

Biological Information, causality and specificity – an intimate relationship

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In this chapter we examine the relationship between biological information, the key biological concept of specificity, and recent philosophical work on causation. We begin by showing how talk of information in the molecular biosciences grew out of efforts to understand the sources of biological specificity. We then introduce the idea of ‘causal specificity’ from recent work on causation in philosophy, and our own, information theoretic measure of causal specificity. Biological specificity, we argue, is simple the causal specificity of certain biological processes. This, we suggest, means that causal relationships in biology are ‘informational’ relationships simply when they are highly specific relationships. Biological information can be identified with the storage, transmission and exercise of biological specificity. It has been argued that causal relationships should not be regarded as informational relationship unless they are ‘arbitrary’. We argue that, whilst arbitrariness is an important feature of many causal relationships in living systems, it should not be used in this way to delimit biological information. Finally, we argue that biological specificity, and hence biological information, is not confined to nucleic acids but distributed among a wide range of entities and processes.

1. Introduction

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The lack of a rigorous account of biological information as a proximal causal factor in biological systems is a striking gap in the scientific worldview. In this chapter we outline a proposal to fill that gap by grounding the idea of biological information in a contemporary philosophical account of causation. Biological information is a certain kind of causal relationship between components of living systems. Many accounts of information in the philosophy of biology have set out to vindicate the common assumption that nucleic acids are distinctively informational molecules. Here we take a more unprejudiced approach, developing an account of biological information and then seeing how widely it applies.

In Section 2 we begin with the most prominent informational idea in modern biology – the coding relation between nucleic acid and protein. A deeper look at the background to Francis Crick’s Central Dogma, and a comparison with the distinction in developmental biology between permissive and instructive interactions, reveals that ‘information’ is a way to talk about specificity. The idea of specificity has a long history in biology, and a closely related idea is a key part of a widely supported contemporary account of causation in philosophy that grounds causal relationships in ideas about manipulability and control. In Section 3 we describe the idea of ‘causal specificity’ and an information-theoretic measure of the degree of specificity of a cause for its effect. Biological specificity, we suggest, is simply causal specificity in biological systems. Since we have already argued that ‘information’ is a way to talk about biological specificity, we conclude that causal relationships are ‘informational’ simply when they are highly specific. Section 4 defends this identification against the claim that only causal relationships in which the relation between cause and effect is ‘arbitrary’ should count as informational. Arbitrariness has an important role, however, in understanding the regulation of gene expression via gene regulatory networks. Having defended our identification of information with specificity, we go in section 5 to show that information is more widely distributed in biological systems than is often supposed. Coding sequences of DNA are only one source of biological specificity, and hence only one locus of biological information.

2. Information in biology

One of the best-known uses of ‘information’ in biology occurs in Crick’s 1958 statement of the ‘central dogma of molecular biology’:

The Sequence Hypothesis

... In its simplest form it assumes that the specificity of a piece of nucleic acid is expressed solely by the sequence of its bases, and that this sequence is a (simple) code for the amino acid sequence of a particular protein. ...

The Central Dogma

This states that once ‘information’ has passed into protein *it cannot get out again*. In more detail, the transfer of information from nucleic acid to protein may be possible, but transfer from protein to protein, or from protein to nucleic acid is impossible. Information means here the *precise* determination of sequence, either of bases in the nucleic acid or of amino-acid residues in the protein. (Crick, 1958, 152-153, italics in original)

Here Crick simply identifies the specificity of a gene for its product with the information coded in the sequence of the gene. By doing so, he linked the idea of information very closely to one of the fundamental organizing concepts of biology. Biological specificity is nothing less than the “orderly patterns of metabolic and developmental reactions giving rise to the unique characteristics of the individual and of its species” (Kleinsmith, 2014)³. From the second half of the 19th to the first half of the 20th century specificity was “the thematic thread running through all the life sciences” (Kay, 2000, 41), starting with botany, bacteriology, immunology and serology. By mid-century quantum mechanics had provided the necessary insight to explain the observed structural complementarity between molecules in terms of the

³ <http://www.accessscience.com/content/biological-specificity/082900>. Accessed 29 January 2015.

quantum-physical forces that underlie ability of enzyme and substrate to form a certain number of weak hydrogen bonds. This development of quantum chemistry, majorly driven by Linus Pauling and Max Delbrück in the 1940s, transformed the stereochemical concept of specificity based on the abstract and intuitive side-chain receptor theory (developed by Paul Ehrlich), and their lock-and-key interaction with a ligand (an image suggested by Emil Fischer, both at the turn of the century), into stereochemical specificity based on weak intermolecular forces (Pauling & Delbrück, 1940).

