Constant Factors and Hedgeless Hedges:
On Heuristics and Biases in Biological Research

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How does a complex organism develop from a relatively simple, homogeneous mass? The usual answer is: through the execution of species-specific genetic instructions specifying the development of that organism. Commentators are sometimes sceptical of this usual answer, but of course not *all* commentators. Some biologists refer to master control genes responsible for the activation of all the genes responsible for every aspect of organismal development; and some philosophers buy this claim hook, line, and sinker. Here I explore both the seeming plausibility of the usual position, and also its ultimate inadequacy.

I

It is fair to say that biological phenomena are a messy lot. Though this may often be true in other domains as well, in biology, at least, a staggering number of simplifying assumptions must be made just to get a research programme off the ground. Historically, the most significant simplifying assumptions employed in genetics and developmental biology to date have resulted in the elision of the organism as both nexus and nadir of developmental interactions. Elsewhere, I explore how the methodological and conceptual framing of development in creative terms may fruitfully guide our investigation of development. Here I provide the first steps in that analysis.

The structure of the argument is as follows: I begin by establishing two widely agreed upon general premises of biological methodology; I then advance arguments in favour of three additional premises in the specific case of organismal development – again, these premises are granted by all concerned. Then I explore how two different readings of the second premise lead to two incompatible conclusions from the five premises, and proceed to provide an argument in favour of the less common but more plausible reading of the second premise.

II

Unlike Laplacean demons, human investigators have limited intellectual, computational, temporal, and financial capacities. Any system to be studied must be simplified in various ways to make it tractable for agents like us. We build simplified models because we are limited beings, and most of the systems we want to understand are too complex in their natural state. So we abstract from them what seem to be the most important or the most easily manipulated variables in order to generate a manageable representation of their workings. For present purposes, I define heuristics as *simplifying strategies to be used in situations of cumbersome investigational complexity* (Gigerenzer *et al.* 2000; Wimsatt 1980, 1986).

One crucial caveat about heuristics is that they are purpose-relative. As Wimsatt notes, "all instruments in the natural, biological, and social sciences are designed for use in certain contexts and can produce biased or worthless results if they are used in contexts that may fail to meet the conditions for which they were designed" (Wimsatt 1986, p. 297). Examples of this phenomenon include: the use of analysis of variance as a surrogate for the analysis of causes (Lewontin 1974; Sober 2000); the application of the methods of quantitative genetics where the assumptions of quantitative genetics do not hold (Pigliucci and Schlichting 1997); and the use of linkage analysis in psychiatric genetics where the conditions of successful linkage are not met (Robert 2000a). In using heuristics, then, we must be careful to select the right one(s).

That notwithstanding, without the use of heuristics we would be much further from solutions to biological problems than we are presently. Here, then, is the first premise, universally acknowledged:

1. Simplifying strategies and assumptions as such are absolutely necessary in biological science.

There are at least twenty reductionistic heuristics in widespread use today. These include heuristics used in conceptualization, model building, theory construction, experimental design, observation, and interpretation. Wimsatt (1980, 1986) has documented these heuristics, and also their characteristic biases. One of the most popular heuristic strategies is to simplify the *context* of a system under study. If we want to learn about intrasystemic causal factors – that is, if we want to learn about what's going on inside a particular system – we build a model or design an experiment wherein the context of the system is simplified, rather than the system itself. Of course, we sometimes have to do both, especially if the system of interest is particularly complex; in such a case, we might use another kind of reductionistic strategy. But the golden rule of experimental design is: simplify the context first. Hence, a second general principle of biological methodology:

2. Simplifying the context of a system is advantageous if we want to learn about intrasystemic causal factors.

The *Interactionist Consensus* on development (Kitcher 2001; *cf.* Sterelny and Griffiths 1999) captures the widely held view that both genes and environments (on many scales) are required for the production of some particular phenotype. Among those who hold to the Interactionist Consensus, one standard approach is to vary genetic factors against a common,

invariant background of environmental factors. Context simplification, instantiated as environmental control, is the basic methodological framework of the Human Genome Project (HGP). HGP scientists and others involved in generating sequence data isolated strands of DNA, cloned them, and employed a variety of techniques to ascertain their nucleotide sequence and their physical relationship to each other. Genomes, or even individual strands of DNA – the systems under study – do not exist in isolation from natural environments except in the pristine artificiality of the lab; moreover, there are good reasons to believe that the functions of strands of DNA cannot be understood in isolation from their organismal context (Nijhout 1990; Neumann-Held 1999; Oyama 2000). Nevertheless, the environments, broadly construed, of DNA were abstracted away and held constant in the effort to generate the consensus sequence of the human genome.[1] The context was simplified, the experimental work proceeded, and draft versions of the genome sequence are now at hand.

