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Mutational randomness as conditional independence and the experimental vindication of mutational Lamarckism

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ABSTRACT

The Modern Synthesis enshrined natural selection as the driver of adaptive evolution mainly by eliminating competing explanations. One of the eliminated competitors was Lamarckism, particularly 'mutational Lamarckism', a hypothesis according to which mutations may be directed towards producing phenotypes that improve the performance of the organism in a particular environment. Contrary to this hypothesis, the Modern Synthesis' view claims that mutations are 'random', even though the precise meaning of the term was never formally explicated. Current evidence seemingly in favour of the existence of legitimate cases of mutational Lamarckism has revitalized interest to seek a clarification of the meaning of the term 'random' in this context. Herein we analyse previous definitions of random mutations and show that they are deficient in three ways: either they are too wide, or too narrow, or dyadic. We argue that the linguistic expression 'random mutation' refers to a triadic rather than a dyadic relationship, propose a new, formal and precise definition based on the probabilistic concept of conditional independence, and finally provide examples of its application. One important consequence of our analysis is that the genomic specificity of the mutational process is not a necessary condition for the existence of mutational Lamarckism.

Key words: randomness, Lamarck, directed mutation, adaptive mutation, conditional independence.

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I. INTRODUCTION

It is frequently pointed out that Darwinism seems to be able to explain adaptive complexity only by referring to 'random' changes (Fox Keller, 1992; Dennett, 1995; Rosenberg, 2001; Brisson, 2003; West-Eberhard, 2003; Futuyma, 2005, pp. 178–179; Razeto-Barry, 2013). However, the precise meaning of the term 'random' in this context has never been fully explicated. Nowadays the common or received view – i.e. that genetic changes are 'random' – is supported by the canonical interpretation of natural selection theory, namely, that provided by the Modern Evolutionary Synthesis (Huxley, 1942). However, the Modern Synthesis enshrined natural selection as the director of adaptive evolution not by providing evidence that it did, or could, account for observed adaptations (Leigh, 1999), but rather by eliminating competing explanations (Mayr, 1993). One of the eliminated competitors was Lamarckism, particularly with respect to genetic variations (hereafter 'mutational Lamarckism'), a hypothesis according to which the environment can induce mutations directed towards producing phenotypes that increase the fitness of the organism in that particular environment. Thus, we suggest that, first, random mutations were implicitly considered as the opposite of Lamarckian mutations by assuming (without the foundation provided by a formal definition) a rigidly dichotomous contrast, i.e. if mutations are not Lamarckian then they are random. Subsequently, when it was accepted through experimentation that Lamarckian mutations are virtually non-existent (i.e. in the 1940s and 1950s, experimental results were generally interpreted as discarding mutational Lamarckism, see Luria & Delbrück, 1943; Newcombe, 1949), the doctrine of the 'randomness' of mutation became firmly established even though the concept of randomness was not defined with the necessary precision in the first place.

Contrary to the Lamarckian hypothesis, the Modern Synthesis' view claims that mutations are 'random' (Lenski & Mittler, 1993; Merlin, 2010). However, current evidence in favour of the existence of legitimate cases of mutational Lamarckism (Jablonka & Lamb, 2005; Koonin & Wolf, 2009) has revitalized interest in seeking clarification of the meaning of the term 'random' in this evolutionary context (Millstein, 1997; Brisson, 2003; Jablonka & Lamb, 2005; Sarkar, 2005; Merlin, 2010). Herein we aim to analyse previous definitions of mutational randomness according to three different criteria. We shall then show that they are deficient in three respects: either because they are too wide, too narrow, or dyadic. We argue that the term 'random' applied to mutational mechanisms refers to a triadic rather than a dyadic relationship and propose a new definition. In the final section we apply our formalization to current possible cases of mutational Lamarckism.

II. PREVIOUS PROPOSALS

A formal definition of mutational Lamarckism is necessary in order to classify mutational phenomena correctly and identify genuine cases of mutational Lamarckism. The implicit risk with informal definitions is that they are too malleable and subjective. More specifically, there exist two possible risks with informal definitions. On the one hand, they can be too wide and include too much, i.e. identify too many mutational processes as genuinely Lamarckian. On the other hand, they could be too narrow and exclude too much, i.e. dismiss apparent Lamarckian processes. We show that the existing literature on the nature of mutation contains instances of both kinds of definitions. Our formal definition is aimed at eliminating interpretive problems inherent in the extant literature. Subsequently, we analyse some definitions that use more formal terms (such as probabilistic 'independence' and 'correlation'), but show that their dyadic nature also makes them deficient. To render the terminology uniform, we use the term 'random mutation' to refer to mutations produced by 'random mutational mechanisms', and 'Lamarckian (or directed) mutation' to refer to certain mutations produced by 'Lamarckian mutational mechanisms'. We then use the term 'mutational Darwinism' to refer to the claim that there are only 'random mutations' in nature, and the term 'mutational Lamarckism' to refer to the claim that 'Lamarckian mutations' exist.

(1) Wide definitions

Jablonka & Lamb (1995, 2005) argued in favour of a Lamarckian approach to evolution. Their general argument is that Lamarckian concepts are necessary in order to describe and explain the nature of the processes of variation generation and inheritance. One of their more specific claims concerns mutational Lamarckism directly. In fact, contrary to neo-Darwinian orthodoxy, Jablonka & Lamb (1995, 2005) believe that genuine instances of mutational Lamarckism exist. We think that their definition is an example of a wide definition, incorrectly identifying as genuinely Lamarckian mutational processes that should not be considered as such.

