

The Apparent Cooperativity of a Two-State Molecule Peaks Where Its Bias Between Shapes Balances the Ratio of Binding Strengths

— even with four binding sites the apparent Hill coefficient does not reach four, and it returns to one when the bias toward the weakly binding shape is too large or too small — the separator is whether the two shapes bind with different strengths or the same — [Paper 936]

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Abstract

When a molecule with four binding sites takes two shapes, one binding strongly and one weakly, and shifts toward the strong shape as binding increases, its binding curve looks cooperative. This paper takes this model (the model of cooperativity through a change of shape), varies the bias between the two shapes and the ratio of binding strengths, and counts how the apparent Hill coefficient at half saturation moves. No new theorem or law is claimed. First, apparent cooperativity peaks with respect to the bias between shapes: varying the ratio L of weak to strong shape from 1 to 10^{10} , with strength ratio $c = 0.01$ the apparent Hill coefficient rose from 1.151611 to **3.008264** at $L = 10^4$ and returned to 1.001870 at 10^{10} (Section 2). Second, the peak lies where bias balances the strength ratio, and is symmetric on either side: the peak coincided with 10^4 , the reciprocal of c to half the number of sites, and the coefficients at $L = 10^3$ and 10^5 , and at 10^2 and 10^6 , were equal within 6.0×10^{-11} . With $c = 0.1$ the peak is lower, **1.809622** at $L = 10^2$ (Section 2). Third, it does not reach the number of binding sites: with $c = 0$, where the weak shape does not bind at all, the coefficient kept rising with L , reaching 3.981056 at 10^{10} , but in every case it stayed below 4 (Section 3). Fourth, if the two shapes bind with the same strength, there is no cooperativity: with $c = 1$ the coefficient was 1.000000 at $L = 1, 10^2, 10^4$ and 10^6 . A first attempt assumed “no bias, $L = 1$, means no cooperativity” and failed (1.152240 at $c = 0, L = 1$) (Section 3). Fifth, the separator is whether the two shapes bind with different strengths or the same: with different strengths, binding pulls the molecule toward the strongly binding shape, and that appears as cooperativity. With the same strength, however the shapes are biased, binding does not move them, and the curve shows no cooperativity (Section 4). **Keywords:** cooperative binding, allosteric model, apparent Hill coefficient, two conformations, binding strength ratio, number of binding sites.

Scope of this paper (scope note): No new theorem or law is claimed: the two-state model of cooperative binding (Monod, Wyman and Changeux), its binding equation, and the fact that the apparent Hill coefficient does not exceed the number of binding sites are all known. No real molecule is claimed: four binding sites, bias L and strength ratio c are model values, not those of haemoglobin or any particular molecule. No comparison with other models: the merits relative to other cooperative models, such as those in which shapes change one site at a time, are not treated. Rates and intermediate shapes are not included: the rates of binding and shape change, and shapes intermediate between the two, are not included; only equilibrium is examined. Relation to earlier papers: Paper 878, in its scope note, did not enter mechanisms and did not treat the model of cooperativity through a change of shape or binding rates; this paper sits in that seat of the model (no earlier occupant). In its body, Paper 878 showed that what sets the concentration range from onset to full effect is not the effective concentration but the degree of cooperativity. Here it is counted how that degree of cooperativity arises from the bias between shapes and the ratio of binding strengths, and where it peaks. What is added: setting out the apparent Hill coefficient for three strength ratios and eleven biases, confirming the position of the peak and its symmetry, showing that the coefficient does not reach the number of sites, confirming that equal strengths give no cooperativity, and placing the separator on “whether the two shapes bind with different strengths or the same”.

1. Notation and the Question

Setting: a molecule with $n = 4$ binding sites takes a strongly binding shape R and a weakly binding shape T. With α the ligand concentration divided by R's binding constant, L the unliganded ratio of T to R, and c the ratio of T's binding strength to R's, the fraction of occupied sites Y is:

$$Y = \frac{\alpha(1 + \alpha)^{n-1} + Lc\alpha(1 + c\alpha)^{n-1}}{(1 + \alpha)^n + L(1 + c\alpha)^n}$$

The apparent Hill coefficient is taken as $d \ln[Y/(1 - Y)]/d \ln \alpha$ at the α where $Y = 1/2$. The check finds that α by bisection on a logarithmic scale and the slope by central differences.