In the case of the HGP, despite occasional slips to the contrary, biologists are careful in employing the strategy of context simplification. For instance, with a few notable exceptions (such as Hamer and Copeland 1998), very few scientists or commentators would today suggest that either nature or nurture is singularly decisive in organismal development. Despite the standard use of experimental or interpretive techniques to partition causation into internal (natural, genetic) and external (nurturing, environmental) components, techniques which may be unable by their very design to detect interactions between genes and environments (Wahlsten 1990; Sarkar 1998), most scholars grant that phenotypic traits arise from complex, possibly nonadditive, interactions between multiple factors at many hierarchical levels.

But not all varieties of interactionism are equivalent, and a vigorous debate has arisen

[1]The same is true, of course, of the genome sequences of model organisms, such as the mouse and the nematode

over which varieties in fact take interaction seriously, and which simply pay lip service to interaction in a reflexive refrain masking secret adherence to the old nature/nurture debate. This debate will figure prominently below in the discussion of how best to interpret the second promise. For now, I want to briefly spell out three additional premises, again universally granted, which are employed as additional steps, beginning with the first two premises, in (roughly) a chain of argument putatively leading to two alternative conclusions.

The third premise, already alluded to, states that:

3. Genes by themselves are not causally efficacious, as genes and environments (at many scales) interact (differentially, over time) in the generation of any phenotypic trait.

Scientists regularly declare the nature/nurture debate dead, settled in favour of both (e.g., Goldsmith *et al.* 1997). There are no (overt) genetic determinists these days, even though some environmental determinists persist (usually in an effort to ward off the spectre of genetic determinism). But, in the main, "nowadays it seems that everybody is an 'interactionist'" (Gray 1992, 172). So much so, in fact, that those perceived to be stirring the ashes of the nature/nurture debate are called apparently nasty names (typically "ideologue" or "Marxist") and relegated to the periphery of accepted scientific practice. This is the legacy of the Interactionist Consensus.

The fourth premise is a methodological one, designed to permit investigation of interacting variables in development (in line with premises one and two):

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worm.

4. We decide to focus on the causal agency of genes against a constant background of other factors, for pragmatic or heuristic reasons.

I mentioned at the outset that experimental tractability is a core scientific *desideratum*. It is nice to imagine the world as full of interconnected parts not meaningfully separable from each other; but just to try analyze the world so-imagined and science grinds to a halt. It turns out that genes are much more experimentally tractable than a wide range of other interacting factors and agents. This may be, of course, simply because we have spent so many decades perfecting techniques for genetic manipulation, and that huge amounts of money are available for such activities compared with others (Griffiths and Knight 1998, 255). Given the enormous amount of money available to study gene sequences, it is little wonder that genetic manipulation is quite easy compared with the experimental manipulation of other factors in development.[2]

What we identify as a cause has its causal effects only in combination with additional necessary conditions (which, for other pragmatic reasons, might have themselves been identified as causes). This idea is epitomized in our fifth and final premise, one that may seem more controversial than the first four but is nonetheless universally acknowledged:

5. We may explain the presence of some trait *X* as caused by some gene *Y* only against a constant background of supporting factors (conditions), without which *X* would not be present.

[2] Though the details cannot be explored in the time permitted, there are at least two scientifically well-regarded philosophical analyses justifying premise four (Schaffner 1998; Gannett 1999).

