Further reading

This annotated reference list includes papers in several categories:

1. **Most listings**: Reports and/or interpretations of genomic features which contribute to evolvability (many more could be included).
2. **Classic texts**: Well-known papers, mostly presenting conventional doctrine.
3. **Contrary viewpoints**: Recent papers which argue against the thesis of this poster, that selection can shape protocols for variation.

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

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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.

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

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

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Caporale LH (2003b) Foresight in genome evolution. *Amer Sci* 91: 234-241.

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

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Dickinson WJ, Seger J (1999) Cause and effect in evolution. *Nature* 399: 30. *(**Contrary viewpoint**: "selection lacks foresight, and no one has described a plausible way to provide it.")*

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

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

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

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. *(**Contrary viewpoint**, argues against advantageous mutation and the "tuning knob" protocol.)*

Fedoroff NV (2012) Transposable elements, epigenetics, and genome evolution. *Science* 338:758-767. *(TEs "play a profoundly generative role.")*

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

Fondon III JW et al. (2008) Simple sequence repeats: Genetic modulators of brain function and behavior. *Trends Neurosci* 31: 328-334.

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Gemayel R, et al. (2010) Variable Tandem Repeats Accelerate Evolution of Coding and Regulatory Sequences. *Ann Rev Genet* 44: 445–477.

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

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

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

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.)*

King DG, Soller M, Kashi Y (1997) Evolutionary Tuning Knobs. *Endeavour* 21: 36-40. *(Introduces the "tuning knob" metaphor for the function of tandem repeats.)*

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.

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

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

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Otto SP, Lenormand T (2002) Resolving the paradox of sex and recombination. *Nature Rev Genet* 3:252-261.

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

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

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

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

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

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

Weissmann A (1889) *Essays Upon Heredity*. Oxford, Clarendon Press.

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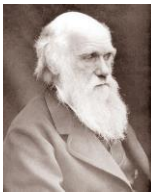
EVOLVABILITY June 2015



Might constrained mutability be as advantageous as sex?

David G. King   Depts. of Anatomy and Zoology, Southern Illinois University Carbondale

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**a

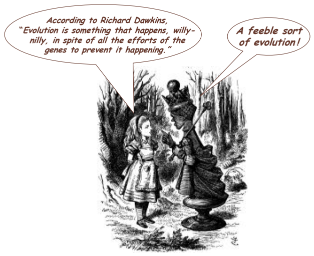
Introduction

This poster advocates a very simple idea:
Mutability can be an evolved function, not just residually imperfect reproduction.

Several sources of genetic variation – not only sexual recombination but also certain mechanisms of mutation -- can confer selective advantage. Variation arising during sexual reproduction provides a model for addressing this idea.

But acceptance of this idea is impeded by another simple idea: A long-standing theoretical argument holds that selection necessarily favors minimal mutation rates.

Nevertheless, certain protocols for mutation have much in common with meiotic recombination.



Historical background

Sex as a source of variation

That sexual reproduction functions as a source of variation seemed evident in the 1800s (see quotations by the portraits above).

However, by the mid-1900s sex had been designated as "the queen of problems in evolutionary biology" (Bell 1982).

Because organisms reproducing sexually must produce twice as many offspring to compete effectively against asexuals, identifying benefit sufficient to overcome such a huge selective disadvantage had become a major theoretical challenge.

Nevertheless, recent theoretical models have finally been vindicating the old view:

"August Weismann [1889] might have been right all along in arguing that sex evolved to generate variation" (Otto, 2008).

Sex really is "a parental adaptation to the likelihood of the offspring having to face changed or uncertain circumstances" (Williams 1975).

Mutation as a source of variation

Unfortunately, in contrast to recent understanding of sex, the prevailing explanation for the existence of mutation remains mired in an outdated argument, that "mutations are accidents, and accidents will happen" (Sturtevant 1937).