Question: what decides the apparent cooperativity of a two-shape molecule, and how large can it become?

2. Varying the Bias Between Shapes

Computation 2.1: apparent Hill coefficients.

L	$c = 0$	$c = 0.01$	$c = 0.1$
1	1.152240	1.151611	1.142866
10	1.675650	1.663976	1.544731
10^2	2.424875	2.361982	1.809622
10^3	3.032047	2.845480	1.544731
10^4	3.430746	3.008264	1.142866
10^5	3.672215	2.845480	1.017836
10^6	3.813287	2.361982	1.001832
10^8	3.940301	1.151611	1.000018
10^{10}	3.981056	1.001870	1.000000

Searching L in steps of $10^{0.05}$, the peak for $c = 0.01$ was 3.008264 at $L = 10^{4.00}$ and for $c = 0.1$ was 1.809622 at $L = 10^{2.00}$, both at $L = c^{-n/2}$. For $c = 0.01$ the coefficients at $L = 10^3$ and 10^5 , and at 10^2 and 10^6 , were equal within 6.0×10^{-11} .

Observation 2.2

apparent cooperativity peaks with respect to bias, and the peak lies where the bias balances the strength ratio. With little bias the molecule is already in the strong shape, and with too much bias binding hardly shifts it: in between, at $L = c^{-n/2}$, the effect of binding in shifting the shape appears largest.

3. An Unreached Limit, and the Condition for No Cooperativity

Computation 3.1: in every case the coefficient stayed below the number of sites, 4. With $c = 0$ it kept rising with L , reaching 3.981056 at $L = 10^{10}$.

Computation 3.2: with $c = 1$ the coefficient was 1.000000 at $L = 1, 10^2, 10^4$ and 10^6 , differing from 1 by at most 1.0×10^{-11} .

Observation 3.3

apparent cooperativity does not reach the number of sites, and vanishes when the two shapes bind with the same strength. A first attempt set the check “no bias, $L = 1$, means no cooperativity” and failed (1.152240 at $c = 0$, $L = 1$): even with a bias of 1, if T does not bind, binding pulls the molecule toward R. What removes cooperativity is not the absence of bias but the absence of a difference in binding strength.

4. The Separator

Observation 4.1

the separator is whether the two shapes bind with different strengths or the same. With different strengths, the more is bound the more the molecule shifts to the strong shape, which invites further binding and steepens the curve: with the same strength, however the shapes are biased, binding does not move the proportion of shapes and the apparent Hill coefficient stays 1. With different strengths, the height and position of the peak are set by the balance of bias L and strength ratio c .

Observation 4.2

what is not said. Values for real molecules, merits relative to other cooperative models, rates of binding and shape change, and intermediate shapes are not treated. What is shown is that in the two-shape model apparent cooperativity does not reach the number of sites, peaks at the balance of bias and strength ratio, and vanishes when strengths are equal.

5. Roll Call and Closing

1. the two-shape binding equation and apparent Hill coefficient (Section 1): L and c .
2. peak **3.008264** at $L = 10^4$ for $c = 0.01$ (Computation 2.1): the balance point.
3. peak **1.809622** at $L = 10^2$ for $c = 0.1$ (Computation 2.1): lower for a smaller difference.
4. symmetric on either side of the peak (Computation 2.1): within 6.0×10^{-11} .
5. **3.981056** even at $c = 0$, below 4 (Computation 3.1): the number of sites is not reached.
6. **1.000000** at $c = 1$ (Computation 3.2): no cooperativity.

7. different strengths, or the same (Observation 4.1): the separator; the scope note of Paper 878.

Closing: The apparent cooperativity of a two-state molecule peaks where its bias between shapes balances the ratio of binding strengths. In the four-site model, the apparent Hill coefficient at strength ratio $c = 0.01$ peaked at 3.008264 at bias $L = 10^4$ and returned symmetrically to 1 on either side: even when the weak shape did not bind at all, the coefficient did not reach 4, and when the two shapes bound equally it was 1 whatever the bias. What removes cooperativity is not the absence of bias but the absence of a difference in binding strength: the separator is whether the two shapes bind with different strengths or the same. Placed among the earlier papers: the degree of cooperativity whose range Paper 878 counted without entering mechanisms was counted here from the bias and strength ratio of the two-shape model. To be honest, which molecules follow this model is not said. Where cooperativity peaks within the model and when it vanishes, and no further.

References

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