

# On Mutational “Randomness”

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Mutations are often described as “random.” That mutations occur randomly (independently) with respect to their effects on organisms is prevalent in evolutionary biology literature, textbooks, and discourse. This idea provides the theoretical backdrop on which emerging molecular mechanistic models of mutation are evaluated. To see this view on mutational randomness, a survey of useful references is compiled, which, as a whole, begins to paint a picture of where this idea about mutation fits historically and conceptually. This list is meant to be a resource, with the hope that it will be useful to those navigating shifting ideas about mutational randomness in the age of molecular genomics.

Interpreting meaning from texts can be tricky, and heated semantic debates quickly arise when the not-so-clear idea of randomness is scrutinized. This collection is simply a reference list, providing some examples of the language around the broad claim of **random mutation with respect to consequences** with an emphasis on research papers and educational materials, and readers are encouraged to seek out the original texts. In some cases, the statements quoted here are simply the author's own summary of the state of the field and not necessarily their own. And as new evidence comes to light, ideas can change, so some statements may only reflect an author's view at the time of writing.

This reference list is not exhaustive, nor does it reflect the only definition in evolutionary biology of randomness.

A more narrow evolutionary definition of mutational randomness regards specifically that mutations are not more likely to occur in specific environments where they are more likely to be beneficial than in other environments relative to other mutations. Whether this assertion of randomness will prove a unifying claim in evolutionary biology in light

of emerging mechanistic models of mutation bias remains unknown, necessitating experiments that have yet to be conducted so we lack empirical evidence to sufficiently examine its validity across biology (but see (Koonin and Wolf 2009; Koonin 2011)).

From a probabilistic view, all emergent phenomena, including evolutionary processes like selection are “random” because we lack complete knowledge to predict the future perfectly, and thus it is best to describe all phenomena through the lens of statistical probabilities. As has been discussed elsewhere, probability theory is therefore incredibly useful for building quantitative predictive models of complex processes but not useful for conceptual or semantic discussions about which evolutionary processes are or are not random (Wagner 2012).

Likewise, metaphysical definitions of randomness (mutations don't happen because they “know” the outcome; the arrow of causality always goes from past to future, etc) are irrelevant for discussions in natural science about the randomness of any evolutionary processes.

For the purposes of contextualizing empirical evidence of functional mutation rate heterogeneity, the most general idea of randomness is the relevant and testable claim that mutations occur independently of their consequences. This is the common definition we explore here.

## **In no particular order:**

**“The occurrence of a given mutation is in no way related to the evolutionary needs of the particular organism or of the population to which it belongs....Neither underlying molecular phenomena nor the mechanical motions**

responsible for this randomness are related to their biological effects.” (E. Mayr 1961)

“Mutations are random in the sense that they arise without reference to their advantages or disadvantages (i.e. their fitness effects)” (Charlesworth, Barton, and Charlesworth 2017)

"Mutations are random because they occur independently of whether they are beneficial or harmful" (Dobzhansky et al 1977)

“the main assumption of molecular population genetics—that genomic mutation rate does not depend on sequence function” (Rodriguez-Galindo et al. 2020)

"The direction of mutation is entirely random with reference to their functional or adaptive value" (Stebbins 1982 p. 69)

“(non-random mutation) is theoretically untenable, especially in the lack of mechanisms that simultaneously tune the mutabilities of multiple genes with similar fractions of deleterious mutations.” (Chen and Zhang 2013)

“Mutations are ‘random’ in the sense that the sort of mutation that occurs cannot generally be predicted based upon the needs of the organism.” (Rockman 2021)

“Any given mutation is merely a chance error in the genetic system, and as such, its likelihood of occurrence is not influenced by whether it will turn out to be detrimental, beneficial, or (most commonly) neutral... Mutation is random with respect to fitness. Natural selection is, by definition, non-random with respect to fitness. ” (Gregory 2009)

‘Biologists usually agree that all genetic mutations occur by “chance” or at “random” with respect to adaptation’ (Merlin 2010)

“This variation is ultimately due to mutations that arise at random with respect to the direction of selection” (B. Charlesworth, Lande, and Slatkin 1982)

“Most biologists agree that mutations in DNA have random effects on fitness.” (Wagner 2012)

"the consequences of a mutation have no influence whatsoever on the probability that this mutation will or will not occur. In other words, mutations occur randomly with respect to whether their effects are useful. “ (Loewe 2008)

