Macromolecular Pluralism

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Different chemical species are often cited as paradigm examples of structurally delimited natural kinds. While classificatory monism may thus seem plausible for simple molecules, it looks less attractive for complex biological macromolecules. I focus on the case of proteins that are most plausibly individuated by their *functions*. Is there a single, objective count of proteins? I argue that the vagaries of function individuation infect protein classification. We should be pluralists about macromolecular classification.

1. Introduction. It has seemed to many philosophers that chemistry was a bastion of monism—roughly, the view that there is just one good way of dividing things up. On the other hand, things get messy in the biological world. The thesis that species have microstructural essences has fallen on hard times. Pluralism now dominates in biology. So goes conventional wisdom. This neat domain division, however, is too simple. I propose to address a case somewhere in the middle. Should we treat biochemical kinds monistically or pluralistically? In particular, I shall focus on the status of proteins.

Biochemists sometimes tell us that the typical human body possesses 100,000 proteins—referring not to the number of individual molecules in the typical human body, but to the number of distinct *kinds* of proteins typically found in the human body. But how should we count? How do we individuate these biological beasts of burden to make the claim come out (approximately) true?[1]

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1. Of course, the phrase "the typical human body" introduces (related) complications that far exceed the scope of this article. But as nothing substantive for the issue of

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Following the lead of natural kinds essentialists of old, one might suggest individuating proteins (and other biological macromolecules) on the basis of their chemical structure. At first glance, this stance affords a tempting monism about biochemical taxonomy. But it is a costly and ad hoc monism. For there are several plausible contenders for the concept of a protein's structure, none of which accommodates biological practice (see Section 2). While structure clearly plays a role in biochemical research, it often plays second fiddle to biochemical function when it comes to biochemical taxonomy (Section 4). However, counting proteins by functions introduces complications that strongly legislate for taxonomic pluralism (Section 5). I tentatively conclude that pluralism about proteins best accommodates scientific practice and our present philosophical resources.

2. An Embarrassment of Riches. Proteins, recall, are polymers of amino acids—"polypeptides"—their order "coded" by DNA. They serve as enzymes (catalysts for biochemical reactions) and structural features of our cells and bodies; they cause our hearts to pump and allow our blood to carry oxygen. They achieve these and countless other feats in large part because of their complex and multilevel structures.

To acquire its characteristic biochemical dispositions, a protein must usually be "folded." From a protein's initial *primary structure* (its amino acid sequence), it usually acquires regular regions of *secondary structure* (e.g., α-helices and β-pleated sheets). Its *tertiary structure* consists in the subsequent three-dimensional folding of these structures. *Quaternary structures* form when multiple subunits with tertiary structure become complexed together. All this structure (at various levels of complexity) might seem a structure-obsessed monist's dream. It's really a nightmare. In the first place, the monist must apparently decide which of these various levels of structure is relevant to a protein's kind.[2] But any choice involves serious compromise.

Consider primary structure. An amino acid sequence alone has no direct link with a protein's ultimate biochemical role. The same amino acid sequence can be folded into a variety of different tertiary structures with different biochemical dispositions and functions. Though one hears of "optimization studies" in which the three-dimensional structure (i.e., tertiary or quaternary structure) of a protein is surmised by computer simulations, these must take into account their different contexts and interactions. While many proteins fold more or less spontaneously into their

macromolecular classification turns on how or if we understand this notion, I leave it unanalyzed here.

2. There is room here for a monist to press: perhaps her monism could be, as it were, "dappled"—employing some levels of structure in some circumstances and other levels in other circumstances. I explore this response in Section 3.

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active forms (as a low-energy conformation), many require a delicate dance of helper proteins, playfully referred to as 'chaperonins', to assist in folding. Different biochemical milieus also make a difference. Certain amino acids have hydrophobic residues and hence, in aqueous environments, tend together toward the center of the protein globule. They are held together—like antisocial members of an agoraphobic society—only by common aversion.