Prima facie, given premise two, this fifth premise is a close relative of premise three. Variations on this fifth premise have been employed as definitions of a "genetic trait". Consider Sterelny and Kitcher's sophisticated treatment (1988, 350):

> An allele *A* at a locus *L* in a species *S* is for trait *P** (assumed to be a determinate form of the determinable characteristic *P*) relative to a local allele *B* and an environment *E* just in case (a) *L* affects the form of *P* in *S*, (b) *E* is a standard environment, and (c) in *E* organisms that are *AB* have phenotype *P**.

In other words, as long as that particular allele, in genetic and standard environmental context, is associated with the relevant phenotypic outcome, then that particular allele may be deemed an 'allele for' that phenotype. Given the necessity of simplifying assumptions (premises one and two), as long as we recognize the critical contextual qualifications (premise three), and also that we focus on allele *A* for heuristic and pragmatic reasons (premise four), then we may deem premise five to be a plausible singling out of a gene as a cause in organismal development. So far, so good.

The conclusion usually derived from these five premises taken together is this:

6. Therefore, against standard background conditions, organismal development is a matter of gene action and activation, as particular alleles have their specific phenotypic effects in standard environments.

Hence, our standard explanation for why organisms develop as they do: there is a program or set

of instructions for development inscribed in the genes. Of course, genes alone do not an organism make; the genetic program must be activated or triggered – there is no unmoved mover in the world as we know it; and the DNA must be suitably housed in appropriate cellular and extracellular contexts, which may themselves be very complex, in order for development to proceed. But, given these caveats, the specificity of development – the reliable, trans-generational reconstruction of form – is widely held to be best explained as a matter of gene action and activation.

But is that in fact true? My answer is that it is not, though we all happily agree with the five premises thought to generate it. Are we then illogical or, worse, illogical because ideologically motivated? Or is it rather the case that the five universally acknowledged premises do not actually generate the inference to the usual conclusion? My thesis is that the inference to the orthodox conclusion is invalid, that the conclusion does not follow from the premises we have before us.

The problem involves two mutually exclusive readings of the second premise detailed above. Recall that premise two stipulates that "simplifying the context of a system is advantageous if we want to learn about intrasystemic causal factors". Context simplification is usually achieved by holding certain factors constant while solving for others. Decisions about what to hold constant and what to investigate are pragmatically motivated, as alluded to earlier (Gannett 1999). But the pragmatic dimension of these decisions renders premise two crucially ambiguous: what counts as a system is not a matter of objective determination, but is itself influenced by pragmatic factors, such that what counts as intra- or extra-systemic is a matter of decision and not, as it were, thrust at us by nature.

III

Several systematic problems (what Wimsatt calls "biases") are associated with environmental control as a context simplifier. First, context simplification is biased toward lower explanatory levels; that is, simplifying the environmental context stems from, and leads to, focusing on simple components of a system. Higher-level components of systems, and higher level systems, are legislated out of epistemological and methodological existence in favour of lower-level systems and their components. Consequently, an investigator who simplifies the context in line with premise two may well be guilty of simplificatory asymmetry (Wimsatt 1986, 300-301). Secondly, we may be prone, should we forget or fail to appreciate the gravity of the simplifying assumption, to draw unjustified causal inferences; it is remarkably easy to fall into the trap of generating causal stories about genes against a constant environmental background (which itself exists only in the laboratory) – hence our fifth premise. We must be eternally vigilant, in simplifying the context, not to exaggerate the conclusions we infer. The strategy of context simplification is extensively employed in investigations of the role of genes in development, usually in the form of "environmental control", according to which one holds environmental variables constant or, worse, actually comes to believe that the environment simply is invariant (302).

I suggested that premise five strikes us as justified by appeal to premises one through four. But there is no necessity in my particular formulation of premise five, nor in Sterelny and Kitcher's instantiation of this premise. Consider that, by parity of reasoning, we might just as well have (again for some pragmatic reason) postulated, not an 'allele for' *P**, but rather an 'extracellular environment for' *P** given standard allelic, cytoplasmic, and other environmental contexts (Gray 1992; Smith 1992; Mahner and Bunge 1997; Robert 2000b). That we do not

postulate such 'extracellular environments for' does not imply that they do not exist; it implies, rather, that we have decided, for whatever reasons, that 'alleles for' are more important to establish. We are thereby guilty of explanatory asymmetry inasmuch as we *a priori* construe the relevant system in strictly reductionistic terms, thereby inviting inference to the conclusion that development is a genetic affair.