“Genetic mutations are random in the sense that they occur independently of the phenotypic variation they produce.” (Johnston et al. 2022)

“The directions of the changes produced by them appear to be unrelated...to the adaptive or functional needs of the organism. Evolutionary direction has to be imposed on random mutation through the sifting and therefore guiding action of selection” (Huxley and Others 1942)

“Variation in the characteristics of organisms in a population originates through mutation of DNA sequences (genes) that affect the characteristics. ‘Random’ here means that the mutations occur irrespective of their consequences for survival or reproduction” (Futuyama and others, 2001)

“mutations are random events with respect to adaptation—that is, their occurrence is independent of any possible consequences.” (Britannica 2021)

“the notion that mutation is random with respect to fitness has been foundational to modern biology...mutations arise without respect to their fitness...” (Roy 2016)

“That the generation of mutations (a process called mutagenesis) is blind to its consequence has since become an established principle of genetics.” (Zhang 2022)

**“A longstanding historical view in evolutionary theory is that mutations occur randomly with respect to their functional consequences” (Burgess 2022)**

**“Evolution is based on mutations that are random with respect to the adaptive needs of the organism” (Douglas J. Futuyma 2015)**

**“A central tenet in evolutionary theory is that mutations occur randomly with respect to their value to an organism; selection then governs whether they are fixed in a population.” (Martincorena, Seshasayee, and Luscombe 2012)**

**“the evidence that some genomic regions have been selected for high or low mutation rates is weak. There are also good theoretical reasons for believing that selection on the mutation rate either would be ineffective or would have to operate at a scale that is larger than we observe” (Hodgkinson and Eyre-Walker 2011)**

**“positive correlation between [fitness] and [mutation rate] in mammals is quite unexpected ... because it would appear to imply that the strength of natural selection acting upon a protein is correlated to the mutation rate.” (Stoletzki and Eyre-Walker 2011)**

**“It has been argued that mutation rates, even at the single-gene level, have been fine-tuned by natural selection to maximize long-term survival and evolvability, yet there is no direct empirical or theoretical evidence that this is generally the case.” (Lynch et al. 2016)**

**“A widely accepted tenet of evolutionary biology is that spontaneous mutations occur randomly with regard to their fitness effect.” (Martincorena and Luscombe 2013)**

**“adaptive evolution based fully on population-level processes occurring over multiple generations and involving the nonrandom sorting of randomly generated genetic variation” (Gregory and Ellis 2009)**

**“the production of genetic variation, is almost exclusively a chance phenomenon” (Ernst Mayr 2001)**

**“The results of these reports suggest that mutants can arise nonrandomly with respect to fitness, contrary to what has been widely accepted.” (Paul D. Sniegowski 1995)**

**“random in that their phenotypic effects, if any, are not directed towards ‘need’...the maintenance of function depends on stabilizing or purifying natural selection” (Douglas J. Futuyma 2017)**

**“The usual analogies we make in such cases involve making random adjustments in a finely constructed watch, or making random alterations of a carefully-written poem” (Felsenstein 2005)**

**“In this model, the effect of a mutation is described by a random vector in an n-dimensional phenotype space, originating from the position of the current phenotype in that space (i.e., the wild-type state). Fitness is evaluated as the Euclidean distance gain toward a fitness optimum that the vector confers.” (Bank et al. 2014)**

**“Mutation is random in [the sense] that the chance that a specific mutation will occur is not affected by how useful that mutation would be” (D. J. Futuyma 1986)**

**“mutations are not biased toward adaptedness” (Douglas J. Futuyma 1984)**

**“Random vectors originating from the current phenotype represent new mutations. Those mutations that decrease the distance to the optimum are considered beneficial and can hence contribute to adaptation, whereas those that increase the distance to the optimum are considered deleterious.” (Hietpas et al. 2013)**

**“A fundamental tenet of evolutionary biology is that mutations are random events...the likelihood of any particular mutational event is independent**

of its specific value to the organism" (Lenski and Mittler 1993)

**"A central tenet of evolutionary theory is that mutation is random with respect to its adaptive consequences for individual organisms; that is, the production of variation precedes and does not cause adaptation"** (P. D. Sniegowski and Lenski 1995)

**"neo-Darwinist emphasis on random variation (that the cause of a new mutation is not influenced by its real or potential benefit or cost)"** (Wideman et al. 2019)

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