Crick introduces a new, more abstract conception of high selectivity or absolute specificity in terms of how one molecule can precisely specify the linear structure of another. For him it is the *colinearity* between DNA, RNA and amino acid chains that embodies its specificity. The information that specifies the product is no longer carried by a three-dimensional structure but instead by the linear, one-dimensional order of elements in each sequence. Amongst other consequences, this means that specificity becomes independent of the medium in which this order is expressed (i.e. DNA, RNA or amino acid chain) and of the kind of reaction by which the specificity is transmitted (i.e. transcription or translation). The same information/specificity flows continuously through these three media and two processes.

According to Crick the process of protein synthesis contains “the flow of energy, the flow of matter, and the flow of information.” While he notes the importance of the “exact chemical steps”, he clearly separated this transfer of material substances from what he regarded as “the essence of the problem”, namely the problem of how to join the amino acids in the right order. The flow of “hereditary information”, defined as “the specification of the amino acid sequence of the protein”, solved for him this critical problem of “sequentialization” (Crick 1958, 143-144).

In his later paper “Central Dogma of Molecular Biology” Crick clarified these earlier arguments:

The two central concepts which had been produced ... were those of sequential information and of defined alphabets. Neither of these steps was trivial. ... This temporarily reduced the central problem from a three dimensional one to a one dimensional one. ... The principal problem could then be stated as the formulation of the general rules for information transfer from one polymer with a defined alphabet to another. (Crick, 1970, 561)

The philosopher Gregory Morgan⁴ corresponded with Crick late in his career about his original inspiration to use the term 'information'. Crick's replies of March 20 and April 3 1998 show the consistency of his view over forty years. He states that his use of 'information' was influenced by the idea of Morse code, rather than Shannon's information theory, which he sees as more concerned with the reduction of noise during transmission. Like Shannon, however, he was not using the idea of information to express the 'meaning' or 'aboutness' of genes. Rather, information was "merely a convenient shorthand for the underlying causal effect", namely the "precise determination of sequence". Information for him solely meant "detailed residue-by-residue determination".

The concept of information in terms of the precise determination of sequence primarily offered Crick a way to reduce the transfer of specificity from a three-dimensional to a one-dimensional problem by abstracting away from the biochemical and material connotations of specificity. The conception of biological information defended in this paper takes this abstraction of the idea of specificity a stage further, but is very much in the spirit of Crick's original proposal.

Another biological field in which the concepts of information and specificity have been entwined is developmental biology, although here the idea of information is less tightly associated with DNA. We refer here particularly to the problem of tissue differentiation. Interaction between neighboring cells or tissues in development can

⁴ Personal communication. We are extremely grateful to Morgan for making this correspondence available to us.

lead to further differentiation in one, the responder, as a result of its interaction with the other, the inducer. Developmental biologists commonly distinguish between 'instructive' (or active, explicit, directive) induction on the one hand and 'permissive' (or passive, implicit) on the other.

The notion of the specificity of interaction is closely associated with the terms 'instructive' and 'permissive' interaction. When the action system is largely responsible for the specificity of the interaction through the transfer of a specific message, to which the reaction system responds by entering into a particular pathway of differentiation, we speak of an instructive action. When, on the other hand, the specificity of a reaction is largely due to the state of the competence of the reaction system, so that even rather unspecific messages can serve as signals to open up new developmental pathways, we speak of a permissive action. (Nieuwkoop, Johnen, & Albers, 1985, 9)

Papers on this subject cite as the two original sources of the distinction between instructive and permissive interactions either Holtzer (1968) or (Saxen, 1977). All seem to agree that instructive interactions provide *instructions* or *messages* simply because these interactions have a high degree of *specificity*. But the informational language also enters this context regularly:

Embryonic induction is generally described as an instructive event. The problem itself is often posed in terms implying the transmission of *informational molecules* [either proteins or nucleic acids] from one cell to another cell ... (Holtzer, 1968, 152, italics added)

Gilbert's treatment of the vital question regarding the source of specificity illustrates nicely how the instructive/permissive distinction is explained both in terms of specificity and information: "Instructive partners provide specificity to the reaction, whereas permissive partners ... do not provide specificity. ... [They are therefore not] on the same informational level" (Gilbert, 2003, 349).