Jablonka & Lamb (2005) base their defence of mutational Lamarckism on a number of substantive claims. The first (Jablonka & Lamb, 2005, p. 101) is that 'It would be very strange indeed to believe that everything in the living world is the product of evolution except one thing – the process of generating new variation! . . . In fact, it is not difficult to imagine how a mutation-generating system that makes informed guesses about what will be useful would be favoured by natural selection'. Even though it remains an open empirical issue whether 'mutation-generating systems' (i.e. mutational mechanisms) are the product of selection or rather the outcome of biochemical side-effects such as the breakdown of the repair and proofreading machinery of the cell (Brisson, 2003), what is most interesting in this context is to explicate their concept of informed guess. Mutations could be considered 'directed' (i.e. informed guesses) even when they are '. . . not adaptive, but are produced as a consistent and repeatable response to a particular environmental challenge. The terms "random" and "directed" reflect the specificity of the response to the environment, not the adaptiveness'. (Jablonka & Lamb, 1995, p. 76, note 8). Even though there

might exist an historical motivation to call mutations of this kind 'directed', making this terminological choice legitimate in principle, we believe that the choice remains conceptually confusing. The reason is that there exists a widely shared intuition that mutational Lamarckism cannot be defined solely in terms of response specificity but also necessarily in terms of fitness effects (Lenski & Mittler, 1993; Millstein, 1997; Hall, 1998; Rosenberg, 2001; Brisson, 2003; Sarkar, 2005; Koonin & Wolf, 2009; Merlin, 2010). There are many processes that bias mutational responses: some bias them with respect to time of occurrence (e.g. stress-induced mechanisms), others with respect to genomic site of occurrence (e.g. mechanisms targeting specific DNA sequences) and others with respect to intensity (e.g. mechanisms that increase mutation rate). The issue concerning directed or Lamarckian mutation does not concern the existence and nature of these biases. Their existence is not, *per se*, incompatible with mutational Darwinism. The issue is rather that it has been argued that the mutations produced by such biases must not be random with respect to adaptation to be considered directed. A necessary condition that characterizes mutational Darwinism thus concerns adaptiveness, not specificity of response: 'Mutation is random with respect to adaptive advantage, although it is not random in all sorts of other respects'. (Dawkins, 1986, p. 312) The consequence of all this is that, first, not all informed guesses are adaptive and, secondly, that only adaptive informed guesses are genuinely Lamarckian.

Jablonka & Lamb (1995, 2005) suggest that mutational processes exist that produce adaptive informed guesses, such as induced local increased mutation (ILM). Jablonka & Lamb (2005, pp. 97–98) describe ILM as a mutational strategy involving responses to changed conditions with a relatively small increase in mutation rate (i.e. not involving hypermutation). One striking instance of the ILM phenomenon was studied by Wright *et al.* (1999) and Wright (2000): *E. coli* bacteria living in stressful conditions (low concentrations of the amino acid leucine in the environment), and with a defective copy of the relevant amino-acid-producing gene (*leuB*). In such stressful environments the crucial defective gene mutated at a higher rate than normal. ILM is a temporally (i.e. the mutational mechanism is stress-induced) and spatially (i.e. the mutational mechanism targets specific genomic sites) biased process. Accordingly, Jablonka & Lamb (2005, p. 97) conclude that in the ILM case '[m]utations are therefore both induced by the environment and are specific to the gene that can save the day. In no sense is this type of mutation random – the mutations are both required and acquired'.

The problematic aspect of Jablonka & Lamb's (1995, 2005) informal definition of mutational Lamarckism is that they assume that specificity of response (i.e. the temporal, spatial and rate biases) necessarily affects positively the occurrence of beneficial mutations. In the ILM case '. . . the gene relevant to the crisis conditions became more mutable, so the chances that a cell could have the lucky mutation that enabled it to survive increased'. (Jablonka & Lamb, 2005, p. 98). We consider this argument fallacious for the reason that, although ILM cannot be ruled out as being Lamarckian, it is not sufficient to establish that a beneficial mutation has a higher probability of occurring in order to show that a mutational process is genuinely Lamarckian. In order to establish that this is the case, we suggest that the net fitness effect of the mutational response, rather than the increase in probability of the lucky mutation, must be taken into account. The rationale of our argument is well known: if the putative genomic specificity of the response is also accompanied by a higher generation of deleterious mutations, then the positive fitness effect due to the higher probability of the beneficial mutation could be cancelled out. If mutational Lamarckism were defined in the loose manner Jablonka & Lamb (1995, 2005) suggest, almost any mutational process involving a mutational bias would be Lamarckian for the reason that, whatever its evolutionary nature, the bias may increase the probability of occurrence of a lucky mutation, independently of the detrimental effects caused by other induced mutations. Indeed, following Jablonka & Lamb's (1995, 2005) definition, general (i.e. non-local) increases in mutation rate under stressful conditions should also be considered Lamarckian, even though the net fitness effect of this increased mutation rate may be clearly deleterious for the organism (although not for the population, see Section II.3*c*). However, detrimental inductive mutagenesis for the organism should be excluded from the definition of Lamarckism. If you start playing roulette more often, then your chances of winning go up. But it does not follow that your overall winnings go up, because in addition to winning more, you will lose a lot more too.

