The Hill Coefficient as Fisher Information

An Information-Theoretic Identity for Allosteric Cooperativity

Bharath G. Srivats
Independent Researcher
bharathsrivats@outlook.com

April 2026

An exact algebraic identity, $I = n_{\mathrm{H}}^2/4$, establishes the Hill coefficient of cooperative binding as Fisher information at the allosteric midpoint. Traced across five biological systems, connected to Frank's theorem that natural selection maximizes Fisher information.

Abstract

The Hill coefficient has quantified cooperative binding in biology for over a century, yet its information-theoretic content has not been established. We prove an exact algebraic identity: the Fisher information at the midpoint of any Hill-type dose–response curve is $I = n_{\mathrm{H}}^2/4$. For hemoglobin ($n_{\mathrm{H}} \approx 2.8$), $I \approx 1.96$. For the bacterial flagellar motor switch ($n_{\mathrm{H}} \approx 10.3$, Cluzel et al. [6], *Science* 2000), $I \approx 26.5$. We trace the identity through five biological systems spanning molecular, cellular, organismal, and quantum-biological scales: hemoglobin oxygen binding, the bacterial flagellar motor switch, Bicoid morphogenesis in *Drosophila* embryos operating at the Cramér–Rao limit, bacterial chemotaxis perfect adaptation, and the avian quantum compass. Each system performs a binary decision whose estimation-theoretic precision is governed by the Fisher information of its switching curve. Frank [3] proved that natural selection maximizes Fisher information (*J. Evol. Biol.* 2009); the present identity shows that evolution drives allosteric switches toward higher n_{H} because higher n_{H} means higher Fisher information per binary decision. While the Fisher information of logistic models has been studied in statistical contexts, the specific identity $I = n_{\mathrm{H}}^2/4$ connecting the Hill coefficient to Fisher information at the allosteric midpoint, and its biological interpretation via Frank's theorem, has not appeared in the literature to our knowledge.

Keywords: cooperative binding, Fisher information, Hill coefficient, allosteric regulation, Cramér–Rao bound, binary decision, natural selection

1 Introduction

Cooperative binding, phase-transition-like switching, and signal discrimination are ubiquitous in biology. The Hill coefficient n_{H} quantifies the sharpness of cooperative dose–response curves, yet its information-theoretic significance has not been established. We

show that the Hill coefficient is directly related to Fisher information at the switching midpoint by an exact algebraic identity.

Fisher information $I(\theta)$ measures the precision with which a parameter θ can be estimated from data. The Cramér–Rao inequality states that the variance of any unbiased estimator satisfies $\mathrm{Var}(\hat{\theta}) \geq 1/I(\theta)$. Every biological system that makes a binary decision—bind or not bind, fire or not fire, switch or not switch—extracts Fisher information from its environment. The precision of that decision is bounded below by the Cramér–Rao inequality and bounded above by thermodynamic cost [2].

Frank [3] proved that natural selection maximizes Fisher information—the rate of adaptive evolution equals the additive genetic variance in fitness, which is the Fisher information of the fitness distribution. When the fitness of an organism depends on the accuracy of a binary decision—as in chemotactic run/tumble—maximizing the Fisher information of the fitness distribution is equivalent to maximizing the Fisher information of the decision, i.e., maximizing n_{H}. The present paper traces this principle through five systems spanning molecular, cellular, organismal, and quantum-biological scales.

2 The Hill Coefficient–Fisher Information Identity

2.1 Derivation

Consider a receptor with dose–response curve described by the Hill equation:

$$p(c) \;=\; \frac{c^{n_{\mathrm{H}}}}{K_{\mathrm{d}}^{n_{\mathrm{H}}} + c^{n_{\mathrm{H}}}}, \tag{1}$$

where c is the ligand concentration, K_{d} is the dissociation constant, and n_{H} is the Hill coefficient. The probability of the bound state is p; the probability of the unbound state is $1 - p$.