This result is fostered by only one of the two possible interpretations of premise two. In fact, both interpretations are heuristics in their own right. I shall refer to the suspect one as the 'hedgeless hedge' heuristic; the other is the 'constant factor principle' heuristic. The phrase 'hedgeless hedge' is owed to McCain (1980), who diagnosed hedgeless hedging as a major limitation of early sociobiological thinking, but the notion is more broadly applicable.

A typical definition of "hedging" is: protecting oneself from loss or failure by undertaking a counterbalancing action, as in hedging one's bets by not placing all one's eggs in a single basket. "Hedgeless hedging" is a win-win strategy, denoting a fail-safe type of hedging: one puts virtually all one's faith in *A* and relatively little in *B*, and then attempts to establish *A* but not *B*; but betting on *B* at all (say, by publicly announcing that *B* is true, likely, or possible) provides a measure of safety just in case *B* and not *A*. Less formally, in proceeding according to the hedgeless hedge heuristic, "one admits the existence of an anomaly or problem of theory and then proceeds as though one had not. If one is then accused of neglecting the anomaly, one then produces the admission of its existence as conclusive evidence of one's innocence of the charge" (McCain 1980, 126). The hedgeless hedge is well-characterized as a simplifying assumption, in particular a simplification of context: one admits the implausibility of the assumption, but proceeds with the simple model nonetheless, generating results inadequate to the reality of the situation; when challenged, one refers back to the original admission of implausibility for

exoneration.

McCain's example of this strategy is sociobiologists' treatment of inheritance. While complexes of many genes are involved in the generation of any trait, for purposes of tractability early models of sociobiological inheritance (such as E.O. Wilson's)[3] reverted to one-locus theory, according to which we assume that one and only one gene is associated with a given inherited trait. As Wilson's mathematical models depend so heavily on one-locus theory, and the assumption of single loci is so inadequate to the reality of both inheritance and development, the model is rendered immediately suspect. McCain observes that Wilson is well-aware of his simplifying assumption, and Wilson notes that future models will have to take polygenism into consideration. But to take polygenism into consideration is completely to undermine the model on which Wilson's treatment of sociobiology rests – so much so that the one-locus model itself is rendered virtually worthless. And yet admitting the limitations of the model functions as a hedge against the probability that the model is in fact not at all a good one.

The hedgeless hedging heuristic shares with all heuristics the property of fallibility, which is a function of the cost-effectiveness of heuristic-use. But the failures of heuristics tend to be systematic rather than random, such that we might identify their failures and correct for them (often by applying a new heuristic). That is, thanks to the systematic biases of simple heuristics, we are able to learn from our false models in generating truer, more complex theories (Wimsatt 1987). What is unique about the hedgeless hedge is that the limitations of the heuristic are so obvious that, even though a hedgelessly hedged model may initiate the production of more adequate models, such models will themselves be so drastically different from the original model that its catalytic role may be overestimated. Moreover, the hedgeless hedge heuristic wears its

[3]McCain discusses Wilson's treatment in the latter's *Sociobiology: The New Synthesis* (Cambridge: Harvard

bias on its sleeve, implying that its putative openness is sufficient to make the heuristic appear honest and true. Unlike other context simplification heuristics, the hedgeless hedge heuristic contains within itself the additional mechanism of theoretical exoneration, thereby providing an excuse for denying, say, complexity while nonetheless admitting the existence (and importance) of such complexity.

There are abundant examples of hedgeless hedging in biological research. In the context of developmental biology, they may be construed as instances of paying lip service to interactionism. Many of these examples concern a curious phenomenon, one that Lloyd (1999) refers to as "ritual recitation" (my "reflexive refrain"), whereby investigators favourably cite the papers of those who have challenged the investigators' theoretical framework, perhaps to demonstrate awareness of the ideas of detractors, but then proceed as if there are in fact no problems with the framework. According to Lloyd, there is "a peculiar disconnect between what the authors explicitly acknowledge as serious theoretical and evidential problems, and how they actually theorize and evaluate evidence" (225).