(2) Narrow definitions

By contrast, definitions of mutational Lamarckism exist that are too stringent and effectively render the possibility of observing genuine cases of mutational Lamarckism almost impossible. Lenski & Mittler (1993, p. 188) define mutational Lamarckism in these terms: 'We define as directed a mutation that occurs at a higher rate specifically when (and even because) it is advantageous to the organism, whereas comparable increases in rate do not occur either (*i*) in the same environment for similar mutations that are not advantageous or (*ii*) for the same mutation in similar environments where it is not advantageous'. We believe that this definition is both unclear and too strict, making mutational Lamarckism practically impossible. It is unclear because it is difficult to understand what the linguistic expression 'similar mutations' means in the first condition and what 'similar environments' means in the second condition. We suggest that these ambiguities need to be clarified by formalization. Lenski & Mittler's (1993) definition is similar to other proposed definitions. For instance, Hall (1990) characterized directed mutations in terms of two conditions: (*i*) mutations that occur only in the genes that would relieve the environmental stress and are not part of a generalized increase in mutation rate; (*ii*) mutations that occur during specific environmentally induced stress but only when they alleviate this stress. Similarly, Merlin (2010) defines a mutation as 'directed' if and only if: (*i*) it is more probable in an environment where it is beneficial than other

deleterious or neutral mutations (in the same environment); and (*ii*) it is more probable in an environment where it is beneficial than in other environments where it is deleterious or neutral. There is a deep analogy between these definitions. The first condition refers to the adaptiveness (and genomic specificity) of the mutational response, while the second refers to the inducing action of the environment. These definitions are comparable with the definition of Lamarckian mutation supplied by Koonin & Wolf (2009) which refers to three conditions: (*i*) environmental factors cause genomic (heritable) changes; (*ii*) the induced changes (mutations) are targeted to a specific gene(s); (*iii*) the induced changes provide adaptation to the original causative factor. Although this definition lacks reference to ambiguous expressions such as 'similar environments', 'other environment where it is deleterious or neutral' and 'similar mutations', it nonetheless includes ambiguous linguistic expressions such as 'provide adaptation' without specifying whether the expression refers to the 'lucky' adaptive mutation or to a general net effect of the increased mutation rate. More importantly, as we will now show, beyond the ambiguity of the terms used by these definitions, all include narrow conditions that in the last instance are unnecessary if the 'net fitness effect' is included as an explicit condition.

First, we believe that definitions such as those proposed by Lenski & Mittler (1993) and Merlin (2010), that require mutational processes to produce a higher proportion of adaptive mutations compared to non-adaptive ones, are too stringent. In effect, we argue that to ask that they do is tantamount to excluding mutational Lamarckism through a definitional trick. For instance, concerning the ILM case described above (Section II.1), Merlin (2010, p. 14) claims that '. . . .the probability of this beneficial reverse mutation occurring is not higher than for other neutral or deleterious mutations in the same leucine deprived environment'. Merlin's (2010) diagnosis is that ILM does not, contrary to what Jablonka & Lamb (1995, 2005) claim, produce a higher proportion of adaptive mutations compared to non-adaptive ones. We suggest that there is no reason to accept the casual intuition at the basis of this reasoning, according to which, for instance, if a mutational process produces three advantageous mutations and four deleterious or neutral ones in the genomic unit of reference, then the process is not Lamarckian. The problem concerns the net fitness effect of the mutational process, that is, the comparative weight of the fitness effects of beneficial and deleterious mutations independently of their relative proportions. What matters is only that the fitness effect of the beneficial mutations produced by the mutational mechanism overpowers the fitness change produced by the deleterious effect of the other induced mutations, independently of their number.

Secondly, the definitions provided by Lenski & Mittler (1993) and Merlin (2010) include neutral mutations within the 'not advantageous' mutations induced by the environment to be taken into account. However, from our perspective this requirement is irrelevant given that what matters is only the improved fitness of the individual, while neutral mutations, by definition, do not affect such fitness. Indeed, this requirement makes the definitions proposed even more difficult to satisfy for the reason that a high proportion of neutral mutations is produced in the genome (Kimura, 1983; see Razeto-Barry *et al.*, 2012). Consistently, in our definition we will not take neutral mutations into account because they do not change the overall fitness effect.

Thirdly, all discussed definitions endorse the local specificity requirement, that is, specificity of targeting of the induced mutagenic process, restricted to an exclusive increased mutation rate in the specific gene that generates the adaptive mutation(s). However, this requirement is very difficult to satisfy; indeed Merlin (2010, p. 14) excludes the ILM results of Wright (2000) and Wright *et al.* (1999) from the category of 'directed' or 'Lamarckian' mutations for this reason, claiming that '[i]n fact, Wright and her colleagues observed that this increased mutation rate is not only targeted at the *leuB* gene, where a mutation could allow bacteria to survive and reproduce, but at all the genes of the leu operon as well'. However, from our perspective this strict specificity is an irrelevant and practically too-constraining condition. The only reason to include regional specificity of the environmentally induced increased mutation rate is that, if there are many deleterious mutations induced in other regions, then the net effect of the induction is likely to be negative. However, this very strict condition can easily be replaced by the condition that the net fitness effect of the induction must be positive; thus, it does not matter if the increased mutation rate includes many different parts of the genome or a region that includes more than the specific gene involved in the adaptive response. On this point we agree with Sarkar (2005, p. 351) when he claims that '. . . the directionality of mutagenesis should not be lost if the mechanisms of mutagenesis depended on some non-specific increase in DNA mutability under stress'. His position has been criticised by Merlin (2010, p. 20, note 11): 'Sarkar claims that a mutation is directed "if it occurs (or occurs more frequently) in the fitness-enhancing or 'selective' environment", i.e., "in an environment where its associated phenotype has an enhanced fitness." The inherent risk of this definition is that it would consider a mutation [rate] to be "directed" even if it turns out to be beneficial in a given environment but not clearly more probable than other deleterious or neutral mutations'. Contrary to this argument, but in agreement with Sarkar (2005), we suggest that if mutational Lamarckism is defined in terms of net fitness effect, then this risk is eliminated.