We conclude from these examples that there are at least some contexts in which the language of information is a way to talk about the relatively high degree of specificity seen in some causal processes in biology. This matters to us, since in the next section we will present an information-theoretic analysis of specificity. If the argument of this last section is correct, then what follows is also an information-theoretic analysis of biological information.

3. Causal Specificity: an information-theoretic approach

James Woodward (2010), and ourselves (Griffiths & Stotz, 2013; Stotz, 2006) have argued that the idea of *causal* specificity is closely related to the idea of biological specificity. Causal specificity is an idea from the contemporary philosophy of causation. The philosophy of causation has many concerns, some of them entirely in the domain of metaphysics. The interventionist (or sometimes ‘manipulability’) account of causation, however, is primarily aimed at explaining why science cares about causation, and using that explanation to think more clearly about causation in scientific practice. Because of its applicability to actual cases of scientific reasoning it has been widely applied to problems in the contemporary philosophy of the life and social sciences. This account of causation focuses on the idea that “causal relationships are relationships that are potentially exploitable for purposes of manipulation and control” (Woodward 2010, 314). Causation is conceived as a relation between variables in an organized system that can be represented by a directed graph. A variable X is a cause of variable Y when a suitably isolated manipulation of X would change Y. This theory of causation, in its simplest form, can be used to pick out which variables are causes rather than merely correlates. However, a great many things get identified as causes. So, for example, a gene might be a cause for a phenotype, because a mutation (a ‘manipulation’) would change the phenotype. But equally, a change in the environment (another ‘manipulation’) will be picked out as a cause if it changes that phenotype.

A comprehensive theory of causation doesn't just distinguish cause from non-cause, but can also differentiate between causes in various ways—to identify ones that “are likely to be more useful for many purposes associated with manipulation and control than less stable relationships” (Woodward 2010, 315). A number of different ways to distinguish types of causes have been suggested, and two of these—Stability and Specificity—are particularly relevant to understanding biological information. Stability refers to whether an intervention continues to hold across a range of background conditions, and we will not pursue it here. Specificity refers to the fine-grained control that an intervention might have, controlling a gradient of change, rather than a simple on-off switch, for example (Griffiths & Stotz, 2013; Stotz, 2006; Waters, 2007; Woodward, 2010).

The intuitive idea is that interventions on a *highly specific* causal variable C can be used to produce any one of a large number of values of an effect variable E , providing what Woodward terms ‘fine-grained influence’ over the effect variable (Woodward 2010, 302). The ideal limit of fine-grained influence, Woodward explains, would be a bijective mapping between the values of the cause and effect variables: every value of E is produced by one and only one value of C and vice versa. The idea of a bijective mapping does not admit of degrees, but in earlier work with collaborators we have developed an information-theoretic framework with which to measure the specificity of causal relationships within the interventionist account (Griffiths et al., In press; Pocheville, Under review). Our work formalizes the simple idea that the more specific the relationship between a cause variable and an effect variable, the more information we will have about the effect after we perform an intervention on the cause. This led us to propose a simple measure of specificity:

Spec: the specificity of a causal variable is obtained by measuring how much mutual information interventions on that variable carry about the effect variable

The mutual information of two variables is simply the redundant information present in both variables. Where $H(X)$ is the Shannon entropy of X , and $H(X | Y)$ the conditional entropy of X on Y , the *mutual information* of X with another variable Y , or $I(X; Y)$, is given by:

$$I(X; Y) = H(X) - H(X | Y)$$

Mutual information is symmetrical: $I(X; Y) = I(Y; X)$. So variables can have mutual information without being related in the manner required by the interventionist criterion of causation. However, our measure of specificity measures the mutual information between *interventions on C* and the variable E . This is not a symmetrical measure because the fact that interventions on C change E does not imply that interventions on E will change C : $I(\hat{C}; E) \neq I(\hat{E}; C)$, where \hat{C} is read ‘do C ’ and means that the value of C results from an intervention on C (Pearl, 2009).

This measure adds precision to several aspects of the interventionist account of causation. Any two variables that satisfy the interventionist criterion of causation will show some degree of mutual information between interventions and effects. This criterion is sometimes called ‘minimal invariance’ – there are at least two values of C such that a manipulation of C from one value to the other changes the value of E . If the relationship $C \rightarrow E$ is minimally invariant, that is, invariant under at least one intervention on C , then C has some specificity for E , that is, $I(\hat{C}; E) > 0$. Moreover, our measure of specificity is a measure of what Woodward calls the ‘range of invariance’ of a causal relationship – the range of values of C and E across which the one can be used to intervene on the other. Relationships with a large range of invariance have high specificity according to our measure (Griffiths et. al., In press; Pocheville, Under review).⁵

⁵ Here we give a simple, absolute measure of specificity. Normalised relatives of our measure are available, as we discuss in these papers.

