# Mixing limits mitochondrial selection: a critical threshold for mitochondrial genome stability

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**Abstract**

Mitochondrial genome stability depends on purifying selection, yet this selection is fundamentally limited by the mixing of mitochondrial populations. Because selection requires variance, any process that homogenizes mitochondrial populations reduces its effectiveness. We introduce a coarse-grained parameter $\alpha$ describing effective mitochondrial mixing and show that selection efficiency scales with $(1-\alpha)^2$, implying a critical threshold above which purifying selection fails.

This constraint resolves a key limitation of existing models, which assume that variance generated by the mitochondrial bottleneck is preserved. In reality, mitochondrial populations are continuously redistributed by intracellular dynamics, including fusion–fission processes [9], which erode variance in heteroplasmy across cells.

We further show that intracellular dynamics may favor mitochondrial variants with replication advantages but reduced energetic efficiency, creating a conflict between within-cell and between-cell selection. This conflict necessitates selection at the level of whole cells.

We propose that mitochondrial quality control is a temporally structured, multilevel process. Oogenesis generates variance, early embryogenesis provides a window in which variance is preserved and fitness differences are expressed, and processes such as cell competition implement selection at the cellular level [2, 1]. Uniparental inheritance further contributes by suppressing mixing at fertilization [7, 6].

This framework predicts that increasing mitochondrial mixing or reducing variance impairs selection efficiency and provides a unified constraint-based explanation for mitochondrial genome stability.

## 1 Introduction

Mitochondrial genome stability depends on purifying selection, yet this selection is fundamentally limited by the mixing of mitochondrial populations. Due to clonal inheritance and limited recombination, mitochondrial DNA (mtDNA) is expected to accumulate deleterious mutations through Muller's ratchet [5, 4]. The persistence of mitochondrial genome integrity across evolutionary timescales therefore requires effective purifying selection.

Standard explanations rely on the mitochondrial bottleneck, which generates variance in heteroplasmy across cells [3, 8], and subsequent purifying selection. However, these explanations implicitly assume that this variance is preserved long enough for selection to act. This assumption is rarely examined explicitly.

Mitochondrial populations are not static; they undergo continuous redistribution through intracellular transport and fusion–fission dynamics [9]. As a consequence, differences in heteroplasmy between cells can be reduced over time. If variance is eroded before selection operates, the effectiveness of selection is fundamentally limited. We therefore propose that mitochondrial genome stability is constrained not only by mutation and selection, but by the degree of mixing between mitochondrial populations.

## 2 Model and Consequences

Let $x$ denote the fraction of mutant mtDNA within a cell (heteroplasmy fraction). Following a bottleneck, cells exhibit variance in $x$, which provides the substrate for selection. However, mitochondrial mixing reduces this variance. We represent mixing by a coarse-grained parameter $\alpha$:

$$x'' = (1 - \alpha)x' + \alpha\bar{x}$$

where $\bar{x}$ is the population mean heteroplasmy.

Selection efficiency scales with the variance in heteroplasmy across cells:

$$s(1 - \alpha)^2 \mathrm{Var}_0$$

and must overcome mutation and intracellular dynamics:

$$s(1 - \alpha)^2 \mathrm{Var}_0 \gtrsim (r_L - r_G) + \mu$$

This leads to a critical threshold:

$$\alpha_{\mathrm{crit}} = 1 - \sqrt{\frac{(r_L - r_G) + \mu}{s \cdot \mathrm{Var}_0}}$$

Above this threshold, variance in heteroplasmy collapses and selection becomes ineffective.

Intracellular dynamics may, under plausible conditions, favor mitochondrial variants with replication advantages despite reduced energetic efficiency. This creates a conflict between within-cell selection (favoring replication) and between-cell selection (favoring cellular performance). This conflict implies that molecular-level quality control is insufficient and necessitates selection at the level of whole cells.

## 3 Developmental Structure of Selection

Selection is not uniformly effective throughout development but instead operates within a temporal window in which variance in heteroplasmy is high, mitochondrial mixing is limited, and fitness differences are expressed. Following the mitochondrial bottleneck, variance across cells is substantial.

Early developmental stages impose spatial and structural constraints that limit effective mixing, preserving this variance.

As embryogenesis proceeds, metabolic differences between cells become functionally relevant, enabling comparison of cellular fitness. Processes such as cell competition can then eliminate less-fit cells [2, 1]. Outside this window, increased mixing reduces variance and limits the effectiveness of selection. Thus, mitochondrial quality control is temporally structured rather than continuous.

Oogenesis plays a preparatory role by generating variance and maintaining low effective mixing. The oocyte therefore functions as a vehicle for transmitting mitochondrial populations under conditions that preserve selection potential.

## 4 Biological Implementation

Given the constraints of the system—indirect access to mitochondrial quality, the need to compare cellular performance, and the requirement for selective elimination—any effective mechanism must implement relative fitness sensing coupled to cell removal.

Cell competition satisfies these constraints and provides a parsimonious candidate mechanism for implementing cell-level selection [2, 1]. While alternative mechanisms may contribute, this framework predicts that perturbations of such processes should affect mitochondrial quality control.

Multicellularity provides the structural context required for this form of selection. In unicellular systems, metabolic performance is tightly coupled to reproduction, allowing direct selection at the level of the whole cell. In multicellular systems, this coupling is weakened, necessitating additional mechanisms that enable selection at the cellular level without compromising organismal fitness.

Uniparental inheritance further contributes by suppressing mitochondrial mixing at fertilization. The active elimination of paternal mitochondria prevents the introduction of additional mitochondrial lineages, which would increase mixing and reduce variance in heteroplasmy across cells [7, 6].

## 5 Testable Predictions

The model yields several predictions:

1. Increasing mitochondrial mixing reduces the variance in heteroplasmy across cells and impairs selection efficiency
2. Germline cells exhibit reduced effective mitochondrial mixing
3. Perturbations increasing heteroplasmy (e.g., cloning-induced mixing) reduce the effectiveness of mitochondrial quality control
4. Disruption of cell competition pathways alters selection efficiency during early development

## 6 Limitations

The parameter $\alpha$ is a coarse-grained representation of multiple biological processes and is not directly measurable. The model abstracts away spatial structure and detailed mitochondrial network dynamics. The proposed mechanisms should therefore be interpreted as a conceptual framework rather than a complete mechanistic description.

## 7 Conclusion

We propose that mitochondrial genome stability is constrained by the requirement to preserve variance in heteroplasmy across cells in the presence of mixing. Effective selection depends not only on mutation and selection strength, but on maintaining conditions under which variance is not erased. This constraint links mitochondrial genetics, developmental biology, and evolutionary theory into a unified framework.

## References


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