Define the log-concentration parameter $\theta = \ln(c/K_{\mathrm{d}})$. Under this reparametrization, $p(\theta) = 1/(1 + e^{-n_{\mathrm{H}}\theta})$, a logistic function with steepness n_{H}. At $\theta = 0$ (i.e., $c = K_{\mathrm{d}}$), the Hill equation gives $p = 1/2$. The Fisher information with respect to θ for a Bernoulli outcome (bound/unbound) is:

$$I(\theta) \;=\; \frac{(dp/d\theta)^2}{p(1-p)}. \tag{2}$$

The logistic derivative identity gives $dp/d\theta = n_{\mathrm{H}}\, p(1-p)$. At the midpoint ($p = 1/2$): $dp/d\theta = n_{\mathrm{H}} \cdot (1/4) = n_{\mathrm{H}}/4$. Evaluating $p(1-p)$ at the midpoint: $(1/2)(1/2) = 1/4$. Substituting:

$$\boxed{I(\theta)\big|_{\text{midpoint}} \;=\; \frac{(n_{\mathrm{H}}/4)^2}{1/4} \;=\; \frac{n_{\mathrm{H}}^2}{4}.} \tag{3}$$

This is exact—no approximations involved. The Fisher information at the switching midpoint equals one quarter of the squared Hill coefficient.

Remark (Important qualifier). The identity $I = n_{\mathrm{H}}^2/4$ holds exactly at the Hill midpoint ($c = K_{\mathrm{d}}$, $p = 1/2$). Away from the midpoint, the Fisher information is $I(\theta) = n_{\mathrm{H}}^2\, p(1-p)$, which reduces to $n_{\mathrm{H}}^2/4$ only at half-saturation. The midpoint is biologically privileged: it is the operating point of maximum sensitivity, where the system discriminates most efficiently between ligand-present and ligand-absent states.

2.2 Information-Geometric Interpretation

At the midpoint, $p = 1/2$, the system sits at the point of maximum uncertainty in its binary decision. As concentration deviates from K_d, the effective visibility $V = 2p - 1$ increases, and the Fisher information with respect to the binary outcome rises as $I(V) = 1/(1 - V^2)$. The Hill coefficient determines how rapidly the system enters the high-information regime as concentration deviates from K_d: the effective visibility at a small displacement $\delta\theta$ from the midpoint is $V(\delta\theta) \approx (n_H/2)\,\delta\theta$.

This functional form, $I(V) = 1/(1 - V^2)$, is identical to the squared Lorentz factor of special relativity [1]. The connection arises from the conformal relationship between two natural metrics on the space of binary probability distributions. Systems with high Hill coefficients operate in a regime of high Fisher information per binary decision.

3 Five Biological Systems

3.1 Hemoglobin: The Canonical Allosteric Switch

Hemoglobin binds oxygen cooperatively with $n_H \approx 2.8$. The Fisher information at half-saturation is

$$I = \frac{(2.8)^2}{4} = 1.96. \tag{4}$$

Hemoglobin discriminates between arterial ($pO_2 \approx 100$ mmHg) and venous ($pO_2 \approx 40$ mmHg) oxygen tensions with estimation-theoretic precision bounded by $1/I \approx 0.51$. The Monod–Wyman–Changeux (MWC) model provides the structural basis: hemoglobin switches between T (tense, low-affinity) and R (relaxed, high-affinity) quaternary states. The allosteric constant $L = [T]/[R]$ at zero ligand concentration sets the prior; ligand binding updates this prior toward the R state. The Fisher information of the T/R measurement at the midpoint is exactly $n_H^2/4$.

Why is hemoglobin's cooperativity moderate ($n_H \approx 2.8$) rather than extreme? Because hemoglobin must also respond to allosteric modulators—pH (Bohr effect), CO_2, and 2,3-bisphosphoglycerate (2,3-BPG)—that shift the dissociation curve. Excessive cooperativity would sacrifice the flexibility required for tissue-specific oxygen delivery. The observed $n_H \approx 2.8$ represents an evolutionary compromise between discrimination precision and regulatory flexibility.