In light of the examples in Sections 2, we propose that causal relationships in biological systems can be regarded as informational when they are highly causally specific. Biological specificity, whether stereochemical or informational, seems to us to be simply the application of the idea of causal specificity to biological systems. The remarkable specificity of reactions in living systems that biology has sought to explain since the late C19th can equally be described as the fact that living systems exercise 'fine grained control' over many variables within those systems. Organisms exercise fine-grained control over which substances provoke an immune response through varying the stereochemistry of recognition sites on antibodies for antigens. They catalyze very specific reactions through varying the stereochemistry of enzymes for their substrates, or of receptors and their ligands. Organisms reproduce with a high degree of fidelity through the informational specificity of nucleic acids for proteins and functional RNAs. Genes are regulated in a highly specific manner across time and tissue through the regulated recruitment of *trans*-acting factors and the combinatorial control of gene expression and post-transcriptional processing by these factors and the *cis*-acting sites to which they bind. These are all important aspects of why living systems appear to be 'informed' systems, and what is distinctive about all these processes is that they are highly *causally* specific.

4. Arbitrariness, information and regulation

In this section we consider another property that has been said to essentially characterize informational relationships in biology. This is 'arbitrariness', the idea that the relationship between symbols and the things they symbolize represent only one permutations of many possible relationships between them. This is a familiar property of human languages – 'cat' could equally well be used to mean 'cow' and vice-versa. Like Crick, we have so far eschewed ideas of meaning and representation, so with respect to our proposal arbitrariness would mean that the systematic mapping between values of C and E is only one of may possible systematic mappings.

Sahotra Sarkar imposes just such a condition on the informational relationships in biology. Sarkar, known for his critical stance towards the use of informational language in biology, argued that “[e]ither informational talk should be abandoned altogether or an attempt must be made to provide a formal explication of ‘information’ that shows that it can be used consistently in this context and, moreover, is useful” (Sarkar, 2004, 261). He makes a serious attempt to provide the required formal explication, a definition of information that both performs a significant explanatory or predictive role and applies to information as it is customarily used. He proposes two adequacy conditions for a biological or genetic account of information:

Whatever the appropriate explication of information for genetics is, it has to come to terms with specificity and the existence of this coding relationship. ... Along with specificity, this arbitrariness is what makes an informational account of genetics useful. (Sarkar 2004, 261 and 266)

Sarkar’s analysis of specificity is similar to Woodward’s and we would urge that he adopt our information-theoretic extension of that analysis. His second condition, arbitrariness, relies on his interpretation of the Central Dogma, according to which it introduces two different *types* of specificity, namely “that of each DNA sequence for its complementary strand, as modulated through base pairing; and that of the relationship between DNA and protein. The latter was modulated by genetic information” (Sarkar, 1996b, 858). Sarkar needs to distinguish these two because the relationship between DNA and RNA is *not* arbitrary – it is dictated by the laws of chemistry. Only the relationship between RNA and protein is arbitrary, because it depends on the available t-RNAs. Many different t-RNAs are available, and substituting these would lead to different genetic codes.

In our view, however, Crick clearly states that ‘genetic information’ applies to the specification “either of bases in the nucleic acid or in amino acid residues in the protein” (Crick 1958, 153). DNA provides informational specificity for RNA as much

as RNA provides specificity for amino acid chains. Ulrich Stegmann agrees that the difference between the two is “irrelevant to the question of whether they carry information: they all do” (Stegmann, 2014, 460). There is just one type of informational specificity, and what distinguishes it from conformational specificity is its independence from the medium in which it is expressed or the mechanism by which it is transferred. Hence if arbitrariness should be regarded as an important condition for informational language in biology, it should be for the reason of this medium-independence in general, rather than the coding relationship between RNA and amino acids in particular. The *coding relationship* between RNA and amino acid is not the reason that led to Crick’s use of the idea of information in formulating the central dogma.

Like ourselves, Sarkar aims to explicate the notion of information in such a way as to make it a useful tool for biology. But adding the second condition of arbitrariness, at least when applied just to the coding relationship, to his definition of information seems to us to come with some substantial costs. It may exclude the concept of information from what seems to us one of its most useful roles, namely as a way to compare different sources of biological specificity, as we do in Section 5. This is because many of these alternative sources of specificity, like the DNA-RNA relationship, are not arbitrary.

