of stacked blocks, with a unique label attached to each block; the sentential representation is long conjunction, the conjuncts of which have the form "X_i is on top of X_j." Lewis argues that, while both representations convey information about which blocks are on top of which other blocks, the diagram provides information about "constraints which allow this [particular] situation to support a host of other situations involving movements of these blocks," and that the diagram does so in a way that the sentential representation of the configuration does not, by virtue of making "information available to controlled processing with the minimum demand on processing resources" (1991: 556). For, he argues, while the "which blocks are on top of the block labeled X_1" question can be answered by inspecting the diagrammatic representation, it cannot be answered by inspecting the sentential one: "after inspecting the expression(s) containing X_1, the viewer must perform additional mental operations to identify symbols related to X_1 through transitivity" (1991: 556). One reason the diagram permits this kind of inspection is that the diagram, unlike its sentential counterpart, directly provides information about the global position of each block with respect to all other blocks. (Similar points seem to hold for other topological problems, such as the Bridges of Konigsberg, the solutions of which involve finding minimal sequences of transformations that allow specific results.)[4]

So, too, with Kitano and Oda's diagram of the immune system cellular interaction pathway (Fig. 1). Because their diagram of the pathway directly represents network-wide relationships for each pathway element, one can determine by inspection the results of removing particular elements. Equivalent prose or graph-theoretical sentential representations of the same pathway contain the same information about such network-wide relationships. However, using a sentential representation to extract information about the global effects of removing a particular element from the network requires, first, identifying by inspection the local relationships involving that element and, second, performing additional inferences to determine the effect of removing any elements that would be removed if the particular element in question were removed. For this reason, the diagram makes information about the global repercussions of particular "what if" experiments available to controlled processing in a more direct manner than its sentential counterparts.

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[4] I thank an anonymous referee for this observation.

While performing a “what if” experiment on Kitano and Oda’s diagram of the immune system pathway provides support for the hypothetical conditional in their explanans, the “what if” experiment does not yield the conditional itself. That further inference requires generalizing from claims about particular bowtie structures to a claim about all bowtie structures. Kitano and Oda, by endorsing the particular conditional they do, seem to have engaged in some such generalization; and it is plausible to suppose that the results of the “what if we remove CD4+ T-cells from the immune system pathway” experiment provide some kind of support for that generalization, as well as confidence that, even if the particular conditional they formulate is technically incorrect, it approximates a correct conditional about pathways which exhibit the same kind of bowtie structure as the immune system pathway.

This is not to say, however, that this kind of generalization is necessarily reliable. Inferences made about the general consequences of a particular architectural structure, on the basis of a diagram for some particular pathway, need not hold generally for all pathways exhibiting that structure. Kulpa refers to this as the generalization problem and discusses some ways to avoid it when using diagrams to reason about geometrical properties (2009: 82–83; see also Shin 2012). Because the hypothetical explanans in Kitano and Oda’s explanation concerns properties that are quite similar to geometrical ones (they are graphical properties, in the mathematician’s sense), it is reasonable to expect that Kulpa’s suggestions apply when using diagrams to reason about pathway architectures. But even if the suggestions do not apply, and even if Kitano and Oda’s diagram facilitates a generalization that happens to be unreliable, the diagram still facilitates an inference in a way that its sentential counterparts do not. This suffices to show that their diagram facilitates an important process of explanatory reasoning unavailable to scientists who restrict themselves to the diagram’s sentential counterparts.

5 The Differing Roles of Pathway Diagrams in Mechanistic and Topological Explanation

Bechtel and Abrahamsen provide an alternative account of why diagrams facilitate important processes of explanatory reasoning, arguing that diagrams facilitate mental animations of mechanisms (2005: 430). They understand a mechanism to be a “structure performing a function in virtue of its component parts, component operations, and their organization” (2005: 423). For example, a typical diagram of the mechanism by which the heart pumps blood represents various components of this mechanism (tissues, vena cava, atria, ventricles, arteries, veins, lungs) as well as the flow of blood through these components (see Bechtel and Abrahamsen 2005: 425, Fig. 1). Following the work of Hegarty (1992), they understand mental animation to be “the activity of inferring ‘the state of one component of the system given information about the states of the other components, and the relation between the components’” (2005: 430). So, for example, since the diagram of the mechanism by which the heart pumps blood makes apparent the operation of the mechanism—by using arrows to represent the directionality of blood flow and spatial relations to represent relations among mechanism components—scientists can mentally animate the diagram in order to understand how the mechanism produces various phenomena.