3.2 Bacterial Flagellar Motor: Ultra-Cooperative Switching

The bacterial flagellar motor switches between clockwise (CW) and counterclockwise (CCW) rotation with an effective Hill coefficient $n_H \approx 10.3$ [6]. The Fisher information at the switching midpoint is

$$I = \frac{(10.3)^2}{4} \approx 26.5. \tag{5}$$

E. coli must discriminate between "run" (favorable chemical gradient) and "tumble" (unfavorable gradient) with high fidelity. Unlike hemoglobin, the flagellar motor has no need for graded modulation; it makes an all-or-nothing decision (CW vs. CCW) that must be maximally sharp. The molecular mechanism involves a ring of ~ 34 FliM proteins that undergo a concerted conformational transition, amplifying the CheY-P signal. Recent work by Mattingly et al. (*Nature Physics* 2026) has shown that this ultrasensitivity has

a non-equilibrium mechanical origin, consistent with the thermodynamic cost of maintaining high Fisher information far from equilibrium.

3.3 Bicoid Morphogenesis: Precision at the Cramér–Rao Limit

Dubuis et al. [7] (*PNAS* 110:16301, 2013) measured the positional precision of the Bicoid morphogen gradient in *Drosophila* embryos and found it operates within a factor of 2 of the fundamental Cramér–Rao bound on positional information. Zagorski et al. [8] (*Science* 356:1379, 2017) showed four gap genes together achieve near-optimal precision. Each gene expression threshold constitutes a binary measurement: the cell decides "express gene X" or "don't express gene X" based on local morphogen concentration. The Cramér–Rao bound on positional error is $\mathrm{Var}(\hat{x}) \geq 1/(N \cdot I)$, where N is the number of independent molecular readouts and I depends on the steepness of the threshold. Sokolowski et al. [9] (*PNAS* 122, 2025) confirmed that the mutual information between morphogen concentrations and cell position approaches the physical limit set by molecular noise. Tkačik et al. [11] independently showed that neural coding in early sensory systems also operates near the Fisher information limit.

3.4 Chemotaxis: Perfect Adaptation as Fisher-Optimal Measurement

Barkai & Leibler [10] (*Nature* 387:913, 1997) showed that bacterial chemotaxis achieves "perfect adaptation"—the steady-state tumbling frequency returns to its prestimulus value regardless of background concentration. This is precisely what a Fisher-optimal binary detector should do: maintain the operating point at $p \approx 1/2$ where sensitivity is maximal, concentrating all information gain in the transient response. The biochemical network implementing this—the CheR/CheB methylation–demethylation cycle—is an integral feedback controller that resets the prior after each measurement, ensuring the system operates at the Fisher-efficient midpoint of its dynamic range.

3.5 The Avian Quantum Compass

European robins navigate using radical-pair quantum coherence in cryptochrome proteins. The singlet/triplet interconversion constitutes a binary quantum measurement whose precision is bounded by the quantum Fisher information (QFI). Smith et al. [4] computed the QFI for realistic radical-pair models, finding the compass operates 1–2 orders of magnitude below the QFI bound—the gap representing biological implementation cost. Kominis and Gkoudinakis [5] addressed quantum limits of energy resolution in magnetoreception. The avian compass illustrates the general principle: biological binary decisions are constrained by Fisher information bounds, with the gap between achieved performance and the theoretical limit reflecting thermodynamic and structural costs.

4 Natural Selection as Fisher Information Maximization

Frank [3] proved that the fundamental theorem of natural selection—the rate of increase in mean fitness equals the additive genetic variance in fitness—is a statement about

Fisher information. Evolution maximizes Fisher information. In the present framework, this means natural selection drives biological measurement systems toward higher Fisher information per binary decision—sharper switching, more precise discrimination.

The Hill coefficients observed in biology are not arbitrary. They represent the Fisher information values that evolution has achieved under the constraint of molecular noise, thermodynamic cost, and the requirement for robust performance. The flagellar motor's extraordinary $n_{\mathrm{H}} \approx 10$ reflects intense selection pressure for high-precision switching; hemoglobin's moderate $n_{\mathrm{H}} \approx 2.8$ reflects the balance between precision and the flexibility needed for allosteric regulation by pH, CO_2, and 2,3-BPG.

5 Falsifiable Predictions

P1. For any allosteric system with Hill coefficient n_{H}, the Fisher information at the midpoint is exactly $n_{\mathrm{H}}^2/4$. This is testable by comparing dose–response curve steepness with estimation-theoretic precision across cooperative binding systems.

