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The Central Dogma as a Thesis of Causal Specificity

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ABSTRACT – I present a reconstruction of F.H.C. Crick's two 1957 hypotheses 'Sequence Hypothesis' and 'Central Dogma' in terms of a contemporary philosophical theory of causation. Analyzing in particular the experimental evidence that Crick cited, I argue that these hypotheses can be understood as claims about the actual difference-making cause in protein synthesis. As these hypotheses are only true if restricted to certain nucleic acids in certain organisms, I then examine the concept of causal specificity and its potential to counter claims about causal parity of DNA and other cellular components. I first show that causal specificity is a special kind of invariance under interventions, namely invariance of generalizations that range over finite sets of discrete variables. Then, I show that this notion allows the articulation of a middle ground in the debate over causal parity.

KEYWORDS – Molecular biology, Central Dogma, F.H.C. Crick, H. Fraenkel-Conrat, protein synthesis, causation, intervention, experiment, actual difference-making cause, causal specificity, causal parity, biological evolution, horizontal gene transfer, genetic variation, evolution genes, natural selection, universal genetic code.

1. Introduction

Much has been written recently by philosophers of biology on how to conceptualize the role of genes and DNA in living organisms (e.g. Griffiths and Gray 1994; Sterelny and Griffiths 1999; Oyama, Griffiths and Gray 2001; Moss 2003; Weber 2005a; 2005b; Rosenberg 2006; Griffiths and Stotz 2006; Waters 2006). Controversial issues include the question of whether there is a sense in which genes are privileged causes of development versus the 'causal parity thesis' of Developmental Systems Theory, and whether there is a substantial concept of information that is predicated properly (as opposed to merely metaphorically) and possibly uniquely of the genetic material. Famously, Crick's 'Central Dogma of Molecular Biology' was expressed in terms of information flow from DNA to RNA to protein (see Section 2). Some authors (Sarkar 1996; Weber 2005a) believe that this use of the term 'informa-

tion' should be viewed as a metaphor, even if a heuristically fruitful one, while others have tried to explicate this way of speaking as a proper application of a substantial information concept (Stegmann 2005; Sarkar 2007). I will remain neutral on this issue here. What I would like to investigate in this paper is whether Crick's 'Central Dogma' and its corollary, the 'Sequence Hypothesis', can be explicated by using a recent philosophical theory of causation. This theory is due to James Woodward (2003) and has recently been extended by Kenneth Waters (forthcoming) to cover such cases as genetic causation. The basic step required for this is to develop, within Woodward's framework, two causal concepts: the concepts of *actual difference-making causes* and of *causal specificity*. In this paper, I shall not so much be concerned with the truth of Crick's two hypotheses as with their exact *content*. As I will show, this sheds some light on the history of molecular biology as well as the epistemology of experimental testing, the philosophy of causation, and last but not least on the issues concerning the role of the genetic material mentioned at the beginning.

In Section 2, I shall examine some of Crick's claims made in his landmark paper especially with respect to the experimental support that Crick cited in their favor. Section 3 outlines Woodward's theory of causation and Waters's analysis of difference-making causes and applies them to the content of Crick's 1958 paper. In Section 4, I turn to the concept of causal specificity. In a friendly amendment to Waters's account, I show how causal specificity can be understood as a special kind of Woodward-invariance, which admits of *degrees*. Section 5 concludes my considerations and proposes a possible middle ground in the debate as to how causally privileged the genetic material is.

2. Crick on Protein Synthesis

The core of Crick's 1958 paper are two hypotheses, the 'sequence hypothesis' and the 'Central Dogma'.[1] The former is the following claim:

> [T]he specificity of a piece of nucleic acid is expressed solely by the sequence of its bases, and [...] this sequence is a (simple) code for the amino acid sequence of a particular protein. (Crick 1958, 152)

[1] Apparently, the term 'dogma' was chosen solely for the purpose of lexical variation; Crick made it clear that he considered it a hypothesis as well.

And here is the original statement of the 'Dogma':

> [O]nce 'information' has passed into protein *it cannot get out again*. In more detail, the transfer of information from nucleic acid to nucleic acid, or 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, 153)

Given the philosophical debates as to whether the term 'information' is applied metaphorically or not, it is interesting to note that Crick put it into distance quotation marks. Furthermore, Crick makes it quite clear that he means nothing but the 'precise determination of sequence'. However, due to Crick's use of the terms 'information', 'code', and 'specificity', these statements are in need of explication. As they stand, it is not entirely clear what they mean, unless the reader already has in mind the whole theory of protein synthesis as it was emerging at that time. As I will show later, it is possible to reconstruct these two claims as purely causal hypotheses and thus explicate their content. But first, I would briefly like to examine what problem Crick set out to solve.