We can now anticipate one aspect of our formalization by clarifying the notion of 'positive net fitness effect'. Let us define the random variable S as the expected net fitness effect of mutations produced by a mutational mechanism (or process) in a given environment, that is

$$S \equiv \text{Exp}\,(S) = p_1 s_1 + p_2 s_2 + \ldots + p_n s_n \qquad (1)$$

where s_i is the selection coefficient of the mutation i, which can be defined as $s_i = (w_i - w^+)/w^+$, with w_i the average fitness of individuals with the mutation i, and w^+ the average fitness of the wild-type (i.e. individuals without the mutation i)

(see, e.g. Razeto-Barry *et al.*, 2011, 2012), and p_i is the probability of occurrence of the mutation i. Then, although advantageous, neutral and deleterious mutations induced by a given environment might occur, we can define the overall fitness effect according to the value of S: advantageous when $S > 0$, neutral when $S = 0$, deleterious when $S < 0$. Note that S depends on the environment E, to identify which in our formal proposal we will use the function S(E) (see Section III.3).

In summary, this formal condition aims to elude the pitfalls and ambiguities of all preceding definitions. The intuition behind our proposal is that mutational Lamarckism means that the net fitness effect of a mutation rate increase is favourable and thus the process generates benefits for the organism. To demand that a mutational process is gene-specific and that it must produce a higher proportion of adaptive rather than non-adaptive mutations (furthermore including neutral mutations among the non-adaptive ones) puts the bar too high and writes mutational Lamarckism off in advance. Our proposal clearly indicates how it should be established that a mutational process is Lamarckian. The issue, we suggest, should be solved empirically: assuming that it is possible to identify the fitness effects of the various mutations caused by the environmental stimulus, the issue can be solved by determining whether the net effect is positive.

Note that we are not concerned with methodological problems in this context: whether measurement is realized by evaluating the fitness effect of many mutants (many individuals with different induced mutations) and averaging their fitness effects, or by detecting all induced mutations and measuring the fitness effect of each one (assuming additive fitness effects) is conceptually irrelevant. How the adaptiveness of mutational changes can be evaluated (i.e. whether in terms of relieving the immediate environmental stress or in long-term effects) is a serious methodological issue that does not affect our conceptual proposal.

(3) Dyadic conditions

We will now critically evaluate the evolutionary significance of definitions of mutational randomness couched in terms of the dyadic relationships between only two of the three relevant variables (i.e. occurrence of mutations, M; environment, E; and fitness effect, S). Our analysis will try to show that defining mutational randomness in dyadic terms does not make evolutionary sense.

(*a*) *Occurrence of mutation and fitness (M, S)*

Many definitions exist of mutational randomness (see Merlin, 2010) in terms of the relationship between mutation and fitness. For example, 'Random from the point of view of adaptation and functional integration' (Simpson, 1944, pp. 55–56); 'Random with respect to the direction of adaptation' (Stebbins, 1966, p. 35); 'A random process with respect to the adaptive needs of the species' (Dobzhansky, 1970, p. 65); 'The type of variation that arises through a mutation of a gene is random if and only if the probability of its occurrence in an environment has no correlation with the fitness of the phenotype induced by it in that environment' (Sarkar, 2005, p. 305).

The main problem with this type of definition is that, contrary to these claims, it is widely accepted that a statistical correlation exists between the occurrence of a mutation and fitness. In fact, it is a well-known thesis of the Modern Synthesis that the majority of mutations are deleterious (Simpson, 1953, p. 87). Thus, if we define mutational randomness as the absence of a statistical correlation between the probability of occurrence of a mutation and its adaptiveness, then mutational randomness could not be considered as acceptable within the Modern Synthesis framework. In fact, in general, if we know that a mutation is advantageous, then we can predict that its probability of occurrence is very low, a working hypothesis on which even opposed theorists in the selectionist/neutralist debate agree (Razeto-Barry *et al.*, 2012); a debate that has nothing to do with the issue concerning mutational Lamarckism. The natural selection explanation for the fact that deleterious mutations are more probable than advantageous mutations is that previous selection leaves populations near to local and global optima (Fisher, 1930; Orr, 1998; Charlesworth, 2012). This hypothesized selective scenario, in which populations are assumed to be located near fitness peaks in the adaptive landscape, would explain the high conservation of DNA sequences, and thus the difficulty of incorporating advantageous mutations (in relative proportion to deleterious ones) into the genome (see Razeto-Barry *et al.*, 2012). To summarize, independence between M and S cannot define mutational randomness (nor mutational Lamarckism) because the probabilities of mutation and fitness are in general correlated (i.e. they are not independent). Again, acknowledgement of this dependence is a traditional, accepted thesis of the Modern Synthesis that constitutes part of the current anti-Lamarckian consensus.

(*b*) *Fitness and environment (S, E)*

The relationship between fitness and environment is also important here. Merlin (2010, p. 5) criticized some definitions of random mutation that focus on 'the absence of connection between the probability of a mutation occurring and its probability of being beneficial', arguing that, according to the Modern Synthesis, 'the probability of developing an advantageous mutation is higher when organisms are faced with adverse environmental conditions to which they are not adapted'. In fact, this claim is part of the Modern Synthesis interpretation of mutation and as such does not imply Lamarckism (Dobzhansky *et al.*, 1977; Brisson, 2003; Futuyma, 2005). The reasoning is very easy to understand using the well-known adaptive landscape model. In adverse environments it is more likely that a mutation will be beneficial, that is, it is more probable that a mutation is advantageous compared with the same mutation in a favourable environment (Fig. 1, see also Poon & Otto, 2000). Thus, independence between S and E not only cannot define mutational randomness (nor mutational Lamarckism), but,

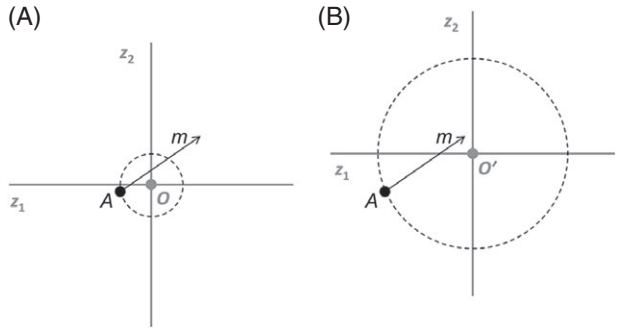

Fig. 1. In the adaptive landscape model of Fisher (1930) where possible phenotypic traits are represented by axes z_1 and z_2, the same mutation m in an organism with phenotype A has a negative effect (A) in an environment in which the optimal phenotype O is nearer to A, while m has a positive effect (B) in an environment in which the optimum O' is further from A.

in addition to this, it does not generally hold true. In fact, it is a traditional, accepted statement of the Modern Synthesis that the probability of mutations being advantageous is not independent of the nature of the environment.