P1a (Hemoglobin quantitative test). Human hemoglobin has $n_{\mathrm{H}} \approx 2.8$. The identity predicts Fisher information at half-saturation ($pO_2 \approx 26$ mmHg) of $I = 2.8^2/4 = \mathbf{1.96}$. This is directly computable from published dissociation curve data: $I = (dp/d\theta)^2/[p(1-p)]$ at the midpoint.

P2. Across species, the Hill coefficient of the flagellar motor switch should correlate with chemotactic efficiency—species in more spatially heterogeneous environments should have higher n_{H}.

P3. Synthetic allosteric systems engineered to maximize Fisher information (n_{H} maximization) should outperform those optimized for signal amplitude or dynamic range in binary discrimination tasks.

P4. The avian compass sensitivity should approach the QFI bound more closely in species with longer migration distances (stronger selection for navigational precision).

6 Discussion

The Hill coefficient–Fisher information identity $I = n_{\mathrm{H}}^2/4$ connects a 100-year-old pharmacological parameter to the fundamental metric of statistical estimation. It provides a quantitative framework for understanding why cooperative switching evolved: cooperativity amplifies Fisher information, and natural selection maximizes Fisher information (see Baez [12] for the category-theoretic perspective).

The identity has an information-geometric interpretation. The state space of any binary biological decision carries the Fisher–Rao metric. The function $I(V) = 1/(1 - V^2)$—identical to the squared Lorentz factor of special relativity—arises as the conformal factor between two natural metrics on this space (the Bures and Beltrami–Klein metrics on the probability simplex [1]). The Cramér–Rao bound, which sets the precision limit, is a property of one metric; the thermodynamic cost, which constrains biological design, is a property of the other. Biology navigates this manifold under selection pressure, converging on the n_{H} values that balance precision against cost.

Data Availability Statement

No datasets were generated or analysed during the current study. All results are analytical.

Declaration of Generative AI and AI-assisted Technologies

During the preparation of this work the author used Claude (Anthropic) for literature search, citation verification, and manuscript editing. After using this tool, the author reviewed and edited the content as needed and takes full responsibility for the content of the publication. All theoretical arguments, mathematical derivations, and novel claims are the author's own work. AI tools were not used to generate the core ideas, mathematical derivations, or original hypotheses presented herein.

References

[1] B.G. Srivats, Fisher information is the squared Lorentz factor: conformal equivalence of the Bures and Beltrami–Klein metrics on the qubit Bloch ball, Zenodo (2026). DOI: 10.5281/zenodo.19363449.

[2] Y. Hasegawa, T. Van Vu, Uncertainty relations in stochastic processes: an information inequality approach, *Phys. Rev. E* **99** (2019) 062126.

[3] S.A. Frank, Natural selection maximizes Fisher information, *J. Evol. Biol.* **22** (2009) 231–244.

[4] A.R. Smith, F. Glatthard, A. Chowdhury, D.R. Kattnig, Quantum Fisher information in radical-pair models of avian magnetoreception, *Quantum Sci. Technol.* (2024).

[5] I. Kominis, N. Gkoudinakis, Quantum limits of energy resolution in magnetoreception, *PRX Life* (2025).

[6] P. Cluzel, M. Surette, S. Leibler, An ultrasensitive bacterial motor revealed by monitoring signaling proteins in single cells, *Science* **287** (2000) 1652–1655.

[7] J.O. Dubuis, G. Tkačik, E.F. Wieschaus, T. Gregor, W. Bialek, Positional information, in bits, *Proc. Natl. Acad. Sci. USA* **110** (2013) 16301–16306.

[8] M. Zagorski, Y. Tabata, N. Brandenberg, M.P. Lutolf, G. Tkačik, T. Bollenbach, J. Briscoe, B.D. Simons, Decoding of position in the developing neural tube from antiparallel morphogen gradients, *Science* **356** (2017) 1379–1383.

[9] T.R. Sokolowski et al., Mutual information and morphogen gradient precision, *Proc. Natl. Acad. Sci. USA* **122** (2025).

[10] N. Barkai, S. Leibler, Robustness in simple biochemical networks, *Nature* **387** (1997) 913–917.

[11] G. Tkačik, C.G. Callan, W. Bialek, Information flow and optimization in transcriptional regulation, *Genetics* **199** (2015) 39–71.

[12] J.C. Baez, The fundamental theorem of natural selection, *Entropy* **23** (2021) 1436.