In illustrating this claim, Lloyd discusses the emerging field of evolutionary psychology. According to Lloyd, central texts in evolutionary psychology (e.g., Barkow *et al*. 1992; Cosmides and Tooby 1995) are rife with footnotes citing, for instance, Gould and Lewontin's (1979) paper on the limits of adaptationism, indicating awareness of problems of pan- or hyper-adaptationist evolutionary theory, and sometimes acknowledging the need to avoid committing the errors Gould and Lewontin warn against. But, as Lloyd shows, these citations are smuggled into papers and monographs expressly giving adaptation by natural selection an exclusive role in the evolutionary origin of phenotypic traits. Accused of naive adaptationism, the authors may

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University Press, 1975).

simply point to the references as putative evidence of their innocence. The issue here, as elsewhere, is "a matter of the *actual weight given in practice* – not in lip-service" (Lloyd 1999, 226) to the *B* term of the hedgeless hedging heuristic.[4]

IV

How, then, are we to avoid paying lip-service to interactionism? What we need is a better, less suspect variant of a context simplification heuristic, a more honest one, one more adequate to investigating biological reality, and one less likely to yield inference to an inappropriate conclusion from our five premises. Following Woodger (1952), I refer to this alternative variant of the second premise as the "constant factor principle" heuristic.

Woodger noted the importance of heuristics in biological experimentation. For Woodger, as for others, the assumption of constant factors is often a necessary simplifying strategy in order to achieve experimental tractability. In attempting to understand how genes function, for example, we may assume that the environment is a constant factor; against a constant environmental background, we may then solve for phenotypic differences by exploring the genotype (the variable factor) (Woodger 1952, 186). Where such differences are found, we may account genetically for the existence of variations. The heuristic assumption of constant factors is methodologically legitimate and commonplace, but it is by no means infallible, as should be evident from the discussion thus far. Nonetheless, I will urge here that Woodger's "constant factor principle" heuristic works against the particular biases of the hedgeless hedge heuristic,

[4]Ritual recitation as an instance of hedgeless hedging is evident in philosophical commentaries on biology, as well as in actual biological practice. But philosophers tend to go beyond ritual recitation in their application of the hedgeless hedge, building more sophisticated safeguards into the heuristic. An exemplar here would be Rosenberg's (1997) use of this heuristic in his critical analysis of physicalist antireductionism. For an extended discussion of hedgeless hedging (though not referred to by that epithet) in the case of genetic research on the aetiology of schizophrenia, see Robert (2000a).

and so is a more legitimate simplification heuristic.

Considering Woodger's own example permits a further bias of context simplification through holding factors constant to emerge. The strategy of solving for genes by holding the environment constant presumes that there are only two sources of variation: genetic or environmental. But other potential sources of variation are stochasticity (Lewontin 1995) and epigenetic interactions, neither of which is, strictly, genetic or environmental – they result from development as such (Molenaar *et al*. 1993). Especially instructive is the work of Gaertner (1990) who, over a period of thirty years, developed genetically identical strains of laboratory mice and rats, and reared them under identical environmental conditions – and yet the mice and rats that were, nonetheless, phenotypically *non-identical*, thereby demonstrating the existence of a neither-genetic-nor-environmental source of ontogenetic variation. Thus, phenotypic differences against a constant environmental background may not legitimately be presumed to be genetically based (or environmentally based), even though some versions of context simplification heuristics simply do not guide us to investigate alternative possibilities.

But the most encompassing problem with simplification heuristics, especially as instantiated in hedgeless hedging, is the tendency to downplay or simply neglect the causal significance of those factors held constant. This is, as it were, the practical fallout of the hedgeless hedge heuristic. Consider loss-of-function experiments. A typical loss-of-function experiment is one in which, against a constant background, a particular gene is manipulated so that it is not expressed at the right time and place; the investigators then observe the phenotypic outcomes and conclude that the outcomes are caused by the misexpressed gene. But often investigators will draw an additional, unwarranted conclusion, namely that the gene, when properly expressed, is itself causally responsible for the correct phenotypic outcome. But this

latter inference simply does not follow. As Keller (1994, 90) notes, "such an inference appears to make sense only to the extent that the entire physical-chemical apparatus of the organism and its environment are effaced".[5]