Even in the same biochemical context, the same sequence of amino acids may take on multiple conformations. So-called dual-topology proteins—for which the direction of insertion and orientation of the protein subunits depend only weakly on their charge characteristics—have recently come to light. It is hypothesized that the possibility of assuming multiple conformations within cells' plasma membranes may in fact be crucial to their characteristic function (see Rapp et al. 2006). All these points apply equally to a polypeptide's secondary structure.

Thus, just as individuating chemical kinds by their ingredients significantly undercounts the variation introduced by different structures (hence 'isomers', from 'same parts'), counting proteins by primary or secondary structure is thus apt to count too few. This stance presumes, of course, that the individuation of proteins will to a certain extent represent important biochemical facts about them. Tertiary and quaternary structure—the level at which the majority of a protein's enzymatic prowess is realized—might thus seem better candidates. For it is the particular three-dimensional folding of a polypeptide that confers a protein's enzymatic specificity. As the well-worn analogy has it, enzymes "recognize" their substrates rather as locks recognize their keys.

How should we understand tertiary structure? A natural suggestion would be to treat it as simply analogous to chemical structure. The examples are familiar. When asked to describe the structure of H_2O, we respond that an oxygen atom covalently bonds to two hydrogen atoms in a "bent" shape. We might go on to explain the tetrahedral orbital structure, the average bond angles that result, and so on. Such models can take physical form (think of Watson and Crick's model of the DNA double helix), but it is well to remember that they are models. The angles between the pieces of wood in a "ball and stick" model do not straightforwardly describe the *essence* of any protein. Individuating proteins—or, indeed, any other molecule—by such a condition casts too fine a net. At any given time, extraordinarily few if any water molecules have precisely the same bond structure—for molecules are not static entities.[3] The complexity of proteins only magnifies this problem.

3. There might even be a question about whether the notion of precise bond angles makes good sense in the context of quantum mechanics.

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More nuanced approaches to chemical structure are surely possible. Instead of describing various constituents united by bonds with certain precise internal angles, we might specify a *range* of bond angles through which a molecule of a certain kind might traverse. The essence of chemical kind could be represented as a volume in a certain kind of variably dimensional space depicting atomic connection, bond length, and angle ranges (among other potential parameters). Chemical kinds on this model would be clumps in a sort of abstract state-space.

Whatever the plausibility of this model is for "micromolecular" kinds—and it would take some spelling out—it seems far less plausible for macromolecular kinds. Molecular simulations reveal that the tertiary structure of many proteins undergoes dramatic changes. Remember: only the primary structure is held together by covalent bonds; tertiary structure accrues from hydrogen bonding and other weak intermolecular forces, perhaps at only a few points. Imagine a long hose fixed with magnets at certain points along its length which, when folded up, stuck together. Even if those magnets were strong, the structure of the folded hose might yet "flop around" a bit. This analogy suggests an alternative model. Perhaps we should understand a protein's tertiary structure as a series of nodal "connections" (if weak) at different spots on the polypeptide chain. But this too underestimates the extent of a polypeptide's flexibility, as I shall explain below.

It might be objected at this point that molecular biologists *do* speak of a protein's structure—they invest large sums of money and many computing clock-cycles trying to determine their structure, after all. Molecular biology texts and journals include scores of pictures and three-dimensional representations of these structures. The devil may be in the details, as usual, regarding how specifically to understand a protein's structure—but what are these representations *of* if not protein structure?

While molecular biologists do indeed speak this way, it's rarely (to my knowledge) in the context of describing a protein's *essence*. It is well to remember that the X-ray crystallographic techniques often used for elucidating a protein's structure require precipitating and crystallizing a quantity of the protein, stopping (or anyway *significantly slowing*) its native motion. These "snapshots" no more capture the essence of a protein than a single satellite photo does of a hurricane. More importantly, a protein's motion—the normal structural change it undergoes—is often crucial to its catalytic activity. Proteins are structures in motion.[4] Emil Fischer's long-standing static "lock-and-key" model of enzyme-substrate interaction—where target molecules fit precisely like molecular keys into

4. I owe this neat turn of phrase to Moira Howes.

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the larger rigid protein lock where the reaction is catalyzed—has been replaced by Koshland's (1958) "induced-fit" model. For Fischer's model makes sense of the target specificity of proteins but not their enzymatic activity. As Matthews and van Holde put it, "a lock does nothing to its key" (1996, 368). Consider hexokinase, the first enzyme involved in glycolysis (the digestion of glucose). When a glucose molecule binds to this enzyme's active site, it initiates a significant conformational change in hexokinase that initiates the phosphorylation of glucose to glucose-6-phosphate (i.e., adds a phosphate ion to the sixth carbon of the glucose molecule), leveraging the energy stored in an ATP molecule.

