Mutations are accidents, and accidents will happen.
Alfred Sturtevant **1937**

Whence Variation? Rethinking Mutation and Evolvability

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What the devil determines each particular variation? What makes a tuft of feathers come on a cock's head, or moss on a moss-rose? Charles Darwin **1859**

Some authors believe it to be as much the function of the reproductive system to produce individual differences ... as to make the child like its parents.
Charles Darwin **1859**

Introduction

The concept that production of variation is a proper biological function is older than Darwin's *Origin of Species*.

But this idea has been eclipsed for most of the past century, by a conviction that "mutations are accidents."

Unnecessarily conflating the fundamental meaning of "mutation" (any alteration of DNA sequence) with a presumption of "replication error" can obscure the role of several mutational mechanisms as *protocols** for generating variation.

* A protocol is an implicit rule or architecture that defines permissible avenues for behavior. A mutation protocol adjusts the probabilities for mutations of particular styles, at particular loci.

Background

For too long evolutionary theory has simply presumed the adequacy of mutation to sustain adaptive evolution. Although mutation is acknowledged as the ultimate source for all standing genetic variation, that source is presumed to require no further explanation than "accidents will happen."

The conflation of "mutation" with mere "accident" and "error" has deep historical and theoretical roots. Emphasis on a gene-centric perspective has even led to defining "fitness" in terms of exact copies of a gene being passed from one generation to the next.

A few classical examples

"*Evolution is something that happens, willy-nilly, in spite of all the efforts of the replicators (and nowadays of the genes) to prevent it happening... By definition, a copying error is to the disadvantage of the gene which is miscopied.*" R Dawkins **1976**

"*The fittest possible degree of stability is absolute stability. In other words, natural selection of mutation rates has only one possible direction, that of reducing the frequency of mutation to zero... Evolution has probably reduced mutation rates to far below species optima, as the result of unrelenting selection for zero mutation rate in every population... So evolution takes place, not so much because of natural selection, but to a large degree in spite of it.*" GC Williams **1966**

"*Any organism as it now exists must be regarded as a very complex physicochemical machine with delicate adjustments of part to part. Any haphazard change made in this mechanism would almost certainly result in a decrease of efficiency...*
Only an extremely small proportion of mutations may be expected to improve a part or the interrelation of parts in such a way that the fitness of the whole organism for its available environments is increased." C Bridges **1919**

Current relevance

Unfortunately, this argument endures beyond any historical interest. It continues to be used against any suggestion that mechanisms of mutation might evolve to facilitate evolution. Here is one example:

"*However, a well-established and supported tenet of evolutionary theory is that, because most new mutations are deleterious, selection in all organisms will act to reduce mutation rate toward the physiology- or selection-imposed minimum* [*]. *Thus, in principle it is unlikely that a type of variation with high mutational instability, like* [tandem repeats], *would be a major contributor to phenotypic evolution.*" MH Elmore *et al.* **2012**

* A citation here is explicitly relevant only for base pair substitutions, not for the subject of the paper, which is tandem repeats.

Rethinking **mutation**

Traditional	*Reconceived*
"Mutation" carries a connotation of accidental error, such that selection is expected to minimize all processes of mutation.	Several sources of variation, including some of those commonly called "mutation," can confer adaptive benefit.
The vast majority of mutations that affect fitness are deleterious.	Not all mutational processes are necessarily disadvantageous.
Mutational processes have not been positively adapted or focused by natural selection.	Indirect selection can exploit varying probabilities of mutational effect to create adaptive mutation protocols.
Recombination is excluded *by definition* from the concept of "mutation," because the resulting alterations of DNA sequence are widely recognized as adaptive.	Excluding recombination from the category of "mutation" is arbitrary, dating from the "beads-on-a-string" era when genes were conceptualized as discrete entities.

Rethinking **evolvability**

Traditional	*Reconceived*
Standing variation, originating from "accidental" mutation, has been sufficient for all adaptation.	The evident adequacy of standing variation is a phenomenon which calls for explanation beyond imperfect replication.
Evolvability is nothing more than a fortuitous but inevitable consequence of imperfect DNA replication.	Evolvability depends on evolved mutation protocols, which impose "grammatical" constraints on sequence variation.
Because individual organisms do not evolve, evolving special features to confer evolvability must require group selection.	Evolvability is an emergent consequence of mutation protocols. Group selection need not be invoked.
Group selection is implausible under most circumstances (it is much weaker than individual selection).	Mutation protocols are shaped by indirect selection, which can be effective at all levels *except* narrowly-defined gene selection.