This is not to say that arbitrary relationships play no vital role in biology. It is interesting that the notion of arbitrariness has been introduced in another area of biology that regularly deploys informational language, namely the regulation of gene expression through gene regulatory networks.

The pioneers of research into gene regulation, Francois Jacob and Jacques Monod, derived a notion of arbitrariness from their operon model (Jacob & Monod, 1961). The biosynthesis of the enzyme β -galactosidase is indirectly controlled by its substrate, β -galactosides. This indirect control is made possible by the intervening repressor of the gene, an allosteric protein, which is rendered inactive by its effector,

the substrate of the enzyme expressed by the gene. The repressor thereby indirectly transduces the controlling signal.

There is no chemically necessary relationship between the fact that β -galactosidase hydrolyses β -galactosides, and the fact that its biosynthesis is induced by the same compounds. Physiologically useful or “rational”, this relationship is chemically arbitrary – “gratuitous”, one may say. This fundamental concept of gratuity – i.e., the independence, chemically speaking, between the function itself and the nature of the chemical signal controlling it – applies to allosteric proteins. (Monod, 1971, 78)

Most controlling environmental stimuli have only an indirect controlling effect on gene expression, which is mediated or transduced by the processes of transcription, splicing or editing factors. The latter relay the environmental information to the genome. So the role of allosteric proteins in signal transduction due to their chemical arbitrariness that Monod has identified, could be assigned to many signaling molecules in biological signal transduction systems, just as is the case for many human-designed signaling systems. It is this arbitrariness that renders the system flexible and evolutionarily evolvable.

“The result – and this is the essential point – is that ... everything is possible. An allosteric protein should be seen as a specialized product of molecular “engineering” enabling an interaction, positive or negative, to take place between compounds without chemical affinity, and thereby eventually subordinating any reaction to the intervention of compounds that are chemically foreign and indifferent to this reaction. The way hence in which allosteric interactions work permits a complete freedom in the choice of control. And these controls, subject to no chemical requirements, will be the more responsive to physiological requirements, by virtue of which they will be selected according to the increased coherence and efficiency they confer on the cell or organism. In short, the very gratuitousness of the systems, giving

molecular evolution a practically limitless field for exploration and experiment, enabled I to elaborate the huge network of cybernetic interconnections which makes each organism an autonomous functional unit, whose performances appear to transcend, if not to escape, the laws of chemistry.” (Monod 1971, 78-9)

The mutual information between the specificity of the environmental signal for the regulatory factor on the one hand, and the specificity of the regulatory factors for a certain gene via its regulatory sequence, are chemically arbitrary and subject to the convention of an intervening allosteric biomolecule.

The central feature of such a relationship between any two pathways is that it is subject to heritable variation. This means that an environmental stimulus may lead in future to a quite different, adaptive response by the system, if mediated by a novel signaling protein that has evolved independent specificities to both the environmental stimulus (its effector) and the appropriate regulatory sequence (its substrate). We can understand the regulation of gene expression as an internal signaling game where sender and receiver are not two organisms but parts within one plastic organism (Calcott, 2014). The organism encounters two environments, and a different behaviour is optimal in each environment. The sender is a sense organ, or *transducer*, reacting to the environment by sending a signal inside the organism. The receiver is an *effector* converting the signal into some behaviour that changes how the organism as a whole interacts with that environment. Signaling occurs inside the organism, and the evolution of a signaling system allows it to optimally map the different environments to the appropriate behaviour. Signaling arose because the modular structure – the separation of transducer and effector – created a coordination problem. For the organism to respond adaptively, it needed to coordinate these parts, and a signaling system provided the solution. Signaling, from this internal perspective, is a way of building adaptive, plastic organisms.

What such a signaling system allows is the decoupling of informational dynamics from the dictates of local chemistry. According to Walker and Davies one of the hallmark of biological versus non-biological systems is the separation between their informational and mechanical aspects (Walker and Davies 2012, 4). This reminds us of Crick's insistence on the importance of the medium independence of informational specificity. But more importantly, it stresses the relationship between arbitrariness and informational control.

So arbitrariness is, indeed, an important feature of information processing in living systems. It is at last one of the fundamental keys to evolvability. But this, we would argue, is not a good reason to add arbitrariness to the definition of biological information. Arbitrary relationships are prevalent in biological signaling networks because of their biological utility, not because of the definition of information!