Note additionally that Merlin's (2010) statement quoted above is ambiguous and could be misinterpreted. What the authors of the Modern Synthesis claimed is that it is more probable that the same mutation will be advantageous in adverse rather than in favourable environmental conditions (Fisher, 1930; Razeto-Barry *et al.*, 2011). However, this does not imply that in adverse environmental conditions the probability of occurrence of advantageous mutations is higher compared with the probability of deleterious ones. That is, if the probability of advantageous and deleterious mutations is 2 and 98%, respectively, in a normal environment *E1*, it is possible that in an adverse environment *E2* the probabilities are 4 and 96%. In other words, the fact that the probability of a mutation being advantageous increases in adverse conditions does not imply that its probability is higher than the probability of deleterious mutations.

(*c*) *Occurrence of mutation and environment (M, E)*

Jablonka & Lamb (2005) consider increases of the probability of mutation induced by (adverse) environments (so-called 'mutator mechanisms') as cases of Lamarckian mutations. In our view, Merlin (2010) correctly claims that this interpretation is mistaken because this mutational pattern may be adaptive for the population as a whole rather than for the individual. That the latter corresponds to the correct interpretation of the available evidence can be experimentally verified in the many cases in which the majority of mutations produced overall at the level of the population is deleterious. Processes such as the SOS response, genome-wide mutations, and global increases in mutation rates are putative examples of this mutational pattern. Using Sarkar's (2005, p. 354) terms, 'what is ''random'' at one level of organization is directional at a higher level… The hypermutable state model proposed by Hall, 1990 is an example of this pattern of higher-level Lamarckism but lower-level Darwinism'. In summary, the probability of mutation is not independent of the environment, that is, there exist global 'mutator mechanisms'. This type of mechanism probably would not have been problematic for the fathers of the Modern Synthesis given that increased recombination in response to stress was known (Plough, 1917; see Heininger, 2013). For example, cyclic parthenogenesis, where increases in numbers of sexual variants are environmentally induced was proposed to be an adaptation for the species by Weismann (1889; see Meirmans, 2009), and the increased variability inherent in sexual compared to asexual reproduction was studied in terms of group selection by Fisher (1930) and Muller (1932) (see Nunney, 1989). Thus, independence between M and E cannot define mutational randomness (nor mutational Lamarckism).

III. OUR PROPOSAL

(1) Correlation, independence and definition of variables

In Sections II.3*a–c* we analysed different dyadic definitions that have been proposed in the evolutionary literature in order to define mutational Lamarckism (summarized in Fig. 2). Note that, in the case of these definitions, the statistical notion used to capture the probabilistic relationships between the relevant variables has been that of 'absence of correlation'. However, we suggest that the concept of 'independence' should be used instead: absence of correlation does not imply independence, while independence implies absence of correlation (Stone, 2004). Given that there may be cases in which the occurrence of one event determines the probability of occurrence of another event even in the absence of correlation, the formalization of the probabilistic concepts of causation and explanation is better couched in terms of independence rather than absence of correlation (Hitchcock, 2002). It seems reasonable to assume that the genetic randomness proposed by neo-Darwinian theory refers to some kind of independence (Razeto-Barry & Frick, 2011) and that thus absence of correlation is not a good statistical measure of genetic randomness.

Two variables X and Y are independent iff $P(X \text{ and } Y) = P(X)P(Y)$. In particular, iff X and Y are independent then $P(X|Y) = P(X)$, where $P(X|Y)$ is the conditional probability of X given Y. Thus, previous dyadic relationships can be understood as putative relations of independence among the occurrence of mutations produced by a specific mechanism (M), the net fitness effect of the mutational mechanism (S) and an environmental variable (E) (Fig. 2).

Here, when we refer to the environmental variable (E) we refer to a single specific property of the 'selective environment' (*sensu* Brandon, 1990; e.g. different temperatures, concentration of an amino acid, etc.), that is, those aspects of the external environment that affect the

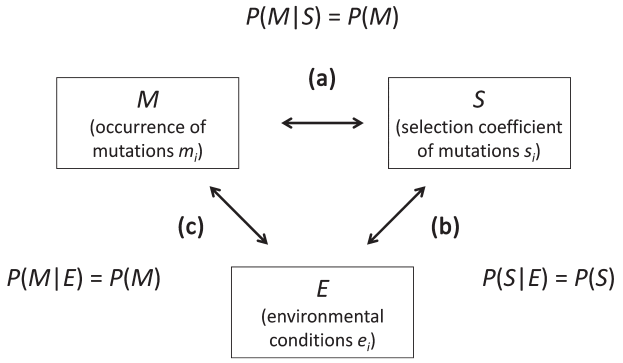

Fig. 2. Relations between occurrence of mutation (M), fitness (S) and environment (E) described in Sections II.3*a–c*. $P(X|Y)$ is the conditional probability of X given Y.

target organism's fitness. Consider also that the variable (M) represents the set of mutations that can be generated by the mutational mechanism, $M = \{m_1, m_2, \ldots, m_n\}$. Thus, for example, $P(M|S) = P(M)$ means that $P(m_1|S) = P(m_1)$, $P(m_2|S) = P(m_2)$, $\ldots$, $P(m_n|S) = P(m_n)$.