What I propose to do is to inquire into the type of hereditary differences ... which nature might use as materials with which to accomplish evolution. R Goldschmidt **1940**

Sample **protocols**

Reversible, incremental adjustability of gene function	›››	Variable-number tandem repeats can behave like "tuning knobs" for practically any aspect of gene function.
On / off switching for individual genes	›››	Bacterial contingency genes are turned on and off, using tandem repeats.
Copy-and-paste of functional modules	›››	Transposable elements play a major role in genome evolution, creating permissive and possibly necessary conditions for adaptive innovation and diversification.
Programmed gene arrangement	›››	Various microorganisms utilize transposition and inversion to shift expressed surface antigens.
Mix-and-match	›››	Reciprocal recombination during meiosis is a fundamental source for variation.
Targeted hypermutation	›››	Even high rates for single basepair substitutions can be advantageous when concentrated in appropriate sites, such as immunoglobin genes.

Summary / What next?

The traditional argument, that selection must minimize mutation rates, has potential validity only for loci where mutator alleles would yield a genome-wide increase in mutations, and even then only when the vast majority of mutations are deleterious.

In spite of such limited applicability, this argument is commonly wielded against the idea that *any* style of mutation could be advantageous.

But mutation protocols circumvent this argument. Indirect selection is capable of shaping, and indeed has shaped, numerous mechanisms that facilitate variation.

Understanding the genetic basis for evolutionary innovation, especially for complex adaptive behaviors, may well depend on appreciating the role of mutation protocols.

Indirect selection

Indirect selection for facilitated variation (i.e., for a mutation protocol) occurs whenever favorable variants arise within constraints that are themselves heritable and linked to the favorable variants.

The potential for indirect selection is most clearly illustrated by site-specific elevation of mutation rate, such as that imposed by tandem repeats. When favorable mutants arise, they retain the site-specific mutation rate by which they arose. Selection for the favorable mutant then also indirectly but inevitably favors localized elevation of mutation rate for this particular style of mutation, thus facilitating future variation of a similar style.

The potential benefit-to-risk ratio for mechanisms that generate variation spans a wide range, from nucleotide substitution (generally minimized by selection) to sexual reproduction (supported by elaborate and expensive mechanisms).

Indirect selection should be expected to shape and maintain, as mutation protocols, any mechanism of mutation whose utility offers even a fraction of the adaptive value provided by sexual reproduction.

Significance of sex

Following meiosis, every chromosome is a new creation, a novel DNA sequence different from any that has ever existed, as a consequence of random, undirected recombination.

Reproducing sexually imposes a huge, two-fold fitness cost, relative to parthenogenesis. But sex prevails in most eukaryotic lineages, thereby demonstrating the powerful advantage that variation can provide.

We should expect that similar benefit could arise from other sources of random, undirected variation, including some mechanisms commonly characterized as "mutation."

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Thinking in terms of protocols, in addition to genes, organisms, and populations, as foci of natural selection, may be a useful abstraction for understanding the evolution of complexity. Marie Csete & John Doyle **2002**

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ABSTRACT:

Throughout the development of evolutionary theory, two divergent views of variation have competed for the allegiance of biologists. The dominant, classical view has been that mutations are nothing more than accidents. This view, which has been argued in essentially the same terms throughout the past century, holds that adaptive diversification of lineages is simply the inevitable consequence of imperfect reproduction paired with natural selection and genetic drift. Challenging this view is an appreciation that living systems appear to be organized at many levels to produce abundant variation, while some styles of variation appear to facilitate evolutionary adaptation. Because the classical view has become a substantial hindrance to understanding how evolvability emerges from molecular sources of natural genetic variation, this conflict needs to be explicitly acknowledged and addressed.

Reconciliation can emerge from realization that the classical view depends on particular but often unspoken assumptions that do not apply to all sources of variation. Mutations, in the broadest sense that encompasses any heritable change in DNA sequence, arise through a wide range of molecular processes. At one extreme (most closely allied to the classical view) lie extrinsic agents of DNA damage, with subsequent failure of adequate repair. In sharp contrast are certain highly-organized mechanisms ("mutational protocols") with a low probability of harm and an evident (though difficult to quantify) probability for beneficial effect, most notably those underlying reciprocal crossing-over during sexual reproduction. In between these extremes lie many mutational mechanisms that present a broad spectrum of potential harm-to-benefit ratios. At least some of these could have been positively shaped by selection to minimize harm while simultaneously increasing evolvability.