Crick's concern was protein synthesis. The problem, in 1957 (when the paper was written), was

> to find a reasonably simple mechanism that could account for specific sequences without demanding the presence of an ever-increasing number of new specific enzymes for the synthesis of each new protein molecule. (Crick 1958, 143)

It was already known then that organisms contain thousands of different proteins each with a specific function, for example, a specific enzyme activity. Were proteins themselves made by specific enzymes? This, of course, was not possible, because it would require an infinity of different enzymes (because the enzyme that specifically makes a protein would itself need a specific enzyme for its synthesis and so on). The problem was how a limited set of enzymes could make all the thousands of different protein molecules. The 'sequence hypothesis' was Crick's proposed solution: nucleic acid somehow determines the order of amino acids in the protein. The central dogma was a corollary to this solution: whatever it meant exactly, it implied that protein sequence variation was explained by nucleic acid sequence variation, but not vice versa. There are no specific enzymes for the synthesis of proteins (specific for a particular protein product, to be more precise). Furthermore, nucleic acid is synthesized by replication, that is, also not with the help of specific enzymes for each different DNA molecule.

I will show how the two hypotheses can be made more precise in the

following section. But before I do this, I would like to examine briefly what *evidence* Crick cited in favor of his two hypotheses. This could be relevant to the question of what their exact content was, as Crick intended them.[2]

The first result cited by Crick as relevant to the problem of protein synthesis is the work of Beadle and Tatum on the genetic control of biochemical reactions in the fungus *Neurospora* (Beadle and Tatum 1941). Crick reports that he 'personally' accepts the one gene-one-enzyme hypothesis proffered by Beadle and Tatum on the basis of their work (Crick 1958, 142). However, this is not of much help here, as this hypothesis requires clarification itself. Surely, it takes more than just a gene to make an enzyme and some genes affect more than one enzyme. This is not to suggest that this hypothesis does not have a clear meaning, but to explicate this meaning already takes us right into the reconstructive problem at hand.

The second result is the work by Vernon Ingram on sickle cell hemoglobin (Ingram 1956; 1957). Ingram showed that the hemoglobin from patients with sickle cell anaemia differed in only one amino acid position with respect to patients that lack this condition. Since the trait was known to be under the control of a Mendelian factor, this was the first time that a Mendelian gene was shown to affect the amino acid sequence of a protein.

The next two pieces of evidence cited by Crick are the Hershey-Chase experiment, which showed that the DNA of bacteriophages enters into a bacterial cell while the protein coat remains outside (Hershey and Chase 1952) and Benzer's (1955) work on the linear arrangement of mutable sites on bacteriophage DNA (see also Weber 1998). The work of Brachet and Caspersson on the role of RNA in protein synthesis is mentioned, but in a context where Crick immediately asks the question of whether there is any more 'direct' evidence for the idea that sequence of amino acids is controlled by RNA (Crick 1958, 145). The 'most telling' of such evidence, in Crick's view, came from work on the tobacco mosaic virus (TMV). That this work was considered the most direct evidence for his hypotheses is highly significant for analyzing their content, as I will show.

I will focus on the work of Heinz Fraenkel-Conrat. He developed an experimental system where virus particles can be separated into protein and nucleic acid (RNA) fractions. First, Fraenkel-Conrat (1955) showed that it was possible to mix these extracts so that infectious virus particles

[2] Some philosophers believe that the meaning of any statement basically consists in the inferential relations that it bears to other statements (Brandon 2000). This might include relations of evidential support.

formed. The infectivity was low (< 1% of untreated TMV) but given the harsh treatments to which the virus particles were subjected this was remarkable nonetheless. Using this experimental system, Fraenkel-Conrat (1956) was then able to do an even more remarkable experiment. He had different strains of TMV available, which were known as 'M', 'HR' and 'YA'. These strains were clearly distinguishable with the help of the disease phenotypes to which they gave rise. Furthermore, it had been shown that the protein coats of HR differed considerably in amino acid composition as well as antigenic specificity. For example, an antiserum against HR protein did not react with the other strains. Fraenkel-Conrat now made hybrid particles, for example, of HR-RNA and protein from non-HR strains (which are more common and more related antigenically). These particles were not sensitive to anti-HR serum, while they were largely neutralized by antiserum against common TMV. When these hybrid particles were used to infect plants, the symptoms were that of HR. But the virus particles now produced by such a plant were sensitive to anti-HR serum. Furthermore, their protein coat was like that of HR with respect to amino acid composition. Fraenkel-Conrat concluded that RNA was 'the main genetic determinant' of the progeny protein (Fraekel-Conrat 1956, 883).