Since biological pathways are networks of relationships between system components that operate in concert to accomplish a biological function, it seems that pathways are a kind of mechanism (see also Thagard 2003: 237). Yet Bechtel and Abrahamsen's account of why diagrams facilitate important processes of explanatory reasoning does not apply to Kitano and Oda's diagram and their explanation of immune system vulnerability to CD4+ T-cell attacks. For while Kitano and Oda's diagram facilitates mental animation of immune system function, mentally animating the diagram only provides understanding of how the mechanism operates when CD4+ T-cells are present. (The cases Hegarty (1992) uses to support her thesis about mental animation are not ones that ask participants to reason about what would happen if particular mechanism components were missing.) If mental animation were to provide understanding of how the mechanism operates when CD4+ T-cells are absent, the diagram animated would be one in which CD4+ T-cells are absent. Yet Kitano and Oda use a diagram that represents CD4+ T-cells as present rather than absent.

Bechtel and Abrahamsen's account does not apply to Kitano and Oda's diagram, because Bechtel and Abrahamsen design their account for diagrams associated with a particular kind of mechanistic explanation. This kind of explanation involves identifying some mechanism, decomposing the mechanism into its parts and operations, and determining how the operation of parts affects other parts in a coordinated way to produce some phenomenon to be explained (Bechtel 2013). These processes yield explanations that show "how some particular effect is actually produced, here and now, and … by what means" (Bechtel and Richardson 2010: 231). (Such explanations resemble what Craver calls *constitutive mechanistic explanations*, because they explain the behavior of a mechanism in terms of the organized activities of and interactions among its components. See Craver 2007; Machamer et al. 2000: 21–22.) Kitano and Oda's diagram is not associated with this kind of mechanistic explanation, because their explanation does not show how the parts of a mechanism operate upon each other to produce a particular effect. Their explanation, instead, appeals to topological properties in order to show why some particular effect is expected to occur regardless of how the parts of the mechanism operate upon each other.

All mechanisms, of course, have some topology or other. This topology reflects the organization structure of the mechanism's components and activities. It also determines the topological properties of the mechanism. Although these topological properties supervene on the organized operations, activities, and interactions of a mechanism's component parts, they have an important kind of explanatory autonomy: they figure in an explanatory pattern (for topological explanation) that makes minimal reference to the features of their supervenience base. (Compare: we explain why a LaTeX file fails to compile by appealing to properties of computer code rather than electrical states, even though the computer code's properties supervene on the computer's electrical states.) Whence the bowtie structure of the immune system pathway carries the explanatory burden in Kitano and Oda's explanation, while the components of the immune system have only a minor role. (Their explanation refers to only one component of the immune system mechanism, namely, CD4+ T-cells.)[5] This is not because Kitano and Oda's representation of the immune system pathway is sketchy or schematic, but rather because the components and activities of that pathway are largely explanatorily irrelevant to their explanandum: the explanatorily relevant feature of the immune system pathway is a topological property (namely, the bowtie structure), and specific components of the pathway (namely, CD4+ T-cells) are relevant only because Kitano and Oda's explanandum makes explicit reference to them.