(2) A triadic concept (M, S, E): conditional independence

We shall now propose a formal definition of random (Darwinian) mutation and directed (Lamarckian) mutation using the triadic probabilistic concept of conditional independence. First we will explain this concept and then we will propose the relevant evolutionary definitions in order to capture the concept of mutational Lamarckism and randomness.

Two variables X and Y are conditionally independent given a third variable Z iff $P(X|Y \text{ and } Z) = P(X|Z)$ or, which is the same, $P(X \text{ and } Y|Z) = P(X|Z)P(Y|Z)$. In other words, we could characterize conditional independence in objective terms as follows: two events X and Y are conditionally independent given a third event Z iff the occurrence or non-occurrence of X and the occurrence or non-occurrence of Y are independent events in their conditional probability distribution given Z. In subjective terms, the characterization of conditional independence may be as follows: given knowledge that Z occurs, knowledge of whether X occurs provides no information on the likelihood of Y occurring, and knowledge of whether Y occurs provides no information on the likelihood of X occurring.

Note that the contrast between 'independence' (symbolized $X \perp Y$) and 'conditional independence' (symbolized $X \perp Y|Z$) is very important given that independence neither implies nor is implied by conditional independence (Stone, 2004).

(3) Definition of Darwinian (random) and Lamarckian (directed) mutational mechanism

We propose the following definition: a mutational mechanism or process is random (or "Darwinian") with respect to a selective environmental variable E if and only if the probability of occurrence of mutations M that can be generated by the mutational mechanism with net fitness effect $S(E)$ satisfies the following condition:

$$P(M|S(E) \text{ and } E) = P(M|E) \tag{2}$$

that is, if the occurrence of mutations is conditionally independent of the fitness effect of the mutations given the environmental variable, i.e. $M \perp S(E)|E$.

In other words, in a Darwinian mutational mechanism, mutations are conditionally independent of the net fitness effect of the mutational mechanism given an environment if (in objectivist terms) the occurrence or non-occurrence of the mutations that can be generated by the mutational mechanism and the occurrence or non-occurrence of an advantageous net fitness effect of the mutations are independent events in their conditional probability distribution given the environment. Or, for example, in subjectivist terms, given knowledge that a particular environmental variable changes (e.g. leucine decreases), knowledge of whether mutations (e.g. *leuB*$^+$) increase the fitness of a bacterium under the new environmental condition provides no information on the likelihood of that mutation occurring, and knowledge of whether mutations occur provides no information on the likelihood of their net fitness effect.

By contrast, we propose that a Lamarckian mutational mechanism may be formalized in terms of a particular kind of conditional dependence. Thus, we define a mutational mechanism or process as Lamarckian (or "directed") with respect to a selective environmental variable E if and only if:

$$(i)\ P(\text{corr}\{M(E)\} > 0 | \text{corr}\{S(E)\} > 0) > P(\text{corr}\{M(E)\} > 0)$$

$$(ii)\ \text{There exist at least some } e \in E \text{ such that } S(e) > 0.$$

Or paraphrasing, when (i) the probability that the correlation between the occurrence of M and E is positive, given that the correlation between S and E is positive, is higher than if the correlation between S and E is not considered, and (ii) the net fitness effect of the mechanism in some particular environment e from E is positive.

In other words, the first condition makes reference to the fact that, in a Lamarckian case, if the set of mutations that can be generated by the mutational mechanism in an environment e_2 (e.g. a low concentration of leucine) has a higher net fitness effect than if they occur in environment e_1 (e.g. normal concentration) — and thus $\text{corr}\{S(E)\} > 0$ —, then the increased occurrence of these mutations in e_2 in comparison with e_1 (i.e. $\text{corr}\{M(E)\} > 0$) is more probable than if $\text{corr}\{S(E)\} \leq 0$ (see Fig. 3). The second condition excludes cases in which the overall fitness effect of mutations has a detrimental effect on the organism in all environmental conditions, which allows us to define the concept of 'directed mutation' consistently with the above arguments concerning the importance of the positive net fitness effect when we

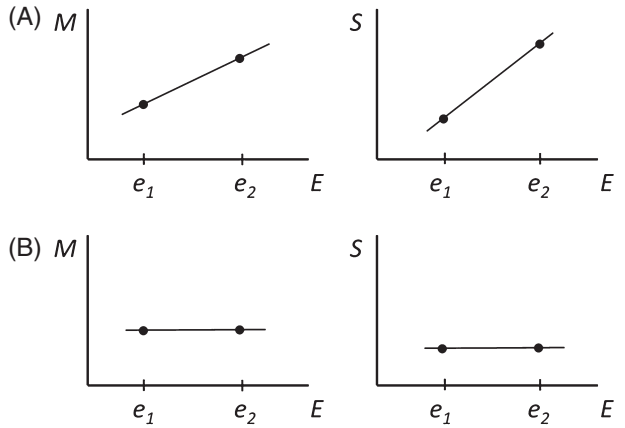

Fig. 3. Illustration of the satisfaction of condition *i* (Section III.3). (A) When the fitness effect (*S*) of the mutation is higher in environmental condition e_2 in comparison with e_1 (right), — and thus corr{$S(E)$} > 0 — the probability of an increased occurrence of these mutations (*M*) in e_2 in comparison with e_1 is high (left) and thus corr{$M(E)$} > 0. (B) When the fitness effect of the mutation is not higher in environmental condition e_2 in comparison with e_1 (right), and thus corr{$S(E)$} ≈ 0, the probability of an increased occurrence of these mutations in e_2 in comparison with e_1 is also not high (left), and thus corr{$M(E)$} ≤ 0.

analysed wide and narrow definitions (Sections II.1 and II.2, respectively).

