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A lesson from sex: Abundant variation can be worth its high price.

David G King, Southern Illinois University Carbondale

Blind, undirected mutational variation is mostly deleterious, but without it evolution would grind to a halt. Blind, undirected variation from sexual reproduction is vital for maintaining population fitness, though it comes at a very steep price. In between these two contrasting ideas -- that replication errors are bad but inevitable while sex is good though expensive -- lies a seldom appreciated reality: Quite generally, sources of suitably constrained variation can be favored by natural selection in spite of seemingly exorbitant cost.

To be sure, sex generates an especially conservative style of variation, guaranteeing a diversity of genotypes simply by rearranging pre-existing alleles. But sex also imposes a huge burden: In addition to the many hazards of mating, sex entails a 50% reduction in fitness relative to the efficiency of asexual reproduction, and meiotic recombination separates favorable alleles just as readily as it brings them together. Quantifying benefits sufficient to balance these high costs remains an elusive goal. Nevertheless, the prevalence of sexual reproduction among eukaryotes proves that at least one source of blind, undirected variation can be worth an enormous price. This understanding of sexual reproduction should prompt us to consider that some mutational sources of variation might similarly confer benefit sufficient to outweigh cost, even if their benefit cannot yet be clearly appraised.

The idea that selection could favor an elevated frequency for any type of mutational variation has long been dismissed: "[N]atural selection of mutation rates has only one possible direction, that of reducing the frequency of mutation rates to zero" (GC Williams, 1966). But such sweeping denial is based on a simplistic argument whose underlying assumptions do not apply to several highly-constrained mutational mechanisms, including expansion and contraction of simple sequence repeats, transposition of mobile elements, gene duplication, horizontal gene transfer, localized hypermutability, and phase switching. Such mechanisms bias the styles and sites for resulting mutations, thereby offering an opportunity to shift the balance between harm and benefit. Abundant evidence that these mechanisms have contributed to adaptive evolution should suggest that their associated constraints might constitute "protocols" for generating advantageous variation. If the obvious harm from deleterious mutation does not exceed the stunningly high cost of sex, then natural selection might also deem the benefits from any such source of variation (including an emergent potential for innovative exploration) as being well worth the price. **Website:** www.siumed.edu/anatomy/KingCoS/index.htm

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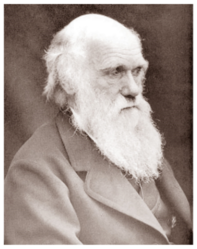
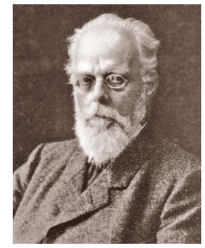


Some authors believe it to be as much the function of the reproductive system to produce individual differences ... as to make the child like its parents.
Charles Darwin **1859**

A lesson from sex:
Abundant variation can be worth its high price.

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

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 (in a letter to TH Huxley, 1859)



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**

Introduction

This poster invites readers to consider an analogy between sex and mutation.

Sex and mutation share fundamental similarities, but their differences are usually emphasized:

Sex is understood as an evolved function. Despite the high cost of reproducing sexually, selection favors the allele-shuffling of meiotic recombination. Some undirected but highly constrained variation is evidently more advantageous than exact genome duplication.

Mutations are understood as accidental errors. Selection for minimal mutation rates is believed to be limited only by the cost of replication fidelity.

Nevertheless, this distinction may not be as great as generally conceived. Fundamentally, both sex and mutation are sources of genetic variation.

In essence, sexual recombination *is* a source of mutation, creating novel DNA sequences.

Certain mutational mechanisms can, like sex, yield highly constrained styles of variation which can be employed for adaptive advantage.

Both sexual reproduction and several styles of mutation should be conceptualized together, as **"protocols"** that can facilitate stochastic but adaptively useful variation.

Background: **History**

Darwin (1859) famously anticipated future inquiry into "the causes and laws of variation."

Sex as a source of variation

That sexual reproduction functions as a source of variation seemed evident by the late 1800s.

However, by the mid-1900s sex had been designated as "the queen of problems in evolutionary biology" (G 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 validating the old view:

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

In other words, sex really is "a parental adaptation to the likelihood of the offspring having to face changed or uncertain circumstances" (GC Williams 1975).

* * *

Mutation as a source of variation

Unfortunately, in contrast to such recent developments concerning sex, theoretical modeling of mutability has lagged far behind growing knowledge of mutational mechanisms.

The prevailing explanation for the existence of mutation remains largely as developed in the mid 20th century, 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" (GC Williams 1966).

But this view properly applies only to a mutator allele which reduces the genome-wide fidelity of DNA replication without remaining linked to any resulting mutations, and only when the "vast majority" of mutations are deleterious.

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

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For many well-known sources of mutation, circumstances for positive selection may closely parallel those for selective maintenance of sex.