This same point can be made in a different way. If Kitano and Oda's explanation were the kind of mechanistic explanation for which Bechtel and Abrahamsen's account is designed, it would not explain why the immune system is vulnerable to attacks on CD4+ T-cells *in chronic persistent EBV infections*. For the interactions among components of the immune system during EBV infections differ from the interactions among components of the same system during HIV infections. (Details are difficult to provide, because there remains widespread and fundamental disagreement concerning the mechanistic details for the role of CD4+ T-cells in immune system responses to HIV infection (Grossman et al. 2002) and large amounts of uncertainty regarding the mechanistic details for the role of CD4+ T-cells in immune system responses to EBV infection (Landais et al. 2005). There must be some difference, however, since immune system responses to EBV differ from responses to HIV.) This difference means that the mechanism operations that explain immune system vulnerability in HIV infections do not thereby explain vulnerability for EBV infections. Kitano and Oda's explanation, however, explains CD4+ T-cell responses for both HIV and EBV infections, because their explanans appeals to topological properties of the immune system pathway rather than sequences of mechanism operations within that pathway.

Batterman (1992, 2001) offers a distinction between types of explanation that helps to clarify the nature of Kitano and Oda's explanation. According to Batterman, *type (1) explanations* explain why instances of a particular pattern obtain, while *type (2) explanations* explain why the pattern itself can be expected to obtain (1992: 332; 2001: 23). Consider, for example, an explanation of the formation of copper dendrites by precipitation out of a copper sulphate solution via electrolysis: copper and sulphate ions in the solution follow random Brownian paths because of random molecular collisions; using an electrode to apply a small voltage to the center of this solution causes a state of relatively high potential energy in which copper ions deposit themselves as copper onto the electrode; over time, the system falls to a state of relatively low potential energy, during which various factors cause the copper ions to deposit themselves randomly onto pre-existing copper; the long-term result of this is a branching fractal structure of copper

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[5] Topological properties do not always carry the explanatory burden. For many mechanistic explanations, topological properties do minimal explanatory work. For example, we explain how an odorant produces an olfactory signal by appealing to the mechanism for the olfactory system. In doing so, however, we appeal primarily to specific activities and interactions among the olfactory system's components, and only secondarily (if at all) to properties of the olfactory system pathway that are invariant under continuous transformations. I thank an anonymous referee for prompting this clarification.

dendrites (Batterman 1992: 334). This is a type (1) explanation: it explains particular instances of copper dendrite formations. It does not, however, explain why, in a wide variety of cases, the copper dendrites formed via electrolysis have a fractal dimension of roughly 1.70. That explanation, a type (2) explanation, appeals to assessments of the probabilities that copper ions deposit at various locations and a proof that processes with such probabilities produce, over time, structures with a fractal dimension of 1.70 (Batterman 1992: 334–335).

While mechanism operations associated with CD4+ T-cells responses to HIV infection explain why the immune system is vulnerable to attacks on CD4+ T-cells in untreated HIV infections, they do not provide explanations for the general pattern of immune system vulnerability to attacks on CD4+ T-cells. Just as type (1) explanations of copper dendrite formation in particular cases do not provide type (2) explanations of why the copper dendrites always have a fractal dimension of 1.70, by virtue of not characterizing what unifies the diverse cases of copper dendrite formation, mechanism operations that explain immune system vulnerability to attacks on CD4+ T-cells in untreated HIV infections (or other particular kinds of infection) do not explain why the immune system is generally vulnerable to attacks on CD4+ T-cells, by virtue of not characterizing what unifies the diverse cases of immune system vulnerability. Perhaps the mechanism operations that produce immune system vulnerability to attacks on CD4+ T-cells are similar for many different kinds of infection. But even if this similarity were to explain why the immune system is generally vulnerable to attacks on CD4+ T-cells, the explanation would not be the kind of explanation for which Bechtel and Abrahamsen design their account of diagrams, because similarity among mechanisms, rather than the operation of mechanisms, does the explaining.