We thus propose that a particular mutation m_i occurring in an environment with a given value *e* of the selective environmental variable *E* is a 'Lamarckian (or directed) mutation' if and only if (*a*) m_i has a positive fitness effect $s_i > 0$ in that environment with $E = e$, and (*b*) m_i was produced by a Lamarckian mutational mechanism with a positive expected net fitness in that environment *e* ($S(e) > 0$).

Note that here we have used the probability of correlations (corr{$M(E)$} and corr{$S(E)$}) – and not only the concepts of independence or dependence – because the latter cannot capture the distinction between positive and negative associations between variables, which is essential to the Lamarckian, but not the Darwinian, position. Note also that the terms corr{$M(E)$} and corr{$S(E)$} represent here random variables and not numbers. More technically, they represent conditional expectations of the form $\mathrm{Exp}(X|Y)$, where *X* is the value of the correlation and *Y* is the set of different random factors that may determine the value of the correlation.

(4) Are the postulated empirical cases of directed mutations genuine cases of Lamarckian mutational mechanisms?

A postulated case of mutational Lamarckism is the clustered regularly interspaced short palindromic repeats (CRISPR) and CRISPR-associated genes system (Koonin & Wolf, 2009). In this system, the bacterium (or archaeum) incorporates into its genome fragments of DNA of potentially infectious bacteriophages (or plasmids). These DNA fragments are inserted in a position that is precisely complementary to the relevant region of the phage genome and are used to produce and mobilize molecules that attack familiar viruses and destroy their RNA or DNA, providing a basic but effective immunity system.

In contrast to the hypermutable *leu* system, in the case of the CRISPR system, the putative Lamarckian mechanism is not related to different levels of mutation rates but rather to inducing specific changes generating a single mutation, i.e. a short DNA or RNA insert. In this case the mutation is the only one induced by the mechanism and thus $m = M$ and $s = S$. The mutation occurs only when the environment has presence of virus (for simplicity, we can assume a dichotomous selective environmental variable *E* that takes only two values: absence e_1 or presence e_2 of viruses), in which $S = s > 0$. Thus, in this case it is clear that mutation *m* satisfies condition *a* in Section III.3 given that it has a positive fitness effect $s_i = s > 0$ in the environment with $E = e_2$. However, although experiments show an increase in the probability of the insertion $P(m(e_2)) - P(m(e_1)) > 0$ (i.e. $P(\mathrm{corr}\{M(E)\}) > 0$) when that insertion is advantageous (i.e. when $s(e_2) - s(e_1) > 0$ or corr{$S(E)$} > 0) (Fig. 3A), it should be additionally shown that if the mutation were not fitter in e_2, then the probability of the insertion would not increase (Fig. 3B). One way to show this would be to determine whether the probability of the insertion in e_2 does not increase in bacteria which already have the insertion — and thus their fitness would probably not increase with a new insertion, i.e. corr{$S(E)$} ≈ 0. In this case, then condition *b* in Section III.3 would be also satisfied and, according to our definitions, the CRISPR system should be considered a genuine case of a Lamarckian mutational mechanism and the inserted DNA should be considered a genuinely Lamarckian mutation.

In the experiments of Wright *et al.* (1999) and Wright (2000), leucine starvation in *E. coli* produced local hypermutability in the gene *leuB* that bears the mutation that produces leucine (*leuB*$^+$). It is clear that *leuB*$^+$ has a positive fitness effect $s > 0$ in the experimental cell culture with a decreased (e_2) level of leucine concentration (*E*). Thus *leuB*$^+$ satisfies condition *a* in our definition of 'Lamarckian mutation'. The second condition *b* is however more difficult to satisfy clearly. The increased mutation rate of the gene (or the operon containing) *leuB* entails a higher probability of occurrence of the set of mutations produced by the mutational mechanism (*M*) (i.e. mutations in gene *leuB* or in the operon containing *leuB*) for lower concentrations of leucine (i.e. for different values of *E*). Thus, condition *i* in Section III.3 is satisfied. However, Wright *et al.* (1999) and Wright (2000) did not measure whether the net fitness effect of mutations in the operon containing *leuB* is positive (i.e. whether $S(e_2) > 0$), which is essential to satisfy condition *ii* in Section III.3, in turn necessary to satisfy condition *b*. In addition to this, it should be shown that if the mutation was not fitter in e_2, then the probability of mutation *leuB*$^+$ would not increase (Fig. 3B). If this was the case, then this process would satisfy condition *ii* and thus be a genuine case of Lamarckian mutational mechanism, and *leuB*$^+$ would satisfy condition *b* and be a genuinely Lamarckian mutation.

The satisfaction of these two conditions remains an open empirical problem.

IV. DISCUSSION

Definitions of 'mutational Lamarckism' are deficient mainly because they define mutational randomness as a dyadic concept or because they are too wide or too narrow. We suggest that random mutation should be considered as a triadic concept that can be captured by means of the statistical concept of 'conditional independence', according to Equation 2. This definition contrasts with the Lamarckian counterpart that specifies the conditions of mutation induction (condition *i*) and of positive net effect of induction (condition *ii*). Condition *ii* demands that the environmental induction of mutations has a positive effect on the organism, while condition *i* is somewhat more complicated: if the net fitness effect of mutations is higher in an environment e_2 than in e_1, the probability of an increased occurrence of mutations in e_2 will be higher than in e_1 in comparison with the probability with which it would occur if the net fitness effect were not higher in e_2 than in e_1.

Our formalization expresses a statistical definition that is clearer and more precise than the loose and often obscure definitions found in the extant literature, while at the same time maintaining the probabilistic spirit of many traditional definitions. In particular, by using the concept of conditional independence, we exclude simple and widely accepted cases of correlations (direct dependence) among E, S and M as evidence for mutational Lamarckism, which have been considered part of the anti-Lamarckian canon that characterizes the Modern Synthesis.