Other "protein machines" like the tetrameric sodium-potassium pump employ similar coupling reactions to power a repeated "airlockesque" motion that pushes ions across cell membranes against their concentration gradients. Another protein, ATP synthase, in turn harnesses the energy of these concentration gradients rather like a turbine to catalyze further reactions. Characterizing tertiary and quaternary structure by elaborations of the foregoing models begins to appear forlorn.[5]

Perhaps we should take instruction from the machine analogy. A suitably competent and well-equipped engineer might, after all, construct a jet engine from a static plan or description. The analogy is not perfect. Jet engines are composed of materials and at scales at which quantum effects do not hold significant sway—but put that aside. Is it not the case that *whatever* a protein's dynamics, those dynamics are dictated by features that are somehow describable? A monist need cleave only to the in-principle possibility of such descriptions, not to their practical possibility. But the monist would also seem to have to answer a difficult further question: Why is this description (be it a range of precise descriptions, a volume in a state-space, or whatever) *what it is* to be a certain kind of protein? What about the world defines this (nonarbitrary) range of possible precise, static structures? Even if our abstract state-space features some actual clumping, this need not correspond to clumping across a wider range of possible worlds.

The monist encounters this embarrassment by taking the range of natural grouping to be properly part of the world. Withdrawing this claim by allowing that, strictly speaking, as the individual molecules of giant protein jiggle, they instantiate distinct "infimic kinds" (Ellis 2001, 3) avoids the embarrassment. It also forces the monist to bite a bullet: whereas we thought there were around 100,000 proteins in the human body, there

5. My argument is perhaps limited by my imagination. Richard Boyd has suggested to me that we might wish to think of natural kinds as *processes*. While the proof is in the pudding, my hunch is that this elaboration would alleviate some problems and introduce new ones. I cannot address this suggestion in an article of this length.

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may in fact be *continuum-many*. However, if monism is properly regarded as a thesis about what natural kinds there are, rather than about the systems of classification that characterize them, the monist can candy coat this bullet. So long as real kind distinctions are only ignored (rather than imputed), a plurality of pragmatically motivated systems of classification might sit atop a plenum of natural kinds. I believe that this kind of radical monism is harder to unseat than may initially appear.[6] So it goes with bit bullets. At best, we can push the radical into further radicality—for example, by pointing to the role of extrinsic properties in determining a protein's classification and thus inviting division of the infimic kinds on the basis of these as well. In such a case, there would be as many kinds as individuals (Ruphy [forthcoming] discusses this suggestion in the case of stars), a rather unpalatable position about which I'll have nothing more to stay here. Can monism be maintained by less radical means?

3. Function's Attractions. The monist might attempt to better mirror the kind distinctions biochemists actually make by abandoning the presumption implicit above that individuating natural kinds of proteins requires cleaving to a single level of structure as relevant. A more opportunistic approach might thus adopt a "mixed stance"—"dappled structuralism," we might call it—picking out primary sequences in some cases and (somehow) tertiary structures in others. However, one might fairly worry either that such decisions would be merely arbitrary, not reflecting anything about what natural kinds actually exist, or that any "mixed" approach to what level of structure was appropriate for a given object would already presuppose some conception of what that object's kind was.

