Consequences of detailed balance in a model for sensory adaptation based on ligand-induced receptor modification

(microscopic reversibility/reaction affinity/turover rates/covalent modification/energy dissipation)

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ABSTRACT A model for exact sensory adaptation has been published by Segel and co-workers in several papers [e.g., Knox, B. E., Devreotes, P. N., Goldbeter, A. & Segel, L. A. (1986) Proc. Natl. Acad. Sci. USA 83, 2345–2349]. The model comprises a pair of states whose relative probabilities are determined by the binding of a ligand. A second pair of states related by the same ligand binding is accessible as a consequence of either a conformational change or a "covalent modification." By taking proper account of detailed balance, we show that the notion of covalent modification in this context includes three cases, two of which involve dissipation of metabolic energy. The condition for exact adaptation is dependent on metabolite concentrations in all cases of covalent modification. The performance of the model is critically examined on thermodynamic and kinetic grounds.

Segel and co-workers (1-3) have published a model for sensory adaptation. The important feature of this model is that it can exhibit exact adaptation—i.e., a return of the receptor response to exactly the same level after each transient perturbation by stimuli. In this model the authors assume that the sensory receptor exists in four different states (see Fig. 1). When dealing with the scheme depicted in Fig. 1a, they assert that microscopic reversibility need not be obeyed under all conditions. In support of this assertion they introduce the more elaborate scheme of Fig. 1b and claim that far from equilibrium the transitions with rate constants $\beta_1$, $\beta_4$, $\beta_2$, and $\beta_3$ can be neglected and consequently under these conditions this scheme "is identical" to that of Fig. 1a (see appendix 2 in ref. 2). However, we will show that this is not the case and that under all conditions both kinetic schemes will always satisfy properly formulated detailed balance relations. As a result some of the rate constants for the transitions between states 1 and 4 and states 2 and 3 may be pseudo-first-order rate constants that, therefore, depend on the metabolic state of the organism. We will examine the ways in which this dependence influences exact adaptation and the transient behavior of the receptor response under physiological conditions.

Application of Detailed Balance to the Kinetic Scheme

As explained very clearly by Hill (4), detailed balance requires that for all cycles of a kinetic scheme the product of the first-order rate constants or pseudo-first-order rate constants at equilibrium, taken for the transitions in the counterclockwise (ccw) direction, be equal to the corresponding product taken in the clockwise (cw) direction—i.e.,

$$\prod_{ccw} \alpha_{ij} = \prod_{cw} \alpha_{ij} \quad \text{ (equilibrium).} \quad [1]$$

To apply Eq. 1, the first step is to identify all the cycles of a given scheme. Thus the scheme depicted in Fig. 1a involves a single cycle only (cf. Fig. 2a). In contrast, as shown by Hill (5), schemes such as that depicted in Fig. 1b comprise six cycles (cf. Fig. 2b) and not just two cycles as claimed by Segel et al. (see figure A2 in ref. 2). The next step is to identify the pseudo-first-order rate constants and to represent them by second-order rate constants multiplied by the appropriate reactant concentrations. For example, for the transition from state k to state l involving the reactant $X_{kl}$,

$$\alpha_{kl} = \alpha_{kl}^0 [X_{kl}].$$

Choosing equilibrium values for the concentrations, Eq. 2 can be substituted into Eq. 1. Thus for any given cycle

$$\prod_{ccw} \alpha_{ij} \alpha_{kl}^0 X_{kl} \text{eq} \prod_{cw} \alpha_{ij} \alpha_{kl}^0 [X_{kl}]. \quad [3]$$

Rearranging Eq. 3 and recognizing the law of mass action,

$$\prod_{cw} [X_{kl}] \text{eq} / \prod_{ccw} [X_{kl}] \text{eq} = K_c,$$

where $K_c$ is the equilibrium constant of the overall chemical
reaction, we finally obtain the relation between constants
\[
\prod_{c,w} a_{ij} a_{ji}^0 / \prod_{c,w} a_{ij} a_{ji}^0 = K_c. \tag{5}
\]

Turning to the schemes of Fig. 1, it is seen that the transition from state 1 to state 2 involves the second-order rate constant \(a_{12}^0\), whereas the reverse transition involves the first-order rate constant \(a_{21}\). Similar considerations apply to the transition from state 4 to state 3. The dissociation constants for ligand binding \(K_R\) and \(K_D\) are then given by
\[
K_R = a_{21}/a_{12}^0 \quad \text{and} \quad K_D = a_{42}/a_{24}^0. \tag{6}
\]

To analyze the scheme in Fig. 1a it is necessary to consider three cases for the transitions between states 1 and 4 and states 2 and 3.

