# The Cost of Mismatch

*Optimal Traits, Plasticity, and Mutation Interactions*

*in Variable Environments*

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**Abstract**

A fixed trait may face several demands within a single lifetime. How much reproductive output can an organism gain by tracking each demand? Suppose a trait $p$ facing a demand $e$ pays a reciprocal mismatch cost $J(p/e) = (p/e + e/p)/2 - 1$ from a common reproductive budget. If $A$ and $H$ are the exposure-weighted arithmetic and harmonic means of the demand, the best fixed trait is $\sqrt{AH}$. Its unavoidable cost is $\sqrt{A/H} - 1$, which gives the exact break-even price of perfect tracking. The same budget predicts the one-generation selection response and the magnitude and sign of interactions between mutations that multiply one trait. We give a bacterial expression experiment that can distinguish these predictions from those of a cost quadratic in log expression.

## 1 One enzyme, two demands

An enzyme concentration that is adequate at low demand may be too small at high demand. Making more enzyme may itself draw resources away from reproduction. In the lactose system of *Escherichia coli*, Dekel and Alon measured the cost and benefit of expressing the lac proteins and followed the evolutionary adjustment of expression at fixed lactose concentrations [1]. Their experiment establishes that both sides of the tradeoff can be measured. Here we ask a different question. If a cell meets both demands before it reproduces, where should it set a single expression level, and how much could it afford to spend on regulation?

Consider demands of one and four units for equal portions of a lifetime. Under the reciprocal cost, expression at two units is twice the first demand and half the second. Both deviations have the same cost, $1/4$. Moving expression toward either demand raises the average cost. A cell that can match both demands therefore has $1/4$ of a mismatch-cost unit to spend on tracking before it loses its advantage. The following results establish when this calculation applies, how it changes with exposure, and why the same cost predicts an interaction between two mutations on the same expression axis.

## 2 From demand to offspring

Let $p > 0$ and $e > 0$ be the expressed trait and the demand in the same units. The ratio $p/e$ is dimensionless. We use the canonical reciprocal cost from ratio matching [2]:

$$J(x) = \tfrac{1}{2}(x + x^{-1}) - 1 = \frac{(x-1)^2}{2x} = \cosh(\log x) - 1. \tag{1}$$

The cost vanishes only at a match. Replacing $x$ by its reciprocal leaves the cost unchanged. Symmetry alone leaves other functions possible. For example, a cost quadratic in $\log x$ shares that symmetry and agrees with $J$ to second order at the match.

Suppose income $I$, maintenance $M$, and cost $c > 0$ per viable offspring are common across the compared types. Let $\kappa > 0$ convert a unit of mismatch into resource expenditure. If $L$ is the organism's lifetime mismatch, its expected viable offspring number is

$$w = \frac{I - M - \kappa L}{c} = \alpha - \beta L, \qquad \alpha = (I - M)/c, \quad \beta = \kappa/c > 0. \tag{2}$$

We consider the range on which the predicted outputs are positive. Here an environmental change can alter the mismatch while the compared organisms share the same budget coefficients. If, for example, high lactose raises income independently of mismatch, one must measure that budget change before interpreting an offspring difference as a cost. Identifying an organismal expenditure with (1) is the biological hypothesis tested by this paper.

## 3 The best fixed trait and the price of tracking

Let the demands $e_1, \dots, e_n > 0$ occupy fractions $\pi_i \geq 0$ of one lifetime, with $\sum_i \pi_i = 1$. The trait stays fixed over these exposures, mismatch expenditure adds across them, and

$$L(p) = \sum_i \pi_i J(p/e_i), \qquad A = \sum_i \pi_i e_i, \qquad H = \left( \sum_i \pi_i / e_i \right)^{-1}.$$

A cell whose demand switches during its life pays this average from one budget. If whole generations alternate environments, population growth instead compounds the offspring factors of successive generations. Those are distinct experimental schedules.