5. Distributed specificity

Griffiths and Stotz (Griffiths & Stotz, 2013) have termed the encoding of specificity 'Crick information'. If a cause makes a specific difference to the linear sequence of a biomolecule, it contains Crick information for that molecule. This definition embodies the essential idea of Crick's sequence hypothesis, without in principle limiting the location of information to nucleic acid sequences as Crick does. Our definition of Crick information can clearly be applied to other causal factors that affect gene expression. However, it is a specifically biological conception of information, rather than a general one such as Shannon's mutual information, or our measure of causal specificity, because by definition it only applies to causes that specify the order of elements in a biomolecule.

Crick's Central Dogma was based on a very simple picture of how the specificity of biomolecules is encoded in living cells. We now know that in eukaryotes coding regions are surrounded by a large number of non-coding sequences that regulate

gene expression. The discrepancy between the number of coding sequences and the number of gene products lead to the insight that the informational specificity in coding regions of DNA must be amplified by other biomolecules in order to specify the whole range of products. 'Precise determination' implies a one-to-one relationship, and if we focus on coding sequences alone, we find a one-to-many relationship between sequence and product. Different mechanisms of gene regulation co-specify the final linear product of the gene in question, first by *activating* the gene so it can get transcribed, second by *selecting* a chosen subset of the entire coding sequence (e.g. alternative splicing), and thirdly by *creating* new sequence information through the insertion, deletion or exchange of single nucleotide letters of the RNA (e.g. RNA editing). Thus specificity, and hence Crick information, is distributed between a range of factors other than the original coding sequence: DNA sequences with regulatory functions, diverse gene products such as transcription, splicing and editing factors (usually proteins), and non-coding RNAs (Stotz, 2006).

Absolute specificity turns out to be not inherent in any single biomolecule in these molecular networks but induced by regulated recruitment and combinatorial control. And it is here that we will find that the networks cannot be reduced to DNA sequences plus gene products, because many of the latter need to be recruited, activated or transported to render them functional. The recruitment, activation or transportation of transcription, splicing and editing factors allow the environment to have specific effects on gene expression (being 'instructive' rather than merely 'permissive' in the terms introduced in section 2). Some gene products serve to relay environmental (Crick) information to the genome. While in embryology and morphogenesis it is often acknowledged that environmental signals play a role in the organisation of global activities, they are rarely seen to carry information for the precise determination of the nucleic acid or amino acid chains in gene products. But this is precisely what occurs. Not just morphogenesis at higher levels of organisation, but even the determination of the primary sequence of gene products is a creative

process of (molecular) epigenesis that cannot be reduced to the information encoded in the genome alone (Stotz 2006; Griffiths and Stotz 2013).

Interestingly, concurrent with Crick's Central Dogma, the ciliate biologist David L. Nanney acknowledged that the 'library of specificities' found in coding sequences needed to be under the control of an epigenetic control system. In other words, in addition to requiring both an analogue and a digital conception of specificity, the study of biological development requires *two* sources of information. In an immediate response to Crick's new picture of sequential information coded in DNA, Nanney pointed out:

This view of the nature of the genetic material ... permits, moreover, a clearer conceptual distinction than has previously been possible between two types of cellular control systems. On the one hand, the maintenance of a "library of specificities," both expressed and unexpressed, is accomplished by a template replicating mechanism. On the other hand, auxiliary mechanisms with different principles of operation are involved in determining which specificities are to be expressed in any particular cell. ...To simplify the discussion of these two types of systems, they will be referred to as "genetic systems" and "epigenetic systems". (Nanney 1958, 712)

In a similar vein, Crick's biographer Robert Olby remarks of the Central Dogma that

Clearly, in concentrating on this aspect of informational transfer he was setting aside two questions about the control of gene expression – when in the life of a cell the gene is expressed and where in the organism. But these are also *questions of an informational nature*, although not falling within Crick's definition. (Olby, 2009, 251, italics added)

As it has turned out, many epigenetic mechanisms are strongly associated with DNA. Developmental biologist Scott Gilbert argues that the specificity of a reaction "has to

come from somewhere, and that is often a property of the genome” (2003, 349). But since all cells start with exactly the same genetic “library of specificities” that can’t be the whole story of differentiation. Nanney describes this as a developmental paradox: “How do cells with identical genetic composition acquire adaptive differences capable of being maintained in clonal heredity” (Nanney, 1989)? Gilbert indeed acknowledges that the action of a gene itself “depends upon its context. There are times where the environment gets to provide the specificity of developmental interaction” (2003, 350). So we conclude that while genes are seen as a key source of specificity, in biology causes are not regarded as informative merely because they are genetic, but whenever they are highly specific.

