

BRK-014 · Evolution without an adaptive explanation for every change

BRK · Conceptual Breaks

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The molecular evidence that became available in the 1960s did more than add small details to evolutionary history. It supplied counts of changes in proteins, and those counts could be extrapolated into a rate of replacement. The question was whether a population could sustain that rate if each replacement required a separate episode of advantageous selection.

Kimura's 1968 argument joined that new evidence to an older calculation of the cost of selection. Reconstructing the connection matters because the neutral-rate formula alone does not explain why neutrality became a proposed solution. It is also necessary to distinguish a historically influential argument from a calculation whose assumptions should be accepted today without re-examination.

1. The historical rate argument

Haldane's 1957 paper considered the reproductive cost of replacing one allele by another through selection. In his model, the accumulated selective loss during a substitution could be large even when the disadvantage in any single generation was small. He proposed an illustrative limit of roughly one substitution per 300 generations under his assumptions. This was not a universal empirical speed limit for every population. [1]

The cost was a population-level bookkeeping problem. Repeatedly removing less successful alternatives, through differential survival or reproduction, cannot be assumed to leave unlimited reproductive capacity available for other simultaneous replacements. The accumulated deficit relative to the favored type matters, not only the advantage in one generation. The translation from that deficit to a sustainable rate depends on the biological model.

Kimura estimated a much faster genome-wide rate from comparisons of a small set of proteins: roughly one nucleotide-pair substitution every two years in mammalian evolution. He contrasted that extrapolation with Haldane's calculation. If each replacement incurred the assumed selective cost, he argued, the resulting load would be intolerable. Neutral or nearly neutral replacement offered a way to avoid assigning that cost to each change. [2]

The conditional structure is the historical premise: a high inferred rate, plus a cost assigned to advantageous substitutions, created a conflict under those assumptions. Neutrality was proposed as a resolution. The argument was not simply that many differences existed, or that organisms contained changes with no imaginable purpose.

2. Why mutation and substitution are different counts

A mutation is a new sequence change. A substitution, in this population-genetic sense, is a change that becomes fixed in a population. Most new mutations need not become substitutions. Confusing the two rates would eliminate the population process that the theory is intended to explain.

Consider the following idealized derivation. A diploid population with N individuals contains $2N$ copies of an autosomal locus. If the neutral mutation rate per copy per generation is μ , approximately $2N\mu$ new neutral mutations arise per generation. Under the

simplest neutral model, a new single-copy variant has probability $1/(2N)$ of eventual fixation.

Multiplying supply by fixation probability gives a long-run expected substitution rate of μ . The population-size terms cancel. This is a model result under stated assumptions, not a measurement proving that all sites are neutral. It helps explain why a rate of molecular replacement need not be a direct measure of adaptive improvement.

For illustrative values $N = 10,000$ and $\mu = 0.000001$, the expected input is 0.02 new neutral mutations per generation at the modeled locus. Multiplication by $1/20,000$ yields a substitution rate of 0.000001 per generation. A larger population supplies more mutations but gives each new neutral copy a smaller fixation probability. These invented inputs are not estimates from Kimura's paper.

3. What the cancellation does, and does not, repair

The rate calculation explains a consequence of exact neutrality: a low fixation probability can balance a large input of variants. The cost argument explains why such a process was invoked in 1968. Reversing that order would make the model's algebra look like the evidence that originally demanded it.

Kimura connected the fixation probability to initial frequency and used this connection to relate mutation input to substitution. The calculation therefore changed which count mattered. A count of differences between lineages need not also be a count of successful adaptive replacements with the assumed reproductive cost. [2]

This is a change in an inference, not a direct observation of selective neutrality. The molecular measurements, the extrapolation to a genome and the population model are three distinguish-

able steps. The historical argument is assessable only if all three remain visible.

4. The original premises were disputable

The extrapolation from proteins to a genome was consequential. Kern and Hahn’s 2018 critique points out that Kimura used a genome-sized number of sites in extending protein-derived rates, rather than the much smaller number of protein-coding sites. They also discuss how alternative selection models and demographic assumptions alter the claimed cost limit. Their assessment is explicitly critical of the original justification. [3]

This prevents a false historical resolution: inserting Haldane’s cost does not complete an unassailable proof of neutrality. It recovers the reasoning that made the proposal intelligible, including the places where that reasoning could be challenged. The accuracy of a rate extrapolation and the appropriateness of a cost model are empirical and theoretical questions in their own right.

The point is not that criticism erases the subsequent research program. A proposed explanation may generate useful calculations and new comparisons even when its original motivating estimate is revised. Conversely, later usefulness cannot retroactively validate every premise of the original paper.

5. A debate changes its questions

King and Jukes’s 1969 “Non-Darwinian Evolution” advanced a molecular case for an important role of neutral change. Ohta’s 1973 treatment of slightly deleterious substitutions then made the boundary between negligible and consequential selective effects part of the problem. These were developments within a continuing argument, not a unanimous conversion following one rate calculation. [4,5]

Galtier's historical review describes how the neutralist–selectionist debate changed with population-genetic and genomic evidence. The relevant continuity is a research problem, not one permanently fixed set of estimates from 1968. Different generations of evidence could challenge different parts of the proposal. [6]

QTC-010 treats the general relationship among variation, selection and drift. This article's narrower concern is the historical change produced by counting molecular replacements and comparing that count with a proposed reproductive cost. That comparison made the assumed explanation of a substitution into something requiring its own argument.

6. The conceptual break survives only with its history intact

The new problem was not merely to supply a functional story for a molecule. It was to reconcile a measured or inferred rate with a mechanism capable of producing it under specified conditions. Molecular comparisons and population calculations now had to constrain one another.

Three claims must therefore stay separate: the estimated historical rate, the cost predicted by a particular selection model and the replacement rate expected under neutrality. Their tension explains why the proposal was consequential. Their limitations explain why the dispute did not end with it.

A history that begins with the neutral formula and ends with a general defense of drift misses that transformation. The more precise break was the emergence of a quantitative challenge to an assumed causal account of molecular replacement, followed by scrutiny of the assumptions on both sides of that challenge.

Related reading

BRK Article 012, “Discrete genes and continuous variation: a statistical reconciliation,” examines an earlier change in how inherited contributions were connected to population-level patterns.

References

- [1] Haldane, J. B. S. “The Cost of Natural Selection.” *Journal of Genetics* 55, 511–524 (1957). <https://doi.org/10.1007/BF02984069>
- [2] Kimura, M. “Evolutionary Rate at the Molecular Level.” *Nature* 217, 624–626 (1968). <https://doi.org/10.1038/217624a0>
- [3] Kern, A. D., and Hahn, M. W. “The Neutral Theory in Light of Natural Selection.” *Molecular Biology and Evolution* 35, 1366–1371 (2018). <https://doi.org/10.1093/molbev/msy092>
- [4] King, J. L., and Jukes, T. H. “Non-Darwinian Evolution.” *Science* 164, 788–798 (1969). <https://doi.org/10.1126/science.164.3881.788>
- [5] Ohta, T. “Slightly Deleterious Mutant Substitutions in Evolution.” *Nature* 246, 96–98 (1973). <https://doi.org/10.1038/246096a0>
- [6] Galtier, N. “Half a Century of Controversy: The Neutralist/Selectionist Debate in Molecular Evolution.” *Genome Biology and Evolution* 16, evae003 (2024). <https://doi.org/10.1093/gbe/evae003>