**Theorem 1.** *Write $p_* = \sqrt{AH}$ and $\lambda = \sqrt{A/H}$. The entire fixed-trait cost curve is*

$$L(p) = (\lambda - 1) + \lambda J(p/p_*). \tag{3}$$

*Its unique minimum is $L_* = \lambda - 1$ at $p = p_*$. Moreover,*

$$\lambda^2 - 1 = \sum_{i,j} \pi_i \pi_j J(e_i/e_j). \tag{4}$$

*The minimum is positive exactly when two demands of positive weight differ.*

*Proof.* Averaging (1) gives $L(p) = \frac{1}{2}(p/H + A/p) - 1$. Since $\lambda/p_* = 1/H$ and $\lambda p_* = A$, expansion gives (3). Equation (1) gives the minimum and its equality condition. For (4), take independent draws $i, j$. Their mean ratio is $\sum_{i,j} \pi_i \pi_j e_i/e_j = A/H$. Interchanging the draws leaves this mean unchanged and replaces the ratio by its reciprocal. Averaging the two expressions and subtracting one yields (4). Each summand with positive weight vanishes exactly when its two demands agree. □

For a perfect tracker let $k$ be the total tracking expense in mismatch-cost units per lifetime. The tracker pays zero mismatch and $\kappa k$ in regulation. Under the common account its advantage over the best fixed type is exactly $\beta(L_* - k)$ viable offspring. At equality the two tie. The threshold is the most one can pay for perfect sensing and response, and is zero in a constant environment.

For the equal exposures to 1 and 4, $A = 5/2$, $H = 8/5$, $p_* = 2$ and $L_* = 1/4$. Choosing either mean itself gives a higher cost, $9/32$. The location of the optimum already has a mathematical precedent. For the symmetrized log-determinant divergence, the centroid of positive matrices is the matrix geometric mean of their arithmetic and harmonic means [3]. On positive scalars its divergence is (1) up to normalization. The biological consequence here depends also on the residual cost: the centroid's value determines how many offspring a tracker can gain.

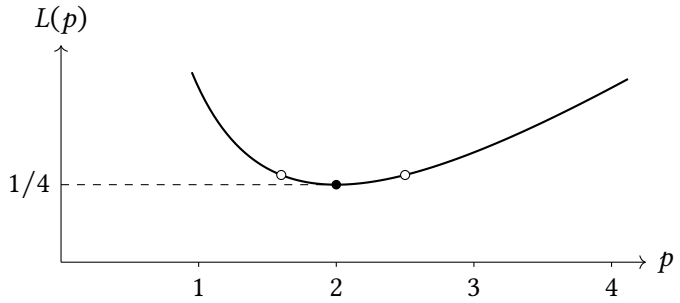


**Figure 1.** Expected mismatch when the two demands are 1 and 4 and each occupies half the lifetime. The filled point gives the best fixed expression. The open points give the harmonic and arithmetic means, which incur the same higher cost. The dashed level is the maximum tracking expense at break-even.

# 4 Selection on variation already present

Let type $i$ have frequency $x_i$ and lifetime cost $L_i$. Each type transmits its trait without change, and offspring face the same exposure schedule. Selection updates the frequencies to $x_i' = x_i w_i / \bar{w}$, where $\bar{w} = \sum_i x_i w_i > 0$. Writing $\bar{L} = \sum_i x_i L_i$ and $\bar{L}' = \sum_i x_i' L_i$, we obtain

$$\bar{L}' - \bar{L} = \frac{\operatorname{Cov}_x(w, L)}{\bar{w}} = -\frac{\beta \operatorname{Var}_x(L)}{\bar{w}}. \tag{5}$$

The first equality follows by subtracting the original mean from the offspring-weighted mean. The second follows by substituting (2). Thus mismatch falls strictly if and only if the costs among types present differ. Distinct traits can have equal costs and undergo no change in frequency. This is the selection term of the Price equation [4]. If offspring change trait or face a new schedule, their own costs must also be compared with the parental costs. Equation (5) alone then gives only the change attributable to reweighting the parents.

# 5 Two mutations on one axis

Two mutations with individually measurable expression effects need not have additive reproductive effects. Fix an environmental demand. Let $u > 0$ be the background trait-to-demand

ratio and let two mutations multiply the trait by $s^2$ and $r^2$, where $s, r > 0$. The double mutant must realize their product on that axis. Fitness epistasis below is measured in viable offspring per parent on the additive scale of (2).