Many years later Nanney looked back on this period in the late 1950s as one in which the powerful image of the double helix caused a “near disruption of an incipient merging of cybernetics with regulatory biology”. It “may have hindered the exploration of the systemic components of living systems, which are not just creatures reified from the ‘blueprints’, but essential complementary components of life that reciprocally regulate the nucleic system” (Nanney 1989). In recent years, however, our image of how biological systems exercise fine-grained control over their internal processes has developed to the point where his description of the two complementary control systems seem quite conservative.

It is now clear that the epigenetic control system, if we still want to call it that, not only regulates *when* and *where* the specificities encoded in the DNA library are to be expressed⁶. It also substantially augments the information of the literal coding sequence. A strange aspect of the management of genetic information is that the epigenetic control system – which Paul Davies likens to “an emergent self-organizing phenomenon” (Davies, 2012, 42) – does not just provide a supervising

⁶ Woodward suggests that specificity includes both the “systematic dependencies between a range of different possible states of the cause and different possible states of the effect, as well as dependencies of *the time and place of occurrence* of E on the time and place of C” (Woodward 2010, 304-305, italics added). So even in Nanney’s original vision, the epigenetic systems is an additional source of specificity.

function on the expression of the specificities encoded in the DNA, in the sense of when, where, and how much will be expressed. Since the information encoded in the DNA does not entail a complete set of instruction for which biomolecules shall be synthesized, the epigenetic control system *amplifies* the information of the literal code (Davidson, 2002). Genes are not only switched on and off, even though this already “leads to exponentially more information being stored in the system (since a set of N genes can have 2^N distinct states)” (Davies, 2012, 43). Eukaryotes have epigenetic mechanisms that allow them to produce many products from a single coding region, ranging from just two up to thousands of isoforms of the resulting protein.

Most epigenetic mechanisms are now fairly well understood at the molecular level, most of them include chemical modifications of the DNA or the tails of the histone protein around which the DNA is wrapped. The posttranscriptional processing mechanisms, mainly alternative slicing and RNA editing that create this large range of gene product, are also fairly well understood. But if epigenetic mechanisms are simply a set of physical modifications of DNA, isn't the organism still an expression of its genome, even if the genome is a little more complex than initially supposed? This will not do because the molecular mechanisms and epigenetic marks are just the final stages of regulatory processes that start far from the genome. For instance the up- or down-regulation of the glucocorticoid receptor gene in the hypothalamus of a rat pup is proximally caused by the increased or decreased methylation state of the receptor's promoter region. This in turn is influenced by the increased or decreased expression and activation of the transcription factor NGF1-A. Increased expression of NGF1-A is due to an increased serotonin tone in the hippocampus. But this in turn is being caused by the mother rat's licking and grooming of her pup, which in turn reflects the more or less stressed state of the mother due to the environment in which she finds herself. The mother's maternal care behavior comprised part of the environmental context of the rat pup. The increased serotonin tone represents a change of the overall state of the whole system, with a range of downstream effects, one of which is a change in the expression of the glucocorticoid

receptor. This in turn produces a range of bottom-up effects on the system in terms of a changed behavioral repertoire. This is just one example of how the environment or the system as the whole is ultimately affecting the expression of genes (Meaney, 2001; Weaver et al., 2007). Therefore we can say that a substantial amount of information needed to construct an organism is derived from elsewhere, such as the organism's environment. This information augments or amplifies the information inherited via the genome.

6. Information and 'downwards causation'

We have argued that additional specificity, or information, is derived from the environmental context, but it may also be generated *de novo* by physical processes of self-organisation. Self-organisation is the spontaneous formation of well-organized structures, patterns, or behaviors. In biology it means the self-maintaining organisation of constraints that harness flows of matter and energy and allow the "constrained release of energy into relatively few degrees of freedom" (Kauffman, 2003, 1094). Biological systems, in Kauffman's term, 'acting on their own behalf' when they constrain exergonic processes in a specific way to produce work, which can be used to generate endergonic processes, which in turn generate those constraints canalizing exergonic processes.⁷ It has often been suggested that such processes are an additional source of order in biological systems.