Setting aside these problems, "dappled structuralism" coheres less well with scientific practice than it might initially seem. Consider the enzyme alcohol dehydrogenase (ADH), which catalyzes the conversion of ethanol to the hangover-inducing acetaldehyde. Insofar as the catalysis involves motion, primary structure would appear to be the indicated choice: there's just one kind of protein here, not continuum-many very slightly different kinds of proteins. But even in this case, counting by primary structure plausibly counts too many kinds of protein. For ADH comes in many "alleloforms"—very slightly different polypeptide sequences whose differences happen to be inconsequential to the protein's tertiary structure

6. I discuss the monist strategy in more detail in my 2005 article.

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and biochemical function.[7] In most populations of the fruit fly *Drosophila melanogaster*, for example, ADH comes in two variants called "slow" (ADH^S) and "fast" (ADH^F), named after their speed through an electrophoresis gel. As Ridley puts it, "the *enzyme* called alcohol dehydrogenase is actually a class of two *polypeptides* with slightly *different amino acid sequences*" (2003, 83; my emphasis). Since normally such differences are inconsequential to the enzymatic activity of ADH, ADH^S and ADH^F are regarded as of a single kind of protein.[8]

The appeal of this sort of dappled structuralism is an artifact of the importance of function for actual biochemical taxonomy. Suppose for the moment that we possessed a satisfyingly deep philosophical account of biochemical function that upheld ordinary scientific intuitions. How might we put it to work as the selection criterion properly sought by the monist? Individuating proteins by their primary structures failed to recognize the different tertiary structures they could attain and thus the function they might perform. The very same polypeptide sequence might get differently folded within a cell membrane to function in signal transduction or as a transcription regulator within different cells. How many kinds of proteins have we here? We hardly hesitate in answering "two," counting by their distinct functions. A cheer for functional individuation! On the other hand, individuating proteins by tertiary structure either forecloses on grouping as a kind the various structures whose motion performs a certain function or leaves wide open the question of what "dynamic range" of structures correspond to a kind of protein. Shifting our focus to *functional* individuation allows us to put aside the complexities of structure—perhaps identifying occasional extensional overlap between structure and function ascriptions—and retain our monistic faith. So goes the optimistic thought. A second cheer!

7. There are various levels of variation: In *Drosophila* ADH, "the amino acid difference appears as a base difference in the DNA, but this was not the only source of variation at the DNA level. The DNA is even more variable than the protein study suggests. At the protein level, only the two main variants were found in the sample of 11 genes, but at the DNA level there were 11 different sequences with 43 different variable sites. . . . At the level of gross morphology, a *Drosophila* with two ADH^Fgenes is indistinguishable from one with two ADH^S genes; gel electrophoresis resolves two classes of fly; but at the DNA level, the two classes decompose into innumerable individual variants" (Ridley 2003, 84).

8. Isn't this just the case of jadeite and nephrite? It is related—but there, function ascription played no role in answering the question of whether jade is a natural kind of stuff. I have purposefully avoided entering into the debates about multiple realization here, fearing that it would take us too far afield and cause more confusion than it would solve. But clearly, this gambit deserves exploration.

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4. Function's Perplexities. You know where this is going (optimism seldom pans out in philosophical essays!): the macromolecular monist now needs a monistic account of biochemical function. If we divide different kinds of proteins by function—and that's a big "if"[9]—how should we divide functions? This is a complex and well-studied question about which I cannot hope to say anything too substantive. Fortunately, my conclusion tolerates some abstraction. However we understand biological function, ascription of function will likely be a holistic enterprise. This gives rise to a deep and theory-neutral pluralism. So long as functions cite different kinds of things (e.g., the function of adding a *phosphate ion* to the sixth *carbon* of the *glucose* molecule), some of which are *functional kinds*, there may be multiple different but equally acceptable ways of ascribing functions and thus of individuating functional kinds. Even if my transcendental approach fails to convince, I am reasonably confident that the details of various theories of function will bear out my pluralism (though I shall only be able to gesture at these lines of argument).