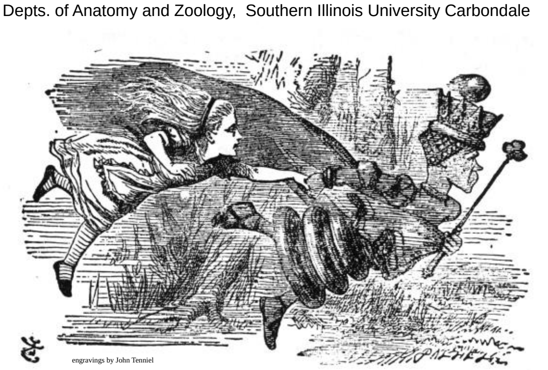
"[N]atural selection of mutation rates has only one possible direction, that of reducing the frequency of mutation to zero. . . . So evolution takes place, not so much because of natural selection, but to a large degree in spite of it" (Williams 1966).

"[S]election lacks foresight, and no one has described a plausible way to provide it" [Dickinson & Seger 1999].

"[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" (Elmore *et al.* 2012).

But this "tenet" depends on simplistic assumptions which properly apply only to mutator alleles (i.e., those which reduce the genome-wide fidelity of DNA replication while remaining unlinked to any resulting mutations). Indirect selection can imbue genomes with "foresight," just as readily as direct selection can shape intelligently-foresightful patterns of animal behavior.

In spite of such limited applicability, the view that mutations are accidents is still commonly wielded against the idea that *any* style of mutation could be advantageous.


engravings by John Tenniel

"Now here, you see, it takes all the running you can do, to keep in the same place." Van Valen 1973, quoting Lewis Carroll's *Through the Looking Glass*

Wherever the Red Queen reigns, genetic variation is vital.

In an ever-changing environment, one must be continually evolving -- not to increase one's fitness but simply to keep from losing ground.

A reliable supply of mutations may be as selectively advantageous as the variation produced through sexual reproduction.

Protocols for variation

Most styles of mutation are not "random." Nor is most mutational variation "unstructured with respect to survival" (Caporale & Doyle 2013).

Patterns which increase the probability that individual mutations might be advantageous (or, equivalently, reduce the probability that they will be deleterious) may be metaphorically characterized as mutation "**protocols**" (Doyle *et al*. 2006).

Examples

A "**protocol for incremental adjustability**" (a "tuning knob") can be implemented by **simple sequence repeats**.

Simple sequence repeats (SSRs, STRs, microsats), although commonly mis-characterized as "junk DNA" or as "meaningless stutters," provide abundant, relatively safe, quantitative variation within many eukaryotic genes (Gemayel *et al*. 2010, King *et al*. 1997).

A "**protocol for redundancy and innovation**" can be implemented by **transposable elements**.

Even though they "play a profoundly generative role in genome evolution …, transposons are today almost universally referred to as 'invaders,' 'parasites,' or 'parasitic sequences' " (Fedoroff 2012).

Indeed, a genome "inexorably driven towards greater complexity" by "an internal arms race with its own DNA," has recently been inferred from the evolution of genes which constrain transposon activity (Jacobs *et al*., 2014).

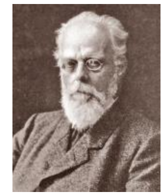
But instead of disparaging TEs as "parasites," it might be more fruitful to appreciate such an "inexorable drive" as the functioning of a feedback system, operating through indirect selection, which regulates the production of innovative variation.

A "**protocol for mix-and-match**" is implemented by **meiotic recombination**.

While quite sophisticated, sex is also remarkably expensive. Once sex is recognized as one among several protocols for variation, the others may seem less surprising or exceptional.

Metaphors of "selfish genes" and "parasitic DNA" may retain some heuristic value for gene-level understanding, but these same metaphors can seriously mislead when extended to address higher levels that yield integrated regulation of adaptive organismal form.

By expanding our repertoire of genetic metaphors to embrace evolutionary change as well as immediate fitness, we may better appreciate how certain mutational mechanisms can comprise "protocols" (Doyle *et al*. 2006) for "natural genetic engineering" (Shapiro 1997, 2005).