Further reading about mutation and evolvability . . .

Indirect selection and the "tuning knob" protocol (listed by date)

Trifonov EN (1989) The multiple codes of nucleotide sequences. *Bull Math Biol* 51: 417–432.

Gerber H-P *et al*. (1994) Transcriptional activation modulated by homopolymeric glutamine and proline stretches. *Science* 263: 808-811.

Rosenberg SM *et al*. (1994) Adaptive mutation by deletions in small mononucleotide repeats. *Science* 265: 405-407.

Kashi Y, King DG, Soller M (1997) Simple sequence repeats as a source of quantitative genetic variation. *Trends Genet* 13: 74-78.

King DG, Soller M, Kashi Y (1997) Evolutionary tuning knobs. *Endeavour* 21: 36-40. (Introduces "tuning knob" as a metaphor for tandem repeat function.)

King DG, Soller M (1999) Variation and fidelity: The evolution of simple sequence repeats as functional elements in adjustable genes. In: S.P. Wasser, ed., *Evolutionary Theory and Processes: Modern Perspectives*, pp. 65-82. Kluwer Academic Publishers, Dordrecht. (Includes an explanation of indirect selection.)

Fondon III JW, Garner HR (2004) Molecular origins of rapid and continuous morphological evolution. *Proc Natl Acad Sci USA* 101(52): 18058-18063.

Verstrepen KJ *et al*. (2005) Intragenic tandem repeats generate functional variability. *Nature Genet* 37: 986–990.

Kashi Y, King DG (2006a) Simple sequence repeats as advantageous mutators in evolution. *Trends Genet* 22: 253-259.

Kashi Y, King DG (2006b) Has simple sequence repeat mutability been selected to facilitate evolution? *Isr J Ecol Evol* 52: 331-342. (Includes an explanation of indirect selection.)

King DG, Trifonov EN, Kashi Y (2006) Tuning knobs in the genome: Evolution of simple sequence repeats by indirect selection. In: LH Caporale, ed., *The Implicit Genome*, pp. 77-90. Oxford University Press, Oxford.

King DG, Kashi Y (2007a) Mutability and evolvability: Indirect selection for mutability. *Heredity* 99: 123-124.

King DG, Kashi Y (2007b) Mutation rate variation in eukaryotes: Evolutionary implications of site-specific mechanisms. *Nature Rev Genet* 8 (doi: 10.1038/nrg2158-c1).

Fondon III JW, Hammock EAD, Hannan AJ, King DG (2008) Simple sequence repeats: Genetic modulators of brain function and behavior. *Trends Neurosci* 31: 328-334.

Vinces MD *et al.* (2009) Unstable tandem repeats in promoters confer transcriptional evolvability. *Science* 324: 1213-1216.

Gemayel R, Vinces MD, Legendre M, Verstrepen KJ (2010) Unstable tandem repeats in promoters confer transcriptional evolvability. *Annu Rev Genet* 44: 445–77.

Gemayel R, Cho J, Boeynaems S, Verstrepen KJ (2012) Beyond junk- variable tandem repeats as facilitators of rapid evolution of regulatory and coding sequences. *Genes* 3: 461-480

King DG (2012) Indirect Selection of Implicit Mutation Protocols. *Ann N Y Acad Sci* 1267: 45-52. (Most appropriate citation for this poster presentation.)

Evolvability and various mutation protocols (listed by first author)

Arber W (2005) Gene products with evolutionary functions. *Proteomics* 5: 2280-2284.

Barry JD (2006) Implicit information in eukaryotic pathogens as the basis of antigenic variation. In: LH Caporale, ed., *The Implicit Genome*, pp. 91-106. Oxford University Press, Oxford.

Bayliss CD, Moxon ER (2006) Repeats and variation in pathogen selection. In: LH Caporale, ed., *The Implicit Genome*, pp. 54-76. Oxford University Press,Oxford.

Caporale LH (1999) Chance favors the prepared genome. In: LH Caporale, ed., *Molecular Strategies in Biological Evolution, Ann N Y Acad Sci* 870: 1-21.

