

A Sequential Model Can Produce Negative Cooperativity, but a Concerted Model Cannot However It Is Set

— with a factor below 1 on neighbouring changed shapes the apparent Hill coefficient drops below 1, but the concerted model never goes below 1 however its shape bias and binding-strength ratio are varied —the separator is whether the change of shape passes between neighbours or happens to the whole molecule at once — [Paper 955]

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Abstract

Cooperativity in a molecule with four binding sites is judged by whether one binding makes the next easier (positive cooperativity) or harder (negative cooperativity). This paper compares the range of apparent Hill coefficients available to a model in which shapes change one site at a time and influence neighbours (KNF) and a model in which all shapes change at once (MWC). No new theorem or law is claimed. First, the concerted-model computation reproduced the values of Paper 936: the apparent Hill coefficient of MWC was **3.008264** at binding-strength ratio $c = 0.01$ and shape bias $L = 10^4$, and **1.152240** at $c = 0, L = 1$, matching Paper 936 within 10^{-6} (Section 2). Second, the sequential model can bring the apparent Hill coefficient below 1: with the neighbour factor s at 0.01, 0.1 and 0.5, the apparent Hill coefficient was **0.038110**, **0.273292** and **0.705882**; at $s = 1$ it was 1.000000, and at $s = 2, 10$ and 100 it was **1.411765**, **2.732919** and **3.810961** (Section 2). Third, the concerted model never goes below 1 however it is set: over 1898 combinations with c at 0 and from 10^{-6} to 1 and L from 10^{-6} to 10^{12} , the minimum apparent Hill coefficient was **1.0000000000** (at $c = 1$) and the maximum **3.994003** (Section 2). Fourth, on the positive side both models approach the number of sites, 4: KNF gave **3.998001** at $s = 10^4$, and MWC **3.994003** at $c = 0, L = 10^{12}$ (Section 2). Fifth, the separator is whether the change of shape passes between neighbours or happens to the whole molecule at once: in the concerted model, cooperativity did not turn negative however shape bias and binding-strength ratio were set. In the sequential model, the factor can be set so that a neighbour's change hinders the next binding, and negative cooperativity was produced (Section 3). **Keywords:** cooperativity, KNF model, MWC model, apparent Hill coefficient, negative cooperativity, allostery.

Scope of this paper (scope note): No new theorem or law is claimed: the concerted model (Monod, Wyman and Changeux), the sequential model (Koshland, Némethy and Filmer), and that the former cannot produce negative cooperativity while the latter can are all known. Arrangement and number are restricted: KNF is treated only with four sites in a square, with the factor applied only to pairs of neighbouring changed sites. Linear and tetrahedral arrangements are not treated. No judgement of merit, which model fits real molecules, or which is better, is not said. What is counted is the range of apparent cooperativity each can produce. Only equilibrium: the rates of binding and shape change are not included (as in Paper 936). Relation to earlier papers: Paper 936, in its scope note, did not compare with other models and did not treat the merits relative to other models of cooperativity, such as one in which shapes change one at a time; this paper sits in that seat and compares not merit but the range of cooperativity available (no earlier occupant). Paper 936 showed that the apparent cooperativity of a two-state molecule peaks where its bias between shapes balances the ratio of binding strengths. Here it is counted that the concerted model cannot reach the opposite side of that peak, where cooperativity falls below 1. Paper 878 showed that the concentration span from first to full effect is set by cooperativity: with an apparent Hill coefficient below 1, that span is on the widening side. What is added: checking the MWC computation against the values of Paper 936, finding KNF's apparent Hill coefficient for each factor s , searching 1898 combinations for MWC's minimum coefficient, and placing the separator on "whether the change of shape passes between neighbours or happens to the whole molecule at once".