The object [of sexual reproduction] is to create those individual differences which form the material out of which natural selection produces new species.
August Weismann **1889**

Indirect selection

So how can natural selection favor mutation protocols whose benefit only occurs in subsequent generations?

Of course, natural selection cannot foresee the future.

But although natural selection cannot *directly* favor genomic patterns which facilitate propitious styles of variation, *indirect* selection for mutation protocols occurs when favorable variants arise within heritable constraints that are themselves linked to those variants (DG King 2012).

An example: The potential for indirect selection is most clearly illustrated by site-specific elevation of localized mutation rate, as represented by simple sequence repeats.

When favorable variants arise, they retain the site-specific mutation rate by which they arose. Selection for the favorable variant then also indirectly but inevitably favors the locally elevated mutation rate for this particular style of mutation, thus facilitating future variation under similar constraints.

Indirect selection should be expected to exploit any mechanism of mutation whose utility offers even a fraction of the adaptive value provided by sexual reproduction.

Indirect selection can plausibly shape mutation protocols just as effectively as natural selection can shape phenotypic adaptation.

What next?

Several concepts merit further exploration.

Genomes have evolved to evolve (*cf*. Earl & Deem 2004). They exploit a wide range of protocols to manage the potential advantages as well as the risks of genetic variation.

Sexual reproduction with meiotic recombination is perhaps the most sophisticated (and expensive) of these protocols.

The surprising prevalence of several additional mutational mechanisms suggests that they too should be understood as implicit protocols for stochastic production of variation rather than as flaws in replication fidelity. Resulting changes in DNA sequence are better viewed not as "mistakes" or "accidents" but as products of these protocols.

If variation from sexual recombination can offer generation-by-generation advantage sufficient to outweigh its "seemingly overwhelming" cost, then perhaps other mechanisms for producing variation can also be maintained by positive selection.

As long as the burden of deleterious mutation does not exceed the 50% cost of sex, positive selection for a protocol should be considered as plausible.

Mutation protocols can thereby be integrated, together with sexual recombination, into patterns of "genetic intelligence" (Thaler 1994).

Mutation protocols complement physiological and epigenetic mechanisms for responding to environmental variation, while offering emergent opportunities for evolutionary innovation.

Mutation protocols form the basis for creative bet-hedging in a complex and inconstant world. The selective value of mutation protocols, although difficult to measure in nature, should be addressed through modelling of indirect selection (*e.g*. Carja *et al*. 2014).

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

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**b

ABSTRACT: *Might constrained mutability be as advantageous as sex?*

David G King, Southern Illinois University Carbondale

In an inconstant environment, fitness depends on variation as well as replication fidelity. Indeed, the blind, undirected variation which emerges through sexual reproduction is practically essential for population fitness, at least among most eukaryotes. And yet, paradoxically, sex imposes a huge burden, entailing a 50% reduction in fitness relative to the efficiency of asexual reproduction. Identifying benefits sufficient to outweigh such high cost remains an elusive goal.

Mutations also inflict obvious cost. Because blind, undirected mutations are often deleterious, it has long been argued that natural selection must necessarily favor the minimization of mutation rates (though a low level of mutation evidently remains inevitable). However, this classical argument rests on overly simplistic assumptions, ignoring the existence of site- and sequence-specific mutational protocols, such as those based on transposable elements and tandem repeats, that can have surprisingly high mutation rates. If the cost for any particular mutational protocol does not exceed the seemingly inordinate cost of sex, then selection might plausibly shape its constraints to exploit the balance between costs and benefits of undirected variation. In fact, meiotic recombination itself is just such a mutational protocol, one which produces molecular variation within especially sophisticated constraints.

The prevalence of sexual reproduction demonstrates a fundamental principle: When suitably constrained, undirected variation can be powerfully advantageous. This principle might apply not just to meiotic recombination but to other styles of mutational variation as well.