**A Use / Disuse Paradigm for CRISPR-Cas Systems**

In his insightful review, Eugene V. Koonin discusses various aspects of CRISPR-Cas systems with a

strong focus on their qualities as “adaptive (acquired) immune systems“ (Koonin 2018, 3). The

CRISPR-Cas system is most famous for its application as a gene-editing tool. Koonin provides a deeper

insight into its biological function in bacteria, which is to immunize the cell against parasite DNA. I

shall comment on one issue discussed in the text, in two steps. First, I shall elaborate on CRISPR-Cas

systems and their supposed Lamarckian character. Criteria for calling biological phenomena

genuinely Lamarckian will be narrowed down and then applied to the CRISPR-Cas system, considering

interference-driven spacer acquisition (IDSA) as an instantiation of a truly Lamarckian paradigm.

Second, I shall consider whether Lamarckian and “canonical” instances of inheritance are a case of

theoretical pluralism, being two non-reducible, yet interconnected paradigms.

Koonin suggests that CRISPR-Cas based inheritance of acquired traits (IAC) might be an example for a

genuine Lamarckian mechanism, because it operates by “i) specific, heritable changes in the genome

caused by an external factor, ii) specific phenotypic effect of those changes that constitutes

adaptation to the causative factor” (Koonin, 2018, 6f). Yet, this definition is not exclusively referring

to Lamarck’s musings. For example, such properties are also associated with Darwin’s “gemmuli” or

“pangenesis” (which have recently been quite more beloved metaphors than any of Lamarck’s

concepts (Chen et al., 2016)). Nevertheless, it is possible to differentiate the general idea of IAC from

a genuinely Lamarckian theme. Lamarck proposed a mechanistic paradigm that coordinates the

inheritance of acquired traits: the “use/disuse paradigm.” This paradigm postulates that through

continuous “use” of certain “organs” these “organs” will be augmented. Contrarily, through “disuse”

of certain “organs”, these “organs” will be reduced (Lamarck, 1809 cited in Burkhardt, 1995).

Naturally, we need to grant some interpretative charity when working with the terms “organ” and

“use/disuse”. Notably, working with Lamarck’s use/disuse paradigm is of great epistemological value

for understanding other instances of IAC (Veigl, 2017).

I want to propose a way how one could fit CRISPR-Cas into a use/disuse paradigm. In so doing, we

must shift our attention to one distinct feature of use/disuse, namely its focus on the quantitative

aspects of the process. In a use/disuse scenario, we do not primarily deal with qualitative yes/no

phenomena, but with gradual processes. Therefore, we shall consider pools of crRNA species instead

of discrete spacers in CRISPR arrays. This should also help to understand the continuum between

Darwinian and Lamarckian types of inheritance (Koonin, 13), as they might work upon different

substrates (DNA vs. RNA), integrating differently from case to case. One instance of the use/disuse

paradigm is interference-driven spacer acquisition (IDSA) (Staals et al., 2016; Hille et al. 2018). IDSA

links interference to adaption, meaning that crRNA/CRISPR targeted parasite DNA becomes a source

for new spacers which are integrated into the CRISPR array. The newly acquired spacers are slightly

different in sequence but target the same parasite DNA.

With IDSA and the use/disuse paradigm at hand I shall now analyze the phase of interference. Here,

we have to consider that Cas molecules as well as their targets (nucleic acids) are present in different

concentrations. There is a pool of Cas proteins, and there is a pool of crRNAs. As a result of

differences in sequence, each crRNA deriving from a spacer region has slightly different biochemical

properties. Such differences might facilitate or impede binding. Ensuing expression, a pool of various

crRNAs competes for binding to Cas molecules. What we shall define as “use” is a situation in which a

specific crRNA (crRNA 1) binds a Cas protein and targets a parasite DNA sequence (thus both, binding

to Cas and the parasite DNA, are required for “use”). Protospacers will be salvaged and inserted into

the CRISPR array during elimination of the parasite nucleic acid. In the next round of expression,

there will be a higher concentration of crRNA 1-associated crRNAs, and this subspecies is more likely

to bind to a Cas protein again, as a result of its higher abundance. Thus, we have augmentation

through use. Of course, use and disuse go hand in hand, as more use of one subspecies implies

disuse of other species and their relative reduction in abundance. It has been shown that CRISPR-Cas

complexes show a preference for more recently acquired spacers, cementing disuse and reduction

on the RNA level for less used spacers. In addition, there are optimal numbers for spacers in CRISPR

arrays (Koonin, 2018, p15, Martynov et al. 2017) and thus, spacers must be lost over time.