In Crick's view, Fraenkel-Conrat's experiments showed the following:

> In other words, *the viral RNA appears to carry at least part of the information which determines the composition of the viral protein.* Moreover the viral protein which was used to infect the cell was not copied to any appreciable extent. (Crick 1958, 145)

Again, Crick expressed his conclusion by using information talk, therefore leaving us somewhat in the dark as to what exactly he is trying to say. His repeated insistence that he means the 'specification of the amino acid sequence of the protein' is of little help, as 'specification' is no clearer a concept than information.[3]

I will now show that Crick's thesis can be reconstructed as a precise causal claim. This reconstruction will also explain why Fraenkel-Conrat's work was the most direct evidence yet for Crick's hypotheses.

3. Actual Difference-making Causes

Philosophical theories of causation have not been able to determine the criteria for identifying actual difference-making causes. For example,

[3] Note also the semantic similarity of these terms. 'Species' and 'form' are both common translations of Aristotle's term *eidos*.

accounts that construe causation as counterfactual dependence have much to say on the conditions under which two events, say the striking of a match and its subsequent lighting, are causally connected. (In brief, they say that the obtaining of a causal connection makes the counterfactual 'Had the match not been struck, then it would not have lit' true). But they have nothing to say on why the striking of a match rather than the presence of oxygen or the absence of moisture caused the ignition, even though the latter are also necessary and make corresponding counterfactuals true (had there been no oxygen present, the match would not have lit either). This has led many philosophers to the conclusion that, when some necessary condition rather than another is identified as the cause of an event, this must have to do with human interests (e.g., Mackie 1980).

Kenneth Waters (forthcoming) proposes a remedy for this conundrum. In a nutshell, he argues that many causal attributions involve the concept of an *actual difference-making cause*. For example, in many cases where the lightning of a match rather than the presence of oxygen is identified as the cause this means that, among many other conditions that bear a causal relation to the event in question, the striking actually made the difference in a relevant population. Perhaps the match came from a box with many other matches that were also exposed to oxygen and dry, contained inflammable sulfur, and so. But only one of them lit up. The striking is what made the difference; it was the actual difference-making cause. The other factors were merely *potential* difference-making causes.

Waters presents an explication of the concept of an actual difference-making cause that is based on James Woodward's manipulationist account of causation (Woodward 2003). On this account, causal claims are analyzed as claims about possible manipulations:

> X causes Y iff
> for at least some individuals there is a possible manipulation of some value of X that they possess which, given other appropriate conditions [...], will change the value of Y or the probability distribution of Y for those individuals. (Woodward 2003, 40)

This account has no ambition to *reduce* the concept of causation to non-causal notions. This is obvious in the above formulation that still contains causal notions in the explicans, for example, the notion of X changing the value of Y. Woodward's goal is rather to exhibit conceptual relations between various causal notions and manipulations or interventions[4] as well as to the issues of scientific explanation and scientific evidence.

[4] Woodward's account is not tied to human agency. Possible manipulations might be machine-operated. Furthermore, 'possible' does not imply that the manipulations must be technically possible.

Woodward has developed an elaborate technical apparatus to spell out the 'other appropriate conditions' that feature in the above-mentioned basic explication of the notion of cause. I can only give a very brief summary of this apparatus here. The next step is to define a more precise notion of manipulation, which is named intervention. An *intervention on X with respect to Y* is a manipulation that changes the value of X without changing, independently of the change in the value of X, the value of any other causes of Y (Woodward 2003, 94).

This notion is best illustrated on a very simple example. Let L stand for a drop in pressure, S for a storm, and B for the reading of a barometer. Intuitively, L is a cause of S but B is not a cause of S. However, manipulating B by changing L might well cause a storm. But such a manipulation does not count as an intervention in Woodward's sense. The reason is that this manipulation changes L independently of the value of B and L is a cause of S. By contrast, changing pressure is an intervention on L with respect to S because no other variables that might influence S are affected.