1. Notation and the Question

Concerted model (MWC, Paper 936): the whole molecule takes two shapes, with bias L , binding-strength ratio c and 4 binding sites. The fractional saturation is:

$$Y_{\text{MWC}} = \frac{\alpha(1 + \alpha)^3 + Lc\alpha(1 + c\alpha)^3}{(1 + \alpha)^4 + L(1 + c\alpha)^4}$$

Sequential model (KNF): four sites in a square, where only bound sites change shape. A factor s is applied for each pair of neighbouring changed sites. The arrangements with j bound and the number of neighbouring pairs are: $j = 0$, 1 way (0 pairs); $j = 1$, 4 (0); $j = 2$, 4 adjacent (1) and 2 opposite (0); $j = 3$, 4 (2); $j = 4$, 1 (4). The binding polynomial is therefore:

$$Z = 1 + 4x + (4s + 2)x^2 + 4s^2x^3 + s^4x^4, \quad Y_{\text{KNF}} = \frac{x dZ/dx}{4Z}$$

Apparent Hill coefficient: the slope of $\ln(Y/(1 - Y))$ against the log of concentration at half saturation (the same measure as Paper 936).

Question: over what range can each model produce the apparent Hill coefficient?

2. The Range of Cooperativity

Computation 2.1: MWC self-check: 3.008264 at $c = 0.01$, $L = 10^4$ and 1.152240 at $c = 0$, $L = 1$ (within 10^{-6} of Paper 936).

Computation 2.2: KNF apparent Hill coefficients.

neighbour factor s	apparent Hill coefficient	$\bar{x}$ at half saturation
0.01	0.038110	1.000000×10^2
0.1	0.273292	1.000000×10^1
0.5	0.705882	2.000000
1	1.000000	1.000000
2	1.411765	5.000000×10^{-1}
10	2.732919	1.000000×10^{-1}
100	3.810961	1.000000×10^{-2}
10^4	3.998001	1.000000×10^{-4}

The values at $s = 0.5$ and $s = 2$ were 0.705882353 and 1.411764706, matching 12/17 and 24/17 to 9 digits.

Computation 2.3: for MWC over 1898 combinations, with c at 0 and from 10^{-6} to 1 and L from 10^{-6} to 10^{12} in steps of a quarter decade, the apparent Hill coefficient had a minimum of 1.000000000 ($c = 1$, $L = 0.316228$) and a maximum of 3.994003 ($c = 0$, $L = 10^{12}$).

Observation 2.4

KNF can produce both sides of 1, MWC only 1 and above. KNF was below 1 for the three values $s < 1$ and above 1 for the four values $s > 1$: MWC never went below 1 by more than 10^{-9} in any of the 1898 combinations, reaching its minimum at $c = 1$, where the two shapes bind equally strongly. On the positive side, both approached the number of sites, 4.

3. The Separator

Observation 3.1

the separator is whether the change of shape passes between neighbours or happens to the whole molecule at once. In MWC, the whole molecule changes shape at once, and however the shape bias and binding-strength ratio were set, the apparent Hill coefficient did not go below 1 (Computation 2.3): in KNF, setting a factor below 1 on pairs of neighbouring changed sites lets one binding hinder its neighbour's binding, and the apparent Hill coefficient fell to 0.038110 at $s = 0.01$.

Observation 3.2

what is not said. Which model fits real molecules, arrangements other than a square, and the rates of binding and shape change are not treated. What is shown is that even with the same four sites, the range of apparent cooperativity depends on how shape changes propagate, and the concerted model did not go below 1.

4. Roll Call and Closing

1. binding equations of MWC and square KNF (Section 1): the same Hill measure.
2. MWC reproduces Paper 936 (Computation 2.1): **3.008264** and **1.152240**.
3. KNF gives **0.038110** at $s = 0.01$ (Computation 2.2): negative cooperativity is possible.
4. MWC minimum **1.000000000** (Computation 2.3): never below 1 in 1898 combinations.
5. both approach 4 on the positive side (Computations 2.2 and 2.3): **3.998001** and **3.994003**.
6. between neighbours, or all at once (Observation 3.1): the separator; the scope note of Paper 936; Paper 878.

Closing: A sequential model can produce negative cooperativity, but a concerted model cannot however it is set. In square KNF, varying the neighbour factor from 0.01 to 10^4 spread the apparent Hill coefficient from 0.038110 to 3.998001, on both sides of 1: in MWC, varying shape bias and binding-strength ratio over 1898 combinations gave a minimum of 1.000000000, never below 1. The separator is whether the change of shape passes between neighbours or happens to the whole molecule at once. Placed among the earlier papers. It was counted that only the sequential model reaches the opposite side of the cooperativity peak that Paper 936 counted in the concerted model. To be honest, which model is correct is not said. How the range of cooperativity differs with how shape change propagates, and no further.

References

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