The case of IDSA shows that shifting our attention to other phases than the DNA phase of CRISPR will

help us to find resonance with a modern interpretation of Lamarck’s “use/disuse paradigm.” DNA

might be the genuine playground of Darwinian paradigms, yet this does not mean that other material

sources are not present. It is often claimed that all forms of inheritance are in the end reducible to

DNA-based mechanisms, as the relevant biomolecules, such as the crRNAs, derive from it. Yet one

must not confuse DNA’s primacy in biochemistry with that in inheritance and evolution, as here,

clearly, other levels can play a role, as shows use/disuse of crRNAs.

I want to highlight one possible implication of CRISPR-Cas for philosophical problems, namely its

potential for discussions centering around scientific pluralism. I define scientific pluralism here very

broadly as the claim that to approach a certain phenomenon, several non-reducible theories,

explanations or methods are, might be or should be required (see Kellert et al., 2006). For the case

considered, we shall adopt the pluralist attitude that there are (at least) two non-reducible

mechanistic paradigms that govern the processes of inheritance. These two mechanistic paradigms

are based on two different theoretical approaches: IAC vs. Natural Selection through Random

Variation. In addition, both approaches have a different understanding of the interplay between the

(inducing as well as selecting) environment, inheritance and evolution. We will add, to be fully fledged pluralists, that we are approving of this situation, because we find it either epistemologically beneficial or claim that this kind of plurality is metaphysically resonant with what the world is like. (I, personally, refrain from the latter and find the former sufficiently desirable.) Now we shall turn again to the phenomenon at stake: CRISPR-Cas systems produce types of inheritance (that might have evolutionary impact) which are not included in an up-to-date version of the modern synthesis. Although CRISPR arrays are subjected to Darwinian random mutation, the arrays also adapt through a Lamarckian type, directed adaption, orchestrated by a use/disuse paradigm. Of course, both processes do not exclude each other, in principle. Yet, it is one key feature of the modern synthesis’

supporters to exclude any instances of IAC, especially forms that can be associated with Lamarck’s

theory.

Now, how shall we characterize this instance of pluralism? What kind of attack on orthodoxy does it

pose if one shows that some core theoretical assumptions do not universally apply? Let me draw an

analogy from a core theoretical assumption in physics: the first law of thermodynamics. Is claiming

“sometimes Lamarckian inheritance is instantiated” the same as claiming “sometimes energy is not

conserved”? What is now key here is that the answer might be “yes” and “no”. To some, such an

analogy is valid (Haig, 2007). I would call these researchers “Neo-Darwinian singularists.” Yet, to

others the answer is clearly “no”: Scientists insisting on instances of Lamarckian inheritance usually

accept all instances where a Darwinian framework has more explanatory power and also accept

“compound cases”, where integration of both modes explains a phenotype (Koonin, 2018, 13). I

suggest calling these actors “dualists”. I am not conscious of actors who would fit the definition of

“Lamarckian singularists”, insisting that all instances of inheritance and evolution are strictly

Lamarckian. Thus, we are encountering certain tensions and assymetries, both for the perspective of

the philosopher vs. actors in the research field, as well as within the scientific community. Whereas

“pluralism” seems to be a category mainly used by philosophers, the categories of “dualism” and

“singularism” might better describe the positions researchers take. Individual takes of researchers

concerning pluralism are not defined by them being dualist or singularist. Yet one could suspect that

dualism might invite a pluralist interpretation of the phenomenon at stake. To conclude, CRISPR-Cas

teaches us a lot about alternative trajectories of inheritance, which might constitute an assymmetric

case for theoretical pluralism. Nevertheless, we should pay close attention to the actors within the

respective field, who will finally negotiate the rise and decline of plurality in their research area.

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