Causal claims are claims about counterfactual dependence: An intervention on X with respect to Y that *would* change the value of X would also change the value of Y. Note that the concept of intervention is appropriately constructed so that such counterfactual claims require no further qualifications (e.g., a *ceteris paribus* or *ceteris absentis* clause). If some manipulation really *is* an intervention on X with respect to Y, then the corresponding counterfactual is true come what may, or else the causal claim is false.

In science, many causal claims take the form of *causal generalizations*. Woodward analyzes such generalizations with the help of an again carefully constructed notion of *invariance*:

> A generalization G (relating, say, changes in the value of X to changes in the value of Y) is invariant if G would continue to hold under some intervention that changes the value of X in such a way that, according to G, the value of Y would change – 'continue to hold' in the sense that G correctly describes how the value of Y would change under this intervention. (Woodward 2003, 15)

Thus, it is merely being the case that G: $Y = f(X)$ is not sufficient for G being an invariant generalization. For example, the occurrence of storms might be a function of the barometer reading such that a variable S takes the value 1 ('storm occurring') whenever $B < z$ (barometer reading smaller than some critical value z). But this is no invariant generalization, because it would not continue to hold under an intervention on the barometer reading, for example, by cooling the barometer (note that

the concept of intervention excludes that the barometer reading be tampered with via the pressure, because there is a direct causal route from pressure to the actual weather). By contrast, an appropriate function that relates the value of S to the actual pressure P might well be invariant under direct interventions on P. This kind of invariance is characteristic of causal generalizations.

Invariance is a matter of degrees. There might be ranges of values for a function under which the function is invariant and ranges where it fails to be invariant. Fundamental laws of physics (e.g., Coulomb's law) are maximally invariant (they hold for any possible value of their variables), while generalizations in the special sciences (e.g., biology, psychology, economics) exhibit a more restricted range of invariance. A generalization is minimally invariant if it holds for just two values of a variable, for example, a function that maps the variable 'light on or off' to the two possible positions of a switch.

So much on Woodward's account of causation and causal generalizations. Waters (forthcoming) extends this account first by introducing three additional concepts: potential difference-making cause, *the* actual difference-making cause, and *an* actual difference-making cause. Here is the definition of '*the* difference-making cause':

X is *the actual difference maker* with respect to Y in population p iff
(i) X causes Y (Woodward)
(ii) The value of Y actually varies among individuals in p
(iii) The generalization 'X causes Y' is invariant with respect to the variables that actually vary in p
(iv) Actual variation in the value of X fully accounts for the actual variation of Y values in p

In this account, the expression 'fully accounts' should be understood in the following way:

(a) Individuals with the same X values in p have the same Y values
(b) An intervention on X with respect to Y that changed the X-value of all individuals in p to the value that one and the same individual had without intervention would change Y values in p such that they no longer differed
(c) There is no variable Z, distinct from X, such that an intervention on Z with respect to Y that changed Z values in one or more individuals in p to the Z value that one of the individuals had without intervention would change Y values in p

Next Waters introduces the concept of *an* actual difference-making cause:

X is *an actual difference maker* with respect to Y in population p iff
(i) X causes Y (Woodward)
(ii) The value of Y actually varies among individuals in p
(iii) The generalization 'X causes Y'is invariant over at least parts of the space of values that other variables actually take in p
(iv) Actual variation in the value of p partially accounts for the actual variation of Y values in population p

where the expression 'partially accounts' is to be understood as follows:

An intervention on X with respect to Y that changed the X values in one or more individuals in p to the X value that one of the individuals had without intervention would change Y values in p ('difference changer' might be more appropriate).

Any cause that satisfies Woodward's criteria for 'X causes Y' but fails to satisfy any of Waters's criteria for actual difference-making causes is a *potential* difference-making cause rather than an actual one.

Waters uses these definitions to argue that prokaryotic DNA qualifies as *the* difference-making cause with respect to a population of proteins within a cell, while eukaryotic DNA is merely *a* difference-making cause. RNA polymerases and splice factors are other actual difference-making causes in such systems, while many other factors involved in protein synthesis are merely potential difference-making causes. He further argues that even eukaryotic DNA is the only *specific* actual difference-making cause with respect to a population of cellular (or extracellular) proteins, thus refuting the idea that DNA is causally on a par with many other cellular components enunciated by proponents of Developmental Systems Theory. I will come back to the concept of causal specificity in the following section. Right now, I would like to show that what Fraenkel-Conrat's experiments showed was exactly that RNA is the actual difference-making cause of viral protein primary structure.