Walker and Davies have recently characterized life by "context-dependent causal influences, and in particular, that top-down (or downward) causation – where higher-levels influence and constrain the dynamics of lower-levels in organizational hierarchies – may be a major contributor to the hierarchical structure of living systems" (Walker & Davies, 2013, 1).

⁷ An endergonic reaction absorbs and stores energy from the surrounding. During exergonic reactions stored energy is released to drive various functions.

Downward causation shouldn't be understood as the direct dynamic interaction of the whole with some of their parts. It has long been acknowledged in the physical science that in dynamic - efficient - causation, only the interaction between parts at the same ontological level has causal effectiveness. The way that the overall biological system is still able to exert real causal effects is by way of informational control via feedback mechanisms that influences the dynamic interaction between the parts (Auletta, Ellis, & Jaeger, 2008). Philosophers Carl Craver and William Bechtel have advocated this view more generally, in an attempt to rid the idea of downwards causation of any mysterious overtones (2006). They suggest that interlevel relationships, such as the interactions between parts and whole, should not be understood as causal relationships at all, even though these relationships exert real influences on the system at different levels. Both top-down and bottom-up causation,

... describe mechanistically mediated effects. Mechanistically mediated effects are hybrids of constitutive and causal relations in a mechanism, where the constitutive relations are interlevel, and the causal relations are exclusively intralevel. (Craver & Bechtel, 2006, 547)

A system as a whole – a higher level entity – is engaged in a process that would not happen without some aspects of the organization of that system, and which therefore needs to be understood at the higher level. But this system is composed of parts, and as the system as a whole changes, so do the parts, obviously. The relation between the process going on at the systems level and a change in one part is not because of an additional causal relation between system as a whole and that part (over and above the interaction of the part with other parts) but the relation of constitution between the system and its parts.

It is in this sense that we understand and endorse Walker and Davies' claim that, "algorithmic information gains direct, context-dependent, causal efficacy over matter" (2013, 2). That does not just mean that the digital information within the

genetic code just by itself gains such control over matter. After all, as Nanney has already realized some 65 years ago, the expression of the repository of information within DNA is in need of epigenetic control. “The algorithm itself is therefore highly delocalized, distributed inextricably throughout the very physical system whose dynamics it encodes” (Walker & Davies 2013, 5). The causal efficacy is achieved through some “unique informational management properties. ... Focusing strictly on digital storage therefore neglects this critical aspect of how biological information is processed” (Walker & Davies 2012, 2-3).

7. Conclusion

Sarkar has argued that the conventional account of biological information as coded instructions in the sequence of DNA nucleotides lacks explanatory power. He calls for, first, the development of a “systematic account of specificity”, and second, an “elaboration of a new informational account” with wider applicability than nucleic acid alone (Sarkar, 1996a, 222). If the latter course was to be adopted, he suggested, it would be “highly unintuitive not to regard [epigenetic specifications] as ‘transfers of information’ if ‘information’ is to have any plausible biological significance” (Sarkar 1996a, 220). Our proposal in this paper represents a synthesis between Sarkar’s two ways forward, namely a systematic account of specificity *and* a new approach to biological information (see Griffiths et al., Forthcoming; Pocheville, Under review).

Biological specificity is simply causal specificity in biological systems. Causal specificity is a degree property of causal relationships – the more specific a relationship the more apt it is for the exercise of fine-grained control over the effect. In section 3 we gave a brief summary of how this property can be measured using tools from information theory. Informational language in biology represents a way to talk about specificity. No doubt informational language is used for many other purposes in biology as well, but the cases we have presented in which it relates to

specificity are central to molecular and developmental biology. As a result we feel justified in calling our information-theoretic analysis of specificity an analysis of biological information.

What is distinctive about living systems, we would argue, is that they are structured so that many of their internal processes have an outstanding degree of causal specificity when compared to most non-living systems. This underlies the phenomenon that first attracted the label of 'specificity' in biology – the ability of organisms to develop in a very precise way, and to respond in a very selective and precise way to their circumstances. The idea that living systems differ from non-living systems by being 'informed' – under the control of information – makes a great deal of sense in terms of our analysis of biological information as causal specificity. However, there is a great distance between a broad, philosophical interpretation like this and an actual scientific theory of the informational nature of living systems. In the final two sections we have reviewed some of the ideas that we think may form part of such a theory.

Acknowledgments

This publication was made possible through the support of a grant from the Templeton World Charity Foundation, "Causal Foundations of Biological Information", TWCF0063/AB37. The opinions expressed in this publication are those of the authors and do not necessarily reflect the views of the Templeton World Charity Foundation.

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