**Theorem 2.** *For $m = usr$, the excess cost of the double mutant over the sum of its two single-mutant changes is*

$$\begin{aligned} D &= J(us^2r^2) - J(us^2) - J(ur^2) + J(u) \\ &= \tfrac{1}{2}(m + m^{-1})(s - s^{-1})(r - r^{-1}). \end{aligned} \tag{6}$$

*The corresponding offspring interaction is $-\beta D$. Its sign is negative for two changes in the same direction, positive for opposing changes, and zero if either multiplier equals one.*

*Proof.* In the mixed difference the constant part of $J$ cancels. Its linear and reciprocal parts give

$$2D = u(s^2 - 1)(r^2 - 1) + u^{-1}(s^{-2} - 1)(r^{-2} - 1).$$

Factoring out $(s - s^{-1})(r - r^{-1})$ leaves $usr + (usr)^{-1}$. This factor is positive. Substitution in (2) gives the offspring result. □

For two same-direction mutations that each raise offspring output on the chosen background, a negative interaction is diminishing returns. Experiments with yeast have documented declining adaptability across backgrounds [5]. A sign alone gives little leverage on the cost law. Equation (6) predicts the interaction's *magnitude* from the measured multipliers, a background ratio, and the common budget scale. Its dependence on the background separates it from a cost quadratic in log mismatch, for which the mixed difference of two fixed log increments is constant. If distinct axes contribute additively and each mutation affects only its own axis, the four terms cancel axis by axis and the interaction vanishes. Shared machinery or a change in resource income can violate that independence.

# 6 An experiment that separates the cost laws

A bacterial expression system offers independent controls for the trait and the environment. The following comparison is prospective. Its decisive measurement is the shape of reproductive output away from the optimum, where otherwise similar cost functions disagree.

**Measure the ratio before fitting the curve.** Use isogenic lines with tunable, approximately fixed lac expression. Measure the expressed enzyme per cell, $p$, throughout each exposure. Define $e$ in the same units from an independent flux assay: at the specified substrate concentration, measure the enzyme abundance needed to deliver a prespecified cellular flux. Verify that the target is achievable in both media and that the assay-defined demand corresponds to the constant-medium output optimum in a separate calibration. External lactose concentration alone cannot serve as $e$. Track viable descendants over a common interval. Converting bulk growth rate to this output requires an independent conversion.

**Challenge a prediction that can fail.** Measure income, maintenance and offspring cost, or establish their common values over the comparison range. Use designated constant-medium training conditions to calibrate the scale and intercept of each candidate cost. Freeze those

parameters and demand measurements before using a second schedule. Alternate the media fast enough that a lineage encounters both demands within the chosen reproductive interval, and confirm that fixed lines retain their expression. Compare the full offspring curve over a prespecified range of $p$, including reciprocal deviations from demand. Predict the best fixed trait and its loss from exposure fractions alone, using (3). Include unequal exposure fractions and off-optimum traits: two equally weighted demands yield the same geometric midpoint under a squared-log cost. A comparison confined to that midpoint cannot decide between the laws.

**Measure what regulation buys.** Measure the overhead of the sensing and expression response independently, in the same resource units as fixed-type mismatch. Observe the achieved expression trace so that delay or imperfect tracking is distinguishable from its overhead. For a tracker that reaches the demanded level throughout each exposure, $\kappa L_*$ is the break-even expenditure. In a second comparison, measure two single-mutant multipliers and the double-mutant expression level before measuring their offspring counts on multiple backgrounds. The product condition and the four-count interaction in (6) can then be checked separately.

A reproducible asymmetry between reciprocal trait ratios at equal demand and budget would reject the proposed cost for that system. So would a held-out cost curve inconsistent with (3) after uncertainties in expression, demand and offspring yield are propagated. If the budget changes or the expression does not stay fixed, the comparison instead identifies which premise has failed. What makes the experiment informative is that the optimum, the amount worth spending on tracking, and the interaction of same-axis mutations are constrained by one independently measurable cost scale.

# References

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