As was already mentioned, Fraenkel-Conrat showed that hybrid virus particles composed of HR-RNA and common TMV protein produced progeny that contained HR coat protein. Using Woodward's technical apparatus, this may be expressed in the following way:

Let X: $[x_1, x_2]$ be a discrete variable that takes two different values, depending on whether HR or non-HR RNA was added to the reconstituted virus. Further, let Y: $[y_1, y_2]$ be a discrete variable that takes two values depending on whether the virus coat contained HR or common TMV protein. Now, what Fraenkel-Conrat showed is the following:

(i.1) There is an intervention on X with respect to Y that changed the value of Y via a route that did not alter any other variables that could change Y: The value of the protein variable depended on the value of the RNA variable.
(i.2) There is no intervention on Y with respect to X that changed the value of X via a route that does not alter any other variables that could change X: The value of the RNA variable did not depend on the value of the protein variable (no matter what coat protein was used, the progeny virus contained the same RNA).

These claims are sufficient for the following states of affairs: X causes Y, Y does not cause X. But Fraenkel-Conrat's results supported a set of even stronger claims:

(ii) The value of Y actually varies in p (in the experimental system used): there are at least two protein species.
(iii) The generalization 'X causes Y' is invariant with respect to the variables that actually vary in p: checks, but only minimally so.
(iv) Actual variation in the value of X fully accounts for the actual variation of Y values in p.

(iv) is true because the following conditions were satisfied:

(a) Particles with the same RNA in p have the same protein
(b) An intervention on RNA with respect to protein that changed the RNA of all particles in p to the value that one and the same particle had without intervention would change the protein molecules in p such that they no longer differed
(c) There is no variable Z, distinct from RNA, such that an intervention on Z with respect to protein that changed Z values in one or more particles in p to the Z value that one of the particles had without intervention would change protein molecules in p.

Thus, viral RNA qualifies as the difference-making cause of protein structure by the lights of Fraenkel-Conrat's experiments. Since Crick considered these results as the 'most telling evidence', it is an attractive proposition to read his two hypotheses as follows:

Sequence hypothesis: Nucleic acid is the actual difference-making cause in protein synthesis with respect to a cell's population of proteins.

Central Dogma: Protein is not the actual difference-making cause in protein synthesis with respect to a cell's population of proteins or in nucleic acid synthesis with respect to a cell's nucleic acid population.

Thus, what Crick enunciated was a thesis about actual difference-making causes in the process of protein synthesis. This concludes my analysis of Crick's classic paper. In the following section, I will make a general conceptual point concerning the relationship of causal specificity and invariance, but I shall come back to the role of DNA in the final section.

4. Causal Specificity and Invariance

Waters claims that the concept of actual difference-making cause singles out nucleic acids in prokaryotic protein synthesis, but not in eukaryotes. The reason is that RNA polymerases and splice agents are also actual difference-making causes in the latter. In order to articulate a sense in which nucleic acids are nonetheless causally unique, another causal notion is needed: the notion of *causal specificity*. In order to explicate this notion, Waters uses David Lewis's concept, causal influence. This is defined as follows:

> Where C and E are distinct actual events, let us say that C influences E iff there is a substantial range C_1, C_2, . . . of different not-too-distant alterations of C (including the actual alteration of C) and there is a range E_1, E_2, . . . of alterations of E, at least some of which differ, such that if C_1 had occurred, E_1 would have occurred, and if C_2 had occurred, E_2 would have occurred, and so on. (Lewis 2000, 190)

Using this idea, it can be said that if there is a multiplicity of different antecedent events that are responsible for a commensurate multiplicity of different causal consequences, then each of the antecedent events counts as a specific cause of the consequent events. Waters suggests that, even in eukaryotic protein synthesis, DNA is the only actual difference-making cause that is specific in this sense. I would now like to show that this claim is in need of correction. I will proceed by first showing that causal specificity is nothing but a special kind of Woodward-invariance. Second, I shall claim that, because invariance comes in degrees, so does causal specificity.