Broadly speaking, two approaches to function have dominated the literature: the etiological or selected-effects approach (championed by Wright [1973], Millikan [1984, 1989], and Neander [1991]) and the causal role or systemic-capacity functions (developed by Cummins [1975], Amundson and Lauder [1994], and Davies [2001]). According to the selected-effects approach, the function of a trait depends on whether performance of that function has figured in the selective history of that trait. Spelling out this intuitive thought has proved complex. How, specifically, must a particular capacity figure in a selective explanation? Must it explain the *increase* of the trait or just its *maintenance*? Cannot traits that are declining in frequency nevertheless possess functions? And, of course, settling these questions does not provide a way of gauging the contribution that a particular trait makes. Some traits are, in Gould and Vrba's (sometimes maligned 1982) term, *exaptations*: traits originally selected because of one kind of functionality but later co-opted for another. Even somehow restricting the contributions that trait has made to a lineage's "modern history" (see Godfrey-Smith

9. I have in mind an objection like this: Surely it's not an a priori necessity that a protein could have only one function! Could we not imagine a single kind of protein accomplishing two distinct functions in different circumstances? I take this objection seriously. At this point, I'm not certain that I want to posit a one-to-one correspondence between biochemical functions and kinds of proteins. That being said, I believe this correspondence could be defended by pointing to an ambiguity in the phrase "same kind of protein" between the functional kind and the different alleloforms that "realize" it. I return to this point in Section 5.

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1994) leaves open the question of how important possession of that trait has been to its possessors' success.[10]

Difficulties like these, while perhaps not insuperable, underlie much of the attraction to the more liberal systemic-capacity approach to function (upon which I shall focus). On this approach, we attempt to understand the function of a component in terms of its contribution to the capacities of the larger system. DNA polymerase, a key enzyme involved in DNA replication, has a "proofreading/error-correction" function that greatly reduces copying errors. High-fidelity DNA replication clearly contributes to the growth and development of organisms (not to mention their reproduction). It's not hard to appreciate how this systemic capacity likewise contributes to the fitness of organisms and serves as an explanation of its own persistence in the lineage.[11]

But we can divide up systemic capacities in various ways. When we ask, What is the function of DNA polymerase? a natural response is that it has several functions: DNA replication and error correction. But this may be an artifact of the fact that we understood its role in replication before we understood its role in error correction. Perhaps we ought to construe its function as *high-fidelity replication*. Which is correct? Is there a single function here or multiple functions? Is there a uniquely privileged way of dividing systemic-capacity functions?

The monist has an obvious response to this kind of pointed question (inspired by the radical monism above): analyze down—divide reality as far as it can be divided. Those divisions are the natural joints. Simply ignoring these fine distinctions—in, say, grouping different alleloforms that carry out the same function or even grouping different functional kinds into a higher-order kind—happens all the time and hardly impugns their reality. There *is* a privileged system of biochemical classification, even if it is not the one we commonly use. In the case of DNA polymerase, while it is natural to include a variety of structures under the functional umbrella of high-fidelity DNA replication, biochemists can distinguish between various types of DNA polymerase on the basis of precisely how they carry out this function: "When [a mismatched DNA complex] was supplied to *E. coli* DNA polymerase I, the incorrectly hydrogen-bonded base was removed by a 3' → 5' exonuclease activity. . . . In DNA polymerase III, this function resides in the Θ subunit of the core polymerase"

10. Another issue that I will not pursue here is the complexity of construing the presence of a certain polypeptide as a *trait*. For if indeed the same polypeptide can carry out very different functions, it may be impossible to separate the contributions of each to the organism's success.

11. Davies (2001) has argued that the systemic-capacity and selected-effect theories are not distinct.

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(Lodish et al. 1995, 387). The committed monist could once again argue that while strictly speaking there are multiple functional biochemical kinds here, whether we group them as a single kind (owing to the sameness of a systemic capacity at a coarse level of analysis) or acknowledge the difference and divide them as different kinds is up to us.

This response may work well for some cases, but I do not think it will wash in general. For whether a proffered systemic capacity represents the "lowest level" of functional analysis will sometimes depend on how we divide into kinds other portions of the world—(crucially) including the very biochemical world which is at issue. I mentioned chaperonins above. These proteins fold other polypeptide sequences into their active tertiary structures. Now imagine two alleloforms of a certain protein that are shaped by a similarly heterogeneous collection of chaperonins. Do these shapings count as two different functions? That depends, presumably, on whether the two alleloforms are in fact the same kind of protein—whether they have the same lowest-level biochemical functionality. Suppose, for example, that one alleloform served to initiate cell division via a pathway that was interruptible by high concentrations of sodium or potassium and the other was only sensitive to sodium. As we "analyze down," we would assign identifiably different (though readily groupable) functions to each alleloform that would potentially trickle down to the alleloforms of the chaperonins that helped form them. So far, so good. But now imagine, on the other hand, that the functionality of our two alleloforms is to dismantle the very chaperonins that built them! A wasteful pathway, to be sure, but certainly a possible one (even if it would not be favored by selection).[12] Any appeal in this case to the objectivity of a lowest level of functional analysis simply goes round in a circle.[13]