Holding factors constant is a good and necessary part of proper science. *But effacing their causal importance is not.* It is for this reason that we should prefer Woodger's constant factor principle heuristic over other simplifying strategies as a methodological heuristic in making and interpreting experimental assumptions. The constant factor principle heuristic asserts that, "if, in a series of experiments, certain factors are constant, not necessarily in the sense of unchanging in time, but in the sense of being of the same kind in each experiment, then *nothing can be asserted on the basis of those experiments about the role of such constant factors in the production of the observed result*" (Woodger 1952, 186; italics added). Prohibited assertions, according to the constant factor principle heuristic, include claims that the constant factors "'play no part' in the processes involved", or that they play only a supportive role. Different experiments, perhaps different sorts of experiments, are required to establish the latter results; they cannot be inferred from scenarios in which the constant factors are never varied.

Immediately, then, we see that the usual conclusion (6, above) cannot be validly inferred if premise two is interpreted according to the constant factor principle heuristic. As long as premise two is interpreted as an invitation to hedge hedgelessly, then our near-universal presumption that genes are more causally relevant than other factors in development generates the conclusion that development is best explained as a matter of genes operating against a constant background of supportive conditions. But if premise two is interpreted along the lines

[5] In a review of loss-of-function experiments involving homeobox genes in the mouse skeleton, Smith and Schneider (1998) are highly critical of a number of studies in which such an illicit inference is drawn, usually as part of a more general claim of the evolutionary role of the homeobox genes in producing skeletal novelties.

of the constant factor principle heuristic, then we are free to imagine (and explore) other scenarios for premise five (such as the notion of an 'extracellular environment for'), and are thus less likely to imagine the validity of inferring the orthodox conclusion. Hence the alternative reading of premise 2:

> 2'. Simplifying the context of a system (the definition of which is contingent) is advantageous if we want to learn about intrasystemic causal factors, but we must not neglect the possible importance of those contextual factors we abstract away.

Note that there is also another, more fundamental, source of the usual conclusion, attendant on the use of heuristics more generally. Even in applying a well-chosen heuristic to a particular problem, a caveat to bear in mind is that the application of the heuristic transforms the problem into one for which an answer is available. Yet, as the new problem is "nonequivalent but intuitively related" to the original problem, *we are no longer in fact solving for the original problem* (Wimsatt 1986, 295). In the case under discussion, our original problem is to explain how a specific complex organism arises from a single, relatively homogeneous cell. When the transformation goes unnoticed, we may believe we have indeed solved the original problem. It is for this reason that the core problem of embryology is not, *pace* Rosenberg, entirely solved by developmental genetics. The translation of embryology's hard problem into a problem about gene action and activation generates explanations at the level of genes; but these explanations solve (or, rather, *begin* to solve) the subsidiary problem of the role of genes in development, not the problem of development as such. The trick, ever more apparent now that we have the human genome sequence at hand, is to integrate these explanations with other developmental (cellular,

environmental, ecological) phenomena within a larger organismal framework, rather than to assume, with Rosenberg (1997), for instance, that we understand development because we are beginning to grasp gene function.

With premise two satisfactorily interpreted according to the constant factor principle heuristic, we are invited to infer the following from premises 1-5 (replacing 2 with 2'):

> 6'. Therefore, against standard background conditions, aspects of organismal development may be partially explained as a matter of gene action and activation, and it remains to be determined whether (and how) extragenetic factors make a specific causal contribution to ontogenesis.

Due to the limitations of the sorts of experiments undertaken thus far, we just do not know enough about development to conclude that the specificity of development is a matter of genetic information; and given much recent work in developmental biology and the philosophy of biology, we will often have good reason to be suspicious of any such claim. An appropriate interpretation of premise two, coupled with non-genocentric variations on the fifth premise, demands further, broader exploration of causal factors in development.