Caporale LH (2000) Mutation is modulated: Implications for evolution. *BioEssays* 22: 388-395.

Caporale LH. (2003) Natural selection and the emergence of a mutation phenotype: An update of the evolutionary synthesis considering mechanisms that affect genomic variation. *Ann Rev Microbiol* 57: 465-485.
Caporale LH (2003) Foresight in genome evolution. *Amer Sci* 91: 234-241.

Caporale LH (2006) An overview of the implicit genome. In LH Caporale, ed., *The Implicit Genome*, pp. 3-22. Oxford University Press, Oxford.

Csete M, Doyle J (2002) Reverse engineering of biological complexity. *Science* 295: 1664-1669. (Introduces the "protocol" metaphor.)

Doyle J, Csete M, Caporale LH (2006) An engineering perspective: The implicit protocols. In: LH Caporale, ed., *The Implicit Genome*, pp. 294-298. Oxford University Press, Oxford.

Doyle J, Csete M (2007) Rules of engagement. *Nature* 446: 860.

Earl DJ, Deem MW (2004) Evolvability is a selectable trait. *Proc Natl Acad Sci USA* 101**:** 11531–11536. ("Life has evolved to evolve.")

Goldschmidt R (1940) *The Material Basis of Evolution*. Yale University Press, New Haven. (Before DNA, a premature inquiry into the nature of mutation protocols.)

Jurka J, Kapitonov VV, Kohany O, Jurka MV (2007) Repetitive sequences in complex genomes: structure and evolution. *Annu Rev Genomics Hum Genet* 8**:** 241–259.

Jurka J (2007) Conserved eukaryotic transposable elements and the evolution of gene regulation. *Cell Mol Life Sci* 65: 201–204.

Kirschner M, Gerhart J (1998) Evolvability. *Proc Natl Acad Sci USA* 95: 8420-8427.

Martincorena I, Luscombe NM (2013) Non-random mutation: The evolution of targeted hypermutation and hypomutation. *BioEssays* 35: 123-130.

Mihola O *et al*. (2009) A mouse speciation gene encodes a meiotic histone H3 methyltransferase. *Science* 328: 373-375. (A protocol for speciation?)

Oliver KR, Green WK (2009) Transposable elements: Powerful facilitators of evolution. *BioEssays* 31: 703–714.

Shapiro JA (1983) Variation as a genetic engineering process. In D.S. Bendall, ed. *Evolution from Molecules to Men*, pp. 253-270. Cambridge University Press, Cambridge.

Shapiro JA (1997) Genome organization, natural genetic engineering and adaptive mutation. *Trends Genet* 13: 98-104.

Thaler D (1994) The evolution of genetic intelligence. *Science* 264: 224-225.

Volff JN (2006) Turning junk into gold: Domestication of transposable elements and the creation of new genes in eukaryotes. *BioEssays* 28**:** 913–922.

Contrary literature (listed by date)

Bridges CB (1919) Specific modifiers of eosin eye color in Drosophila melanogaster. *J Exp Zool* 28(3): 37-384. (Defines "mutation" and establishes the expectation that most mutations are deleterious.)

Sturtevant AH (1937) Essays on evolution. I. On the effects of selection on mutation rate. *Q Rev Biol* 12: 464-467. ("Mutation are accidents.")

Williams GC (1966) *Adaptation and Natural Selection*. Princeton: Princeton Univ. Press. (A classic text, with a strong argument that natural selection must always prefer minimal mutation rates.)

Dawkins R (1976) *The Selfish Gene*. Oxford University Press, New York.

Dickinson WJ, Seger J (1999) Cause and effect in evolution. *Nature* 399: 30. (Cites GC Williams and R Dawkins; argues that selection lacks foresight, and no one has described a plausible way to provide it."

Sniegowski PD *et al*. (2000) The evolution of mutation rates: Separating causes from consequences. *BioEssays* 22: 1057-1066. (Reiterates the classical argument that natural selection favors minimal mutation rates.)

Sniegowski PD, Murphy HA (2006) Evolvability. *Current Biology* 16: R831-R834. (Argues that evolvability is not an adaptation.)

Elmore MH, Gibbons JG, Rokas A (2012) Assessing the genome-wide effect of promoter region tandem repeat natural variation on gene expression. *Genes Genomes Genetics* 2: 1643-1649. (Cites the classical argument against advantageous mutation, against the "tuning knob" protocol.)

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