Mutations are often deleterious, but -- as with sex -- immediate advantages for certain styles of constrained mutability could consistently outweigh the cost.

Sexual recombination: Cost vs. benefit

Meiotic recombination assures unique allele combinations in each individual offspring.

Cost

Sexual reproduction imposes a profound 50% cost relative to asexual reproduction, in the efficiency of transmitting genes to the next generation.

Furthermore, meiotic recombination can separate favorable combinations of alleles.

And the act of mating is time-consuming, effortful, and dangerous.

Specific benefits sufficient to overcome such huge costs are not readily apparent.

"The widespread occurrence of sex, despite its seemingly overwhelming costs, is known as the paradox of sex" (SP Otto 2002).

Benefit

Recent models that avoid unrealistic assumptions have suggested that (SP Otto 2008):

Sex evolves when selection changes over time.

Sex evolves when selection changes over space.

Sex evolves when organisms are less-well adapted to their environment.

Sex evolves when populations are finite.

Apparently, variation from sex can be beneficial under conditions experienced by most natural populations, in spite of "seemingly overwhelming costs."

Mutation protocols: Cost vs. benefit

Mutation protocols are conceived as bet-hedging strategies which promote advantageously constrained styles of DNA variation.

Cost

Deleterious mutations are an inevitable result of all known mutational processes.

Classically, the "vast majority" of mutations are deleterious, no matter what the cause.

Some deleterious mutations can be *severely* deleterious.

Yet for some mutational mechanisms, both the proportion of severely deleterious mutations and the overall cost remain quite low, even with extremely high mutation rates.

No mutational process carries an "overwhelming cost" as high as that paid for sexual reproduction.

Benefit

Several mutational mechanisms could represent beneficial bet-hedging strategies. Thus, just as for sex:

Mutation protocols might evolve when selection changes over time.

Mutation protocols might evolve when selection changes over space.

Mutation protocols might evolve when organisms are less-well adapted to their environment.

Mutation protocols might evolve when populations are finite.

One or another mutation protocol might be favored under conditions commonly encountered in nature.

A sampling of mutation protocols

Bet-hedging strategies for DNA variation range from sophisticated to simple, with corresponding differences in style of mutation, mutation rate, and risk of deleterious effect. Several of these protocols are well-established as the means for rapid and effective microbial adaptation. There is no reason (apart from over-confidence in simplistic theory) to doubt that complex eukaryotes also exploit such protocols.

- **Meiotic recombination** is supported by an astonishing array of anatomical, physiological, and behavioral adaptations. But this protocol is typically excluded, by definition, from the concept of "mutation."
- **Phase switching** shuffles genes in and out of active sites by programmed gene arrangement, without necessity for sex.
- **Horizontal gene transfer** offers access to potentially-advantageous alleles previously evolved by other members of the local community.
- **Tuning-knob sites** based on tandem repeats allow reversible, incremental adjustment of most gene functions, including site-specific adjustment of mutation rate.
- **On/off switching** (also based on tandem repeats) allows stochastically reversible variation in the expression of "contingency genes."
- **Transposable elements** implement copy-and-paste of functional modules. Although seemingly selfish, appropriately domesticated TEs (JN Volff 2006) provide opportunities for adaptive innovation and diversification, especially in times of stress.
- **Targeted hypermutation** concentrates single-nucleotide mutation at mutation hotspots where variation has proven especially advantageous in the past.
- **Epigenetic modification** offers heritable variation without altering DNA sequence and may provide a substrate for subsequent, site-specific mutation.
- **Whole-genome duplication** creates a variety of opportunities for diversifying variation.
- **Conventional mutation** (e.g., non-site-specific alterations of single nucleotides) may be the *only* style of mutation that is adequately modeled by conventional theory, such that mutation rate is minimized rather than optimized by selection.

This is but a partial list of special modes of mutation that are available for exploitation as protocols for generating variation. As with sexual reproduction, each of these protocols may be favored, suppressed, or regulated, depending on a population's circumstances.

Background:
Indirect selection

Indirect selection for mutation protocols (DG King 2012) occurs when favorable variants arise within constraints that are themselves heritable and linked to those variants.

An example: The potential for indirect selection is most clearly illustrated by site-specific elevation of mutation rate, as represented by tandem 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 shape and maintain any mechanism of mutation whose utility offers even a fraction of the adaptive value provided by sexual reproduction.

Although natural selection cannot *directly* favor genomic patterns which facilitate propitious styles of variation, *indirect* selection can nevertheless 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. 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 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" (DS 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 (cf. O 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.

Abstract and references

Please see the handout for references as well as a copy of poster text and abstract.

If handouts are not available, please contact the author at **dgking@siu.edu**.

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**

SIU Southern Illinois University CARBONDALE

SIU School of Medicine