The constant factor principle heuristic is more satisfactory methodologically than either context simplification *simpliciter* or hedgeless hedging just because it provides grounds to avoid the biases of context simplification, and moreover because it guards against the particular biases of hedgeless hedging. But though the constant factor principle heuristic, a heuristic principle to which Woodger claims "most people would give their assent – indeed it is a commonplace of experimental procedure", is a better heuristic, it is itself subject to systematic bias. Woodger

himself remarks that it has "more than once been forgotten in connexion with genetical problems" (1952, 186). Nevertheless, in cautioning against interpretive folly even while promoting the necessity of simplification, the constant factor principle heuristic is a superior guiding principle.

V

How does the constant factor principle heuristic work in practice? What is its cash value? Consider that if, as Woodger holds, nothing can be inferred about the causal contribution of constant factors in a particular experiment, then we are compelled to undertake different sorts of experiments, varying other factors serially and then integrating the results of the serial experiments.

It must be underscored that in conducting such serial experiments, we must be wary of the kind of simplificatory asymmetry Wimsatt cautions against in the use of particular heuristics. For as long as the factors to be varied are restricted solely to the class of systemic or intrasystemic variables (against a constant environmental or extrasystemic background), a systematic bias in favour of the model system's independence of the environment may emerge – and yet go unnoticed (Wimsatt 1980, 233; 1986, 302-303). So a full application of the constant factor principle heuristic requires appreciating the insight that "what one must control is a function of what relationships one is studying" (Wimsatt 1986, 303) and also what we count as comprising our particular system.

If one is interested only in causal relationships independently of environmental context, then one conducts experiments in which the environment is held constant – which is fine, as far as it goes, although the constant factor principle heuristic cautions that interpretation of the

results must be constrained by admission of the limits of the experiment. Such constrained interpretations are few and far between, though, as evinced in recent discussions of what we can expect now that the human genome has been sequenced. But if one is interested in more complete causal analysis, the kind of analysis affording fewer and less onerous interpretive constraints – the kind of analysis legitimately yielding interpretations of real-world significance – then environments cannot be universally held constant.

There are several ways of proceeding toward this end through the constant factor principle heuristic, and I will briefly mention two. One is to adopt the perspective of methodological systemism. Systemism functions as a sort of middle-ground between reductionism and holism, according to which systems are ontologically and epistemologically irreducible to either their composition, their structure, or their environment. As a method, systemism requires theoretical and experimental attention to all three aspects of the system – not all at once, of course; serial experiments will do, as long as the variables cut across environmental, compositional, and structural levels.

Though examples of this sort of approach are relatively rare, one particularly nice instance is Lehrman's experiments on reproduction in ring doves (Lehrman 1965; Gray 2001, 201). The factors that Lehrman and colleagues serially varied are not restricted to any single system level: nest-building behaviour, 'doses' of male courtship, hormone levels, and so on. Having varied one factor, the investigators measured the effects on the system; then having varied another factor, they measured again. The end result is a much more complete analysis of causation than would have been afforded by simply holding the environment constant. With more sophisticated statistical and experimental techniques, it is of course possible to vary more than one factor at a time, generating a still richer perspective.

A second method for generating similarly robust results is to engage in multidisciplinary investigation of the sort becoming commonplace in the new field of evolutionary developmental biology. For instance, Brakefield and colleagues, in their work on eyespot patterns on butterfly wings, brought together tools from population genetics, evolutionary biology, ecology, developmental biology, and developmental genetics in a series of experiments that, taken together, provide an amazingly rich overview of the developmental mechanisms and evolutionary trajectories of this particular aspect of butterfly wing morphology.[6] Such an integrative, even synergistic approach is indicative of future prospects in developmental biology – despite occasional ill-informed protestations (such as Rosenberg's) that methodological reductionism is the only way forward.

Multi-leveled, multi-disciplinary analysis – appropriately heuristically informed – is the surest route for generating results adequate to the complexity of the biological world, though from a comparatively simple, tractable, starting point. Such results are now beginning to be seen, and will eventually enable us to have a fuller understanding not only of the roles of genes in development, but of organismal development as such.

[6]See Brakefield *et al.* (1996); Brakefield and Kesbeke (1997); Brakefield (1998, 2001); Brakefield, Kesbeke, and Koch (1998); Brakefield and French (1999); Roskam and Brakefield (1999); and Oosterhout and Brakefield (1999).

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