To see the first point, consider a function Y=f(X) where X ranges over a finite set of discrete variables X: [x_1, x_2, ... x_n] and Y ranges over

a set Y: [y_1, y_2, ... y_n]. Let *f* be the function that assigns y_i to x_i. Furthermore, let this generalization be invariant in Woodward's sense. This means that there must be interventions on X that change the value of Y. Furthermore, this generalization must be able to answer 'what-if-things-had-been-different?' questions to the effect that, had x_1 occurred, then y_1 would have occurred and if x_2 had occurred, then y_2 would have occurred, and so on, and if x_n had occurred then y_n would have occurred. This is what Woodward's account requires. But this is exactly Lewis's condition for causal influence, re-named causal specificity by Waters. Therefore, causal specificity is nothing but the obtaining of a Woodward-invariance for two sets of discrete variables. To be more precise: it is a *special kind* of Woodward-invariance where there is the type of mapping *f* mentioned above. Note also that a *minimally* invariant generalization qualifies as such a relation of causal specificity unless we specify a number of values for the independent variable greater than two that is necessary for causal specificity.

I see no principled way of specifying such a number, which brings me to the second point. Causal specificity is a matter of *degrees*. Depending on the range of invariance and the number of values that the independent and dependent variables can take, we can speak of a relation being more or less causally specific.

How do these notions apply to nucleic acids and proteins? I think it brings out nicely the difference between actual difference-making causes that are highly causally specific, such as nucleic acid sequence, and actual difference-making causes that are also causally specific, but less so. For example, RNA polymerases are much less causally specific. There are typically three of them (in eukaryotic cells), which means that they may be represented as a variable X that takes three different values. The dependent variable, in such a case, takes only two values: either a given gene is transcribed by one of the polymerases or it is not.

A somewhat greater degree of causal specificity is found in splicing agents that are responsible for alternative splicing (i.e., the production of different polypeptides by using and disusing different coding sequences or exons within a gene). Depending on what protein factors are present, a cell can make a considerable variety of different polypeptides from the same gene. Thus we have some causal specificity, but it is no match for the extremely high number of different protein sequences that may result by substituting nucleic acids (DNA or RNA).

Perhaps the highest degree of causal specificity in any factor other than nucleic acid[5] are chromatin modifications such as DNA or histone methylation and other chemical modifications that affect the transcriptional activity of some eukaryotic genes and can give rise to epigenetic

effects. It has even been suggested that there is a 'language' that maps modification states of the chromatin into gene expression patterns (Strahl and Allis 2000). Thus, among those factors that are actual difference-making causes with respect to an organism's proteome, there is a whole spectrum of degrees of causal specificity in different parts of the biochemical machinery of a cell.

5. Conclusions: A Middle Ground in the Causal Parity Debate?

I have shown that Crick's sequence hypothesis and the central dogma can be reconstructed as claims about the actual difference-making cause in protein synthesis. This reconstruction of Crick's claims is supported by the fact that it is expressible in terms of a philosophical theory of causation that has a very wide range of applications. A consequence of this reconstruction is that Crick's hypotheses apply only to prokaryotes and to eukaryotic mRNAs that are not subject to RNA editing and whose protein products are not post-translationally modified. As soon as nucleic acid is merely *a* rather than *the* difference-making cause, Crick's hypotheses as reconstructed in this manner fail. My analysis is also supported by the fact that Crick considered a certain type of evidence particularly strong, in particular the experiments of Fraenkel-Conrat.[6] This experiment can be construed as making exactly the kind of interventions that Woodward's account requires.

I have further shown that the notion of causal specificity is a special kind of Woodward-invariance, namely invariance of generalizations that range over finite sets of discrete variables. Depending on the size of these sets, we may speak of more or less causally specific relations. I have claimed that nucleic acid has the largest degree of specificity, but there are other cellular components that also have a considerable degree, for example, histone modifications.[7]

This last part of my analysis might allow the articulation of a middle ground in the debate over causal parity, that is, the claim that DNA and genes are causally on a par with other parts of a living cell or developing organism (also referred to as 'causal democracy'; see Oyama 2000).

[5] Note that environmental factors are no candidates for causal specificity because they are usually not *discrete* variables.

[6] Ingram's sickle-cell anaemia case could be given a similar analysis, with the one significant difference that Ingram was not able to *intervene* on the sickle-cell genes. This is not relevant for analyzing the *meaning* of Imgram's claims, but it somehow weakens the force of his experimental *evidence*.

[7] I was trying to make this claim already in my 2005b (Ch. 8) but did not yet have the powerful conceptual tools developed by Woodward and Waters available.

The way this debate has been framed, either there is a qualitative causal property that only DNA has and everything else lacks, in which case the causal parity thesis is false, or there is no such property, in which case the thesis is true. On the account given here, this qualitative property may be replaced by a *quantitative* one: causal specificity. Different parts of a cell may have different degrees of causal specificity with respect to a given dependent variable such as its proteome.

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