This suggests that there will sometimes be no uniquely privileged way of exhaustively carrying out a functional analysis on the systemic-capacity approach. Insofar as the individuation of biochemical kinds depends on just this sort of functional analysis (I believe the story is similar on the etiological approach), there is no uniquely privileged way of dividing up biochemical kinds. By hitching their wagons to function, macromolecular monists face the problems concomitant to functional monism. As with

12. Thus this example would have to be rebuilt for the selected-effects account of function.

13. I argued similarly in my 2005 article that whether different enantiomers (mirror-image molecules) are classified as of the same kind admits of a similar kind of holism—what we might call "circular volunteerism." To claim that, say, L-glucose differs in kind from D-glucose naturally appeals to a dispositional difference (reactivity with other chiral molecules, say), which in turn depends on whether enantiomers are different kinds of molecules (the question at issue).

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the structural route, the functional path has reached a dead end. The foregoing does not yet amount to a knock-down argument for macromolecular pluralism. Other routes may yet reach the monists' destination. I am not hopeful, however.

5. Modes of Biochemical Classification. I began with a question that appears to have an answer: How many kinds of proteins are in the typical human body? Perhaps there is an answer in that it has *many* answers. Is there then any point to calling any of these answers correct? Some answers are clearly *incorrect*: there are considerably more than five or a hundred or even a thousand kinds of proteins. How can our pluralism be made "modest"? This is a difficult question that crops up anywhere pluralism tempts us. As yet, I think we have only the slimmest grasp on how to unite pluralism with some sense of realism. This is a project for another time, but one on which I believe consideration of proteins may shed some light.

Pluralism makes good sense of the actual classificatory activities of biochemists. Our classification schemes typically reflect our best inductive and explanatory strategies—and these are rarely neat and tidy. Coarse taxonomies develop in contexts where fine functional analysis serves no apparent utility. Clearly, these may be revised if circumstances demand it (say, if we cannot make sense of the effect of introducing a particular protein).

Biochemists can avail themselves of a plurality of legitimate classificatory systems simultaneously by invoking what I'd like to call different "modes" of classification. The example of the alleloforms of ADH highlights an important feature of how we classify the world. Notice how Ridley described this case: the same kind of *enzyme* is actually a class of two kinds of *polypeptides*. The role of these organizing terms cannot be ignored. Polypeptides are individuated by their sequence; I conjecture that enzymes (and proteins more generally) are individuated, at least in large measure, by their function. We needn't maintain a one-to-one correspondence between different kinds of proteins and functions in order to appreciate this importance. If proteins are not purely functional kinds, though, the details of their (pluralistic) individuation seem to me an interesting and wide-open area for future research—one that would go a long way toward "de-radicalizing" the pluralism.

I believe the notion of different "modes" of dividing the world may help with this as well. While these different modes may cross-classify reality (or merely reveal different "layers" of structure), they need not be regarded as forcing hard choices. Perhaps the ambiguity of our nomenclature (as perhaps 'protein' is ambiguous between enzymatic function and the various levels of chemical structure) simply eases transitions be-

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tween these modes, discourse that is triggered by other univocal organizing terms. *Drosophila* ADH is a member of what Benach et al. call "a broad and heterogeneous family of alcohol dehydrogenases, named short-chain dehydrogenases/reductases (SDR), and is the only member that utilizes small alcohols as substrates" (2000, 3613). But though heterogeneous, SDRs possess certain structural commonalities; they describe one ADH's membership in this class thusly: "the subunit shows the typical fold of the short-chain dehydrogenase/reductases enzyme cores thus exhibiting a three-dimensional structure similar to that reported for other SDR proteins whose three-dimensional structure has been solved to date. The subunit of [*Drosophila* ADH] has an α/β single domain structure with a characteristic Rossmann fold dinucleotide-binding motif" (3614).

Our rich system of different interleaved levels of functional and structural classification, I think, is best understood as the result of coming to terms with the genuine plurality of systems of functional and structural kinds. I suggest that we look to the role of organizing terms in our conceptualization of the world. There is no dividing the world into the *natural kinds*, perhaps—but that doesn't mean that there aren't natural kinds. There are natural kinds of enzymes, natural kinds of polypeptides, natural kinds of organisms, natural kinds of celestial objects, and so on—each dependent on norms of classification devolving from our best inductive and explanatory practices.[14]

REFERENCES

Amundson, Ron, and G. V. Lauder (1994), "Function without Purpose: The Uses of Causal Role Functions in Evolutionary Biology", *Biology and Philosophy* 9: 443–470.

Benach, Jordi, Sílvia Atrian, Joan Fibla, Roser Gonzàlez-Duarte, and Rudolf Ladenstein (2000), "Structure–Function Relationships in *Drosophila melanogaster* Alcohol Dehydrogenase Allozymes ADH^S, ADH^F, and ADH^{UF}, and Distantly Related Forms", *European Journal of Biochemistry* 267: 3613–3622.

Cummins, Robert (1975), "Functional Analysis", *Journal of Philosophy* 72: 741–765.

Davies, Paul Sheldon (2001), *Norms of Nature*. Cambridge, MA: MIT Press.

Ellis, Brian (2001), *Scientific Essentialism*. Cambridge: Cambridge University Press.

Ereshefsky, Marc (1992), "Eliminative Pluralism", *Philosophy of Science* 59: 671–690.

Godfrey-Smith, Peter (1994), "A Modern History Theory of Functions", *Noûs* 28 (3): 344–362.

Gould, Stephen Jay, and Elizabeth Vrba (1982), "Exaptation—a Missing Term in the Science of Form", *Paleobiology* 8: 4–15.

Kitcher, Philip (1984), "Species", *Philosophy of Science* 51: 308–333.

Koshland, D. E., Jr. (1958), "Application of a Theory of Enzyme Specificity to Protein Synthesis", *PNAS* 44 (2): 98–104.

Lodish, Harvey, David Baltimore, Arnold Berk, S. Lawrence Zipursky, Paul Matsudaira, and James Darnell (1995), *Molecular Cell Biology*. New York: Scientific American Books.

14. Similar conclusions have been reached by Kitcher (1984), Ereshefsky (1992), and Stanford (1995) regarding species.

https://doi.org/10.1086/605817 Published online by Cambridge University Press

Mathews, Christopher K., and K. E. van Holde (1996), *Biochemistry*. Menlo Park, CA: Benjamin/Cummings.
Millikan, Ruth Garrett (1984), *Language, Thought, and Other Biological Categories*. Cambridge, MA: MIT Press.
——— (1989), "In Defense of Proper Functions", *Philosophy of Science* 56 (2): 288–302.
Neander, Karen (1991), "Functions as Selected Effects: The Conceptual Analyst's Defense", *Philosophy of Science* 58: 168–184.
Rapp, Mikaela, Eric Granseth, Susanna Seppälä, and Gunnar von Heijne (2006), "Identification and Evolution of Dual-Topolgy Membrane Proteins", *Nature Structural and Molecular Biology* 13: 112–116.
Ridley, Mark (2003), *Evolution*. 3rd ed. Boston: Blackwell Scientific.
Ruphy, Stéphanie (forthcoming), "Are Stellar Kinds Natural Kinds? A Challenging Newcomer in the Monism/Pluralism and Realism/Antirealism Debate", *Philosophy of Science*.
Slater, Matthew H. (2005), "Monism on the One Hand, Pluralism on the Other", *Philosophy of Science* 72 (1): 22–42.
Stanford, P. Kyle (1995), "For Pluralism and Against Realism about Species", *Philosophy of Science* 62: 70–91.
Wright, Larry (1973), "Functions", *Philosophical Review* 82: 139–168.

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