Case i. No chemical reaction with external reactants occurs. All four rate constants, \(a_{14}, a_{41}, a_{23}, \) and \(a_{32}\), are true first-order rate constants. This corresponds to a conformational change between R and D. In this case the relation for detailed balance reads, in view of Eq. 6,
\[
(a_{32}a_{41}K_D)/(a_{12}a_{24}K_R) = 1. \tag{7}
\]

Case ii. Chemical reaction occurs with the same external reactants for both transitions. The rate constants \(a_{14}\) and \(a_{32}\), the rate constants \(a_{41}\) and \(a_{23}\), or both pairs, are pseudo-first-order rate constants involving the same external reactants. Considering the latter possibility for generality,
\[
(a_{0}^0 a_{24}K_D)/(a_{0}^0 a_{24}K_R) = 1. \tag{8}
\]

This corresponds to a covalent modification of the receptor, which is essentially a ligand binding or generalized ligand exchange reaction.

Case iii. Chemical reaction occurs with different external reactants for the two transitions. The rate constants \(a_{14}\) and \(a_{32}\), the rate constants \(a_{41}\) and \(a_{23}\), or both pairs, are pseudo-first-order rate constants. All alternatives involve overall chemical reactions between the external reactants, and again considering the latter possibility for generality,
\[
(a_{0}^0 a_{24}^0 K_D)/(a_{0}^0 a_{24}^0 K_R) = K_c. \tag{9}
\]

To analyze the scheme in Fig. 1b we introduce an additional case.

Case iv. States 1 and 4 and states 2 and 3 are each connected through a pair of independent transitions. Chemical reaction occurs with different external reactants for the two transitions of each pair. Consider for generality that all of the rate constants \(\beta_{ij}\) and \(\beta_{ji}\) of these four transitions are pseudo-first-order. It is readily shown that the six cycles depicted in Fig. 2b give rise to only four independent detailed balancing conditions, which may be conveniently written
\[
\frac{\beta_{21}^0 \beta_{42}^0 K_D}{\beta_{12}^0 \beta_{41}^0 K_R} = \frac{\beta_{24}^0 \beta_{42}^0 K_D}{\beta_{23}^0 \beta_{32}^0 K_R} = 1 \tag{10}
\]

and
\[
\frac{\beta_{21}^0 \beta_{42}^0}{\beta_{12}^0 \beta_{41}^0} = \frac{\beta_{24}^0 \beta_{42}^0}{\beta_{23}^0 \beta_{32}^0} = K_c. \tag{11}
\]

It is seen that the conditions of Eq. 10 refer to cycles e and f of Fig. 2b, which involve ligand binding only as discussed under cases i and ii. These are the conditions considered by Segel et al. (2). On the other hand the conditions of Eq. 11 refer to cycles a and b, which involve overall reaction only. The conditions pertinent to cycles c and d, which involve both ligand binding and overall reaction as in case iii, can be obtained by combining Eqs. 10 and 11.

An essential difference between schemes conforming to cases i and ii and schemes conforming to cases iii and iv is that the former cannot attain a nonequilibrium stationary state, in contrast to the latter. Nonequilibrium stationary states are characterized by a nonzero overall reaction affinity, \(A\), defined by
\[
A = -\sum \nu_i \mu_i = RT \ln (K_c / \Pi c_i^0). \tag{12}
\]

where \(\nu_i\) and \(\mu_i\) are, respectively, the stoichiometric coefficient and the chemical potential of the \(i\)th external reactant or product of concentration \(c_i\), with \(\nu_i\) taken positive for products and negative for reactants. Substituting \(K_c\) in Eq. 12 from Eq. 5 and recognizing that the external reactants of the counter-clockwise cycle correspond to the products of the overall chemical reaction, while those of the clockwise cycle correspond to the reactants of the overall chemