"Genomes All The Way Down"

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1. *Motivation*

Project: Implication of taking the genome as fundamental.

Examples of genome organization; genomic behavior; genomic events.

Problems with the received view.

2. *The Genome is a Physical System*

While typically described in strictly in informational terms (more on this later), the genome is a physical-chemical system. It comprises DNA, structural proteins and a variety of molecular machines.

Working up from this level of analysis emphasizes physical causality.

Traditionally, molecular genetics was seen as more "fundamental" than Mendelian genetics and the possibility of reduction between the two was an important question (Kitcher 1984).

However, molecular genetics and molecular genomics make more interesting partners. No laws; the issue is not derivability of laws.

3. *Defining and identifying the genome*

As a first approximation I take the genome to be an evolved concrete physical/chemical (goal-directed) system controlled by epigenetic mechanisms that carries developmental & hereditary information.

Stipulations: (1) Individual genome; (2) Includes mechanisms (GEMs); (3) Includes structure, shape and dynamics (4D).

"Genome of *H. sapiens*", meta-genomes etc. are derived notions, abstractions, possibly even metaphoric.

By mechanism I mean (roughly) "evolved molecular machine".

The genome is thus conceptualized as a developmental system.

This order of explanation privileges the role of the genome in development over its hereditary function. In particular, it does not presuppose "gene"-like units of information or replicators.

4. Initial observations

As objects of evolutionary interest genomes can be radically different entities b/c of differences in (2) and (3). Cf. Bendich & Drlica (2000); Evolutionary (genetic) changes are constrained by genome organization (see Lamm 2011).

The genome is arguably not reducible to a strict molecular vocabulary b/c of effects of 3D shape and organization. (See Lange 2004, Frost-Arnold 2004.) This general point is already visible in the claim that the cytological level is the appropriate level for explaining the function of pairing in meiosis. This is issue is benign.

The genome is also not an "aggregate" system composed of genes, in the sense of Wimsatt (see his 2006; following Lewontin 1974). While correct as far as they go, these discussions presuppose individuated genes (e.g., by appealing to population genetics) and consider the genome as paradigmatically comprised solely by genes (for an illustration see Wimsatt 2006, fn. 30) -- The genome is not fundamental.

It is also not reducible to an *organized* collection of genes as it contains non-coding elements.

Critically genome behavior and evolution cannot be reduced to accounts that presuppose individuated genes that are prior to the comprised system:

(1) Genome behavior (causally) individuates genes. Both developmentally and in heredity.

(2) Multiple kinds of /gene/ like concepts (see below)

Thus, in this framework genes *cannot* be fundamental.

5. *Is the genome a well defined entity?*

Which mechanisms are genomic mechanisms?

Example: TEs: junk DNA, SGE, or genomic mechanisms?

"A mechanism is a structure performing a function in virtue of its components parts, component operations, and their organization. The orchestrated functioning of the mechanism is responsible for one or more phenomena." (Bechtel 2006)

“Mechanisms are entities and activities organized such that they are productive of regular changes from start or set-up to finish or termination conditions.” (Machamer et al. 2000)

These definitions do not help in operationally demarcating the set of genomic mechanisms. For example:

To demarcate the set of genome mechanisms using the Bechtel's definition means requiring that their functions, qua mechanisms, be genomic. Adjudicating this criterion can easily lead to circular reasoning (i.e., understanding genome function cannot in general be done without knowing the identity of genomic mechanisms). Our goal was to delineate the genome based on its intrinsic properties. Bake in as few evolutionary commitments as possible.

Machamer et al.'s definition does not depend on ascribing function but it also doesn’t help demarcate the set of genomic mechanisms non-circularly.

Cf. Millikan, Biofunctions: Two Paradigms (2002). Is evolutionary history going to help or does it just push the problem back in time? What if we want resist going to history to determine function?

A possible heuristic for identifying genomic mechanisms (and mutatis mutandis the mechanisms of similarly defined entities) is to start with an element considered part of the genome, by definition, such as chromatin, and iteratively add mechanisms that interact in appropriate ways with elements already considered part of the genome. This process is repeated until no new mechanisms are identified (i.e., until a fixed-point is reached). Clearly, however, this is not how the empirical and conceptual progress happens in scientific practice.

We will include mechanisms required for the developmental activities of genomes and mechanisms involved in transgenerational stability of (epi)genome states. (cf. "recent history" approach)

Whether the genome is a well-defined entity depends on (changing) empirical knowledge and contentious conceptual judgments by scientists. The genome is useful as a fundamental notion in genetics much more so than the alternatives, so heuristically it is reasonable to use it as such.

5. What happens to the gene? The *gene-genome relation.*

What is the relationship between the molecular gene (supposing it exists) and the genome it resides "in"?

The relationship need not be one reflecting ontological levels; it should be explanatorily fruitful.

Genes are idealizations of genome behavior ("*genes are manifestations of the physiology of the genome*").

Genes supervene on genomes (see Lamm 2011). This is a contingent fact. While this framework is open to the possibility of wide supervenience, I focus heuristically on narrow supervenience, focusing strictly on genomic context, developmental and mechanistic (i.e., potential). Genes in this framework are not ontologically prior to development (or evolution).

This provides a family of possible kinds of relations. They each establish a different (class of?) gene concepts. A simple example: gene expression and recombination need not individuate the same "genes".

6. *Genetic/Epigenetic*

Genetic and epigenomic mechanisms are evolutionarily and functionally interrelated (e.g., centromere inheritance [Henikoff et al. 2004]; silencing of transposable elements; developmentally regulated genome rearrangements [Zuffal et al. 2005], template based mechanisms [Nowacki et al. 2008]; RNA mediated process in chromatin maintenance).

Molecular accounts are needed in order to explain the connection between higher level phenomena that share molecular mechanisms. The molecular understanding does not simply provide “explanatory extension” (Kitcher 1984), which provides details that help understand the autonomous laws operating at the higher level. It provides an explanatory connection that explains how independent phenomena operating at the higher levels are connected. This is crucial for understanding their evolution.

The shared molecular mechanisms implicated in both heritable and developmental genomic changes imply that changes in these mechanisms can affect both. This raises the possibility that the evolution of development and the evolution of inheritance significantly affected one another. This suggests that molecular genetics needs to be viewed as supplying explanatory connection between what appear to be autonomous biological categories.

For a theory to be adequate, whether functionally, evolutionarily, or both, this intertwining has to be taken into account. Neither theory can be adequately reduced to a molecular theory independently of the other (due to the “explanatory connection” between them). Hence if either of them cannot be so reduced, then neither can.

Argument:

1) An adequate theory of genetic inheritance cannot be independent of a theory of genomic development, i.e., an adequate theory will encompass both aspects (due to the explanatory connection that is the result of mechanismic decomposition or reduction).

2) From (1) it follows that it is impossible to reduce (in the sense of theory reduction) genic inheritance and genomic development to molecular biology independently of each other.

3) It is impossible to reduce (in the sense of theory reduction) development, including the developmental aspects of the genome, to molecular biology (due to arguments of the type found in Kitcher 1984, Lange 2004, Frost-Arnold 2004).

4) From (2) and (3) it therefore follows that an adequate theory of genetic inheritance cannot be reduced (in the sense of theory reduction) to molecular biology.

7. *Consequences*

Genomic-Inheritance-System (instead of GIS/EIS) (see Lamm 2011).

The relation between heredity and development evolved, and they do not represent dichotomous categories but limit cases along a continuum. Consequently: also developmental plasticity and evolvability are (where relevant) continuous not categorical (Lamm & Jablonka 2008).

8. *Objections*

Q: Viruses and other "naked genes" from the genome perspective.

A: Suggestion: Viruses, prior to engaging with an active genome or supportive environment, should not be understood as naked (or semi-naked) genes, according to this suggestion, but rather as genomic perturbators. They have genomic potentialities, but these have to be actualized for their contents to become full-fledged genes.

Q: How is the success of the gene based paradigm to be explained?

A: We can retain a distinction between a genetic inheritance system and a (underlying) genomic inheritance system on the assumption that a GIS may provide a more productive framework for describing commonly observed inheritance processes, horizontal gene transfer, virus infections etc. In this formulation the GIS depends on ceteris paribus qualifications about the functioning of genomic mechanisms and the limited scope of the changes made to the (*robust*) genome by the genetic events that are being considered.

Q: Why stop at the genome? Why not embrace a radical ontology and privilege cells etc.?

9. *Conclusions*

More "reductive" to physics than some might like; but in a different way perhaps. Anti-reductionism regarding genes or "information".

Genomes, as fundamental units of biology, are physical *and* biological. Genomes are natural kinds. Genes supervene on genomes.

Evolutionary discussions typically neglect the developmental processes in genomes. Case in point: origin of life.

Stochasticity; Attractor selection.

This radical ontology I discussed is perhaps best viewed as a heuristic for work in this area.