One central concept in our proposal is S, i.e. the net fitness effect of the mutational process on the individual organism. The empirical estimation of S is decisive in assessment of mutational Lamarckism. Some important implications of this can now be illustrated. First, given that S can refer in principle to the whole genome of the organism (when the mutational mechanism affects the whole genome), our proposal does not require the 'local specificity' condition so common in the literature (i.e. that the mutational process is targeted to one part of the genome such as a specific gene) (see Hall, 1990; Lenski & Mittler, 1993; Koonin & Wolf, 2009; Merlin, 2010). The only reason to include local specificity of environmentally induced mutations is that, if many deleterious mutations are induced in more than one region or a single wide region, then the net effect of the induction would likely be negative. What we have proposed is to replace this case-relative condition with the general condition that $S > 0$. For analogous reasons, the focus on S implies that it is necessary to take into account the fitness effects of mutations rather than only their absolute numbers and that, additionally, there is no rationale for taking neutral mutations into account for S given that they do not have, by definition, any fitness effect (i.e. they do not affect S) (see Merlin, 2010).

Another result of our proposal is that it does not exclude in advance plausible mechanisms that are intuitively consistent with Lamarckian ideas (e.g. Wright *et al.*, 1999; Wright, 2000; Koonin & Wolf, 2009). The problem at this juncture becomes empirical: it could be that it turns out that $S > 0$ and that we are indeed in the presence of a Lamarckian mechanism (conditions *i* and *ii* in Section III.3). Even though we obviously realize that finding an appropriate methodology to achieve a reliable estimation of the parameters needed to satisfy the proposed conditions is a difficult challenge, our aim herein is to highlight the conceptual nature of definitions and their potential experimental implications.

Let us now conclude with some more general philosophical remarks. The hypothesis of mutational Lamarckism was suggested to promote a teleological view of organic evolution (Fox Keller, 1992). For instance, Lenski & Mittler (1993, p. 193) claimed that: 'The most extreme interpretation of the evidence for directed mutation is that a cell can somehow monitor or anticipate the consequences of potential genetic changes for its fitness and then choose or direct the specific change that would be most advantageous'. Dobzhansky (1951, p. 74) made a similar remark: 'An ideal situation would be if the organism were to respond to the challenge of the changing environment by producing only beneficial mutations where and when needed. But nature has not been kind enough to endow creations with such a providential ability'. The use of the terminology of 'choice' and 'providence' was probably aimed at trivializing an issue that is eminently empirical by rejecting *a priori* an interpretation of the empirical evidence alternative to the orthodox neo-Darwinian (i.e. that there exists some form of directional behaviour on the part of the organism). Interestingly, it could be argued that the teleological view of evolution has been actually vindicated experimentally through the discovery of the CRISPR system of bacterial immunity: this mutator mechanism exactly provides what Dobzhansky (1951) thought was unprovidable, that is, that only beneficial mutations are produced where and when needed. This experimental vindication of Lamarckism should propel, in our opinion, a reflection on the way in which the debate about directed mutation unfolded since the publication of Cairns *et al.* (1988).

Note that our approach does not take the causal mechanisms underlying random and directed mutational mechanisms explicitly into account. However, we would like to stress that several causal mechanisms may be subsumed by our definition of directed mutation. For example, possible causal mechanisms may be understood as evolutionary adaptations ultimately caused by a long-term process depending on what was adaptive in the history of the lineage, or as learning mechanisms *via* which the organism can detect what is currently adaptive that would require a proximate explanation. There is no *a priori* reason to believe that both mechanisms might or might not be Lamarckian. This shows the suitability of our probabilistic approach and its capacity to subsume different potential causal mechanisms as Lamarckian. Needless to say, our analysis is

not empirically exhaustive and we do not focus on the nature of potential mutagenic mechanisms (and their molecular basis) that have been proposed over the last 10 years or so in the specialized literature. An exclusively causal approach aiming to characterize random and directed mutational mechanisms remains viable and legitimate. This compatible but complementary project was not the focus of our review.

We believe that mutational Lamarckism must be taken seriously. It seems clear that research programmes directed to study and find new mutational mechanisms are virtually non-existent. However, if mutational mechanisms can be clearly defined and at least some concrete cases exist, the absolute and relative amounts of Lamarckian *versus* Darwinian mechanisms may be studied. We defined 'mutational Lamarckism' as the claim that there exist cases of Lamarckian mechanisms, and we propose that this is probably true. However, if the relative proportion of both mechanisms is taken as an important evolutionary problem, we can define 'weak mutational Lamarckism' as the claim that Lamarckian mechanisms exist and 'strong mutational Lamarckism' as the claim that the proportion of Lamarckian mechanisms is higher than that of Darwinian mechanisms. Here, we defend the weak but not the strong version of mutational Lamarckism, but realize that although the weak problem may now be solved, the strong problem remains empirically open.

V. CONCLUSIONS

(1) In this article we have suggested that random mutation should be considered as a triadic concept that can be captured by means of the statistical concept of 'conditional independence'. This definition contrasts with the Lamarckian counterpart that specifies the conditions of mutation induction in terms of conditional dependence and of a positive net effect of induction.

(2) Our formalization expresses a statistical definition that is clearer and more precise than the loose and often obscure definitions found in the extant literature, while at the same time maintaining the probabilistic spirit of many traditional definitions.

(3) A central concept in our proposal is the net fitness effect of the mutational process on the individual organism, represented by S. The empirical estimation of $S > 0$ is decisive in assessment of mutational Lamarckism.

(4) The discovery of Lamarckian mutational mechanisms would provide the experimental vindication of Lamarckism and should propel a reassessment concerning the relative frequency of Lamarckian and Darwinian processes in evolution.

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