In any case, Kitano and Oda's explanation does not appeal to similarity of mechanisms. Like Batterman's type (2) explanations, their account explains why, in many different kinds of infection, the immune system is vulnerable to attacks on CD4+ T-cells. It does this by appealing to architectural features—or topological properties—of the immune system: its bowtie structure, the location of CD4+ T-cells in this structure, and the non-redundancy of the cells at this location. Since the immune system which exhibits these topological properties remains the same in different kinds of immune system infection, we should expect a general vulnerability of the immune system to attacks on CD4+ T-cells despite different sequences of mechanism operations involving CD4+ T-cells during different kinds of infection. However, because topological properties are not mechanisms that operate in time, we should not expect to be able to understand the consequences of topological properties by animating pathway diagrams. Hence, even if mental animations of diagrams facilitate reasoning about mechanism operations (for so-called constitutive mechanistic explanations), we should not expect mental animations of diagrams to facilitate reasoning about topological properties (for topological explanations).

6 Concluding Remarks

Bechtel and Abrahamsen (2005) and Perini (2005) offer plausible accounts of why scientists might prefer to use diagrams when representing and reasoning about biological mechanisms: diagrams are more direct and iconic than their sentential counterparts, simultaneously representing mechanism components, spatial relations among those components, and temporal relations among the operations of those components; and diagrams support mental animation in a way that facilitates understanding the operations of various mechanisms. These accounts do not, however, provide a comprehensive understanding of the roles of diagrams in the biological sciences. Specifically, they do not fully explain why the relative directness and iconicity of diagrams is advantageous for scientists, and they do not account for the way in which diagrams facilitate important processes of reasoning associated with topological explanations of biological phenomena.

The pathway diagram associated with Kitano and Oda's (2006) account of immune system vulnerability to CD4+ T-cell attacks supports several theses that contribute to a fuller understanding of the roles of diagrams in the biological sciences. By virtue of its relative directness and iconicity, the diagram avoids repetition in representing the overall topological structure of the immune system pathway and, in the absence of precise and rigorous definitions of key topological notions (such as *bowtie structure* and *bowtie core*), facilitates identifying specific topological properties of that pathway. The diagram also makes counterfactual information about the pathway's topological structure available to controlled processing in a relatively direct manner, thereby facilitating inferences about the consequences of the pathway's topological structure.

What holds of the pathway diagram associated with Kitano and Oda's account holds more generally of pathway diagrams associated with topological explanations. For example, a *chokepoint* in a metabolic pathway is an enzyme that uniquely consumes or produces a particular metabolite. Chokepoint analysis is the process of identifying a pathway's chokepoints in order to explain certain problems for the fitness or survival of organisms, or to explain the effectiveness of pharmaceutical interventions (Yeh et al. 2004; Mehta and Tagore 2009). Yeh et al., for instance, "expect the inhibition of an enzyme that consumes a unique substrate to result in the accumulation of the unique substrate (toxic to the cell) and the inhibition of an enzyme that produces a unique substrate to result in the starvation of the cell (potentially crippling essential cell functions)" (2004: 920). Diagrams of metabolic pathways represent topological information in a way that facilitates identifying a system's chokepoints. For instance, scientists can identify chokepoints by visually inspecting pathway diagrams to find any node in a directed graph that is the tail of the only arc directed toward some node, or any node in a directed graph that is the head of the only arc directed away from some node (see Yeh et al. 2004: 921, Fig. 4). Diagrams of pathways which contain chokepoints also facilitate inferences regarding the counterfactual properties of chokepoint structures, making apparent (among other things) the consequences that chokepoint inactivation has for an organism's functions (see, for example, Mehta and Tagore 2009: Fig. 1).

Metabolic pathway diagrams, like Kitano and Oda's diagram and other diagrams that represent topological information, group together information about the global relationships of a system's components in ways that their sentential counterparts do not. In doing so, they offer more direct representations of the topological structures realized in biological systems. This allows scientists to avoid repetition in representing the overall topological structure about pathways and to more easily identify topological properties of pathway structures, regardless of whether precise and formal definitions of those properties are available. Such diagrams also facilitate relatively direct inferences about counterfactual manipulations of those structures, by virtue of making available for direct inspection the results of various "what if" thought experiments regarding what would happen if certain pathway elements were disabled or removed.

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