Philosophy and Molecular Biology

The Classical Problems

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July 15, 2019

Outline

Section 1

Introduction

Context: Molecularization of Biology

- The creation of molecular biology in the 1950s was one of the most important developments of twentieth-century biology.
- The iconic episode was the double helix model of 1953.
- However earlier developments such as Pauling's model of serological specificity or of protein structure (the α-helix) and later developments were conceptually more important.
- We will return to the significance of the double helix model later: it made possible a theoretical molecular biology based on the concept of information.
- Remember: compared to precursors such as biochemistry, molecular biology was an intensely theoretical science in its classical phase.

Classical Molecular Biology

- This is the molecular biology of the late 1950s and 1960s.
- First success: Pauling's and Landsteiner's theory of immunological specifity, later extended to enzyme specificity.
  - Based on the metaphor of a lock-and-key fit.
  - This model assumed that the physical interactions molding biological mechanisms at the molecular level are very weak.
  - Remember: specificity was *the* (?) central theme of twentieth-century biology (Judson 1979).
- Second success: the double-helix model followed by the model of gene expression.
  - Enabled the informational interpetation of biology.
- Third success: the operon and allostery models.
  - Makes possible the cybernetic interpretation of the cell: *but was it ever plausible*?

Philosophical Implications

- Ontological potential: for the first time in the study of life the thesis of materialism becomes scientifically plausible, rather than a philosophical promise.
- Epistemological potential: for the first time in the history of biology the thesis of mechanism/reductionism becomes scientifically plausible.
- Upshot:
  - The ontological thesis of materialism has not been open to question since then.
  - But, as we shall see throughout this conference, the epistemological thesis of reductionism continues to generate conroversy—as it should.

Biological Practice

- By and large scientists pay little attention to philosophers' agendas; by and large they are justified.
- For instance, if we looked at philosophy of biology in the 1980s we wouldn't know that molecular biology was the dominant practice within biology.
- Almost all of philosophy of biology was about evolution and the focus was on the units of selection which generated almost no scientific interest: look at Sober (1984).
- When philosophers even talked of molecular biology, it was a generation behind the time: look at Kitcher (1984, 1986) on genes, reduction, and explanatory extension though, of course, Kither went on to write an interesting book on the Human Genome Project (*The Lives to Come*, 1997).

Points of Contact between Biology and Philosophy

- The ontological thesis was once interesting: when vitalism was plausible, and when Bergson made a case for an entelechy-based neo-vitalism in the 1910s.
- By and large, that project dissipates by the late 1920s.
- But the organicism versus mechanism was central to both the biology of the time and to philosophers: see the dispute between Woodger and Nagel, both based on systemtic interactions with biologists.
- So, we will begin with reductionism.

Section 2

Reduction

Old Distinctions

- Why are they important?
- We must take care about what we call "reduction"; as an example of spurious problems that arise, take Dan Nicholson's (2019) paper on machine models of the cell. He and I are in agreement of the physical situation.
- But he thinks this destroys reductionism; I think it greatly supports reductionism. Our differences are probably more ideological than philosophical.

Distinction: Formal and Substantive Issues

- Formal versus substantive issues:
  - Will ignore formal issues; thus, can ignore Nagelian models of reduction and criticisms of them without rejecting them.
- Sticking to substantive models, old classification (Sarkar 1998):
  - *Weak reduction*: only satisfies an epistemic primacy condition.
  - *Hierarchical reduction*: also satisfies a graph-theoretic tree condition
  - *Strong reduction*: hierarchy is based on spatial containment.
  - Finally, we get "parts-whole" reduction (anicipated by Wimsatt 1976).
- Since then Hütteman and Love (2011) have added a temporal containment condition. Have some doubts about it—will get to it later.

Crucial Distinction: Genetic versus Molecular Reductionism

- A lot of skepticism about reductionism among biologists, philosophers, and the lay public about molecular reductionism arises because they interpret it as genetic reductionism.
- This is easy enough to understand: molecular genetics came to dominate molecular biology post-1953 in the classical period.
- But, in the post-genomic era, genetic reductionism is clearly impotent as a research strategy let alone as a class of successful explanations. (Only defended by pop psychologists.)

Resource

- Sarkar, S., Love, A., and Wimsatt, W. C. 2018. "Reductionism in Biology." In Pritchard, D. Ed.Oxford Bibliographies in Philosophy. New York: Oxford University Press, http://www.oxfordbibliographies.com/view/document/obo-9780195396577/obo-9780195396577-0359.xml,
- Can be downloaded from https://sahotra-sarkar.org/sahotra-sarkar-papers/.

Parts-Whole Reduction beyond the 1998 Model

- After assuming epistemic primacy, reduction must satisfy these conditions:
  1. *Dynamism*: Explananda must be dynamic features (and much more can be said about this).
  2. *Containment*: Explanations must only involve individuated internal or boundary elements.
  3. *Locality*: If externalities are relevant, this relevance is mediated by local fields or material objects at the boundary.
  4. *Hierarchical organizations, admitting pluralism*: Internal elements can be organized in multiple hierarchies. These can be *incommensurable* without being *incompatible*.
  5. *Temporal antecedence*: No truck with intrinsically goal-directed (teleological) mechanisms; other than that, there is no restriction on mechanisms.

Some Implications

- The most philosophically dense condition is that of pluralism.
  - Abandons unique decomposition into parts.
  - But, following Nagel, how a whole is divided into parts is itself a theoretical claim.
  - What it abandons is naive realism about biological objects.
  - Abandons the machine metaphor.
- The machine metaphor is unhelpful does not challenge reductioism.
- This account is not too loose: there can be many empirical challenges reductionism and counter-examples from microscopic physics.
- The new account excludes cybernetic machine models dependent only on discrete switch mechanisms.
- Will return to cybernetics later—if there is time.

Section 3

Information

Central Dogma

- Common claim: what distinguished the new molecular biology from the old biophysics/biochemistry is the concept of information.
- "Why 'information'?" must have a sociological explanation: all the excitement about computers in the 1950s (which also has a complex relationship with cybernetics).
- Informational thinking crystallizes into Crick (1958), probably the most important theoretical paper in the history of molecular biology:
  - Central Dogma.
  - Sequence Hypothesis.
- Aside: Watson rewriting history about "information": do not know what to make of it.

Information as a Theory of Specificity

- Until the advent of informational talk, the standard theory of biological specificity was stereospecificity.
  - Basic model goes back to Pauling and Landsteiner's work on serological specificity.
  - Then extended to enzyme-substrate specificity.
- Lederberg (1956): information provides an alternative theory of explanation.
- Sequence hypothesis integrates the two theories.
  - But informational theory could remain true, perhaps even become more important, if sequence hypothesis is false.
  - Central Dogma provides a strong testable hypothesis provided that "information" can be empirically operationalized—but that's the problem.

Semantics of Gene Expression

- RNA as a "messenger" molecule assumes that what is relevant is information (or, at least, a linguistic entity—but how else to interpret this entity?).
- Recall Crick: information as the precise determination of sequences.
- Restricted to bacteria, we get a compelling picture of gene expression as the flow of information.
- The "flow of information" replaces the "flow of time."

Critique

- Since the mid-1990s the informational interpretation of biology has come under attack though, as will be emphasized below, some of the arguments go back to a little-known 1977 paper by Gunther Stent.
- The basic point is that no one has ever successfully defined what “information” means in biology.
- It is clear that the communication-theoretic definition of information as entropy is irrelevant—but see the discussion of the recent attempt to revive it by the Griffiths group.
- Philosophical attempts to explication semantic information quantitatively, starting with Bar-Hillel and Carnap (1952), have not gone anywhere, at least in biological contexts.
- “Information” is a metaphor masquerading as a theoretical concept.

Development: Stent (1977)

- Skepticism about the informational interpretaion of biology was already explicitly expressed by Gunther Stent in 1977.
- Though this work was directed to a philosophical audience it was completely ignored by philosophers.
- Was unaware of it in the early 1990s and did not cite it in Sarkar (1996a,b).
- Hans-Jörg Rheinberger drew my attention to it in the early 2000s.
- It is time to analyze Stent's piece and offer critical appreciation.

Stent's Argument

- Stent challenged the claim that genes alone can explain or predict development; for this, he drew on Waddington.
- Philosophically, it was a challenge of genetic reductionism in developmental biology; as such it was a critique of the implicit agenda of developmental genetics.
- He took it for granted that it makes sense of giving an informational, indeed semantic, account of the gene-protein relationship through coding.
- But, beyond that, according to him, informational talk becomes metaphorical.

Stent's Words

- Stent distinguishes explicit information through coding and implicit information coming from the developmental context. Then:

  "Thus it transpires that the concept of information, which in the heyday of molecular biology was of such great heuristic value for unraveling the structure and function of genes, i.e. the explicit meaning of that information, is no loner so useful in this later period when the epigenetic relations that remain in want of explanation reprensent mainly the implicit meaning of that information" (p. 137).

Unexpected Complexity of Eukaryotic Genetics

- The informational interpretation first begins to fall apart with the discovery of ubiquitous "junk" in the eukaryotic genome (Ohno 1973).
  - We need a definition to distinguish informative DNA from junk and we don't have one.
- Then the predictive power gets lost because of a set of complicating discoveries:
  1. "Split genes" in the late 1970s.
  2. Alternative splicing in the late 1970s and early 1980s.
  3. Gene editing in the 1980s, for instance in trypanosomes.
  4. Non-standard coding.

Reconstruction? Coding and Theory

- Associated with Godfrey-Smith and Sterelny who do not make any strong claim about how useful “information” is.
- Partly seem to be guided by biological practice, though not postgenomic biological practice.
- Coding is a “theoretical” claim—yes, but . . .

Reconstruction? Mutual Information and Specificity

- Griffiths group at Sydney has tried to revive communication-theoretic information.
- Idea is that "mutual information" provides a measure of specificity.
- Yes, but only at the sequence level, and so, once again, so what . . .
- Real goal should be to provide a measure that captures divergence from bijection (Sarkar 2002, Woodward 2006).
- Mutual information does that but at a tremendous cost about what we have to assume about probability spaces and measures on them.

Section 4

Cybernetics

What Is/Was Cybernetics?

- Not being able to answer that question easily is part of the problem.
- If we accept Wisdom's (1951) account deifying negative feedback, then we do not capture much of cellular biology.
- But if not, what?
- Ulimately what we are seeing is Monod's influence.

What Is Not Cybernetic?

- Kauffman (1972) calls "articulation of parts" of a cell cybernetic.
- Proposal: must thing of the cell as a system governed by digital switches
- Limitations become obvious.
- More details will be left for Q & A.

Section 5

Final Remarks

Where Are We?

- The information metaphor has outlived its utility; no reason to alter my conclusion from 1996.
- The cybernetic metaphor was never more than a metaphor looking for a model.
- Reductionism continues to be an issue but an unsettled issue.

Contemporary Tasks: Evolution

- Classical molecular biology ignored evolution even though it brought about: (i) the neutral theory of evolution; (ii) recognition of "junk" DNA; (iii) plausible models of gene origination; . . . the list can go on endlessly (and it would be good to have a canonical list).
  - The task is to understand how the molecular level affects the received view of evolution.
- Challenges to the received view of evolution:
  - That all change is continuous: thing of genome duplication.
  - That most change is adaptive: we have the genomic challenge to adaptationism.
  - That all change is "blind": takes us to CRISPR and my talk later today.

Contemporary Tasks: The Problem of Time

- Classical molecular biology ignored time.
  - For Crick and his followers, the flow of information replaced the flow of time.
  - In the Monod-Jacob school, dynamics in form of rate considerations disappears from the papers in early 1960s.
  - We eventually end up with a static "snapshot" picture of biology.

Contemporary Tasks: The Problem of Time, contd.

- But:
  1. Living processes are physical processes and the occur over time: rates matter.
  2. For instance, there is a unique irreversibility in development (and the need to "scrub" the genes during [sexual] reproduction to remove epigenetic markers).
  3. The genome is dynamic: not recognizing that is perhaps a major reason that molecular biology remains at odds with evolutionary theory.

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- The task becomes to give a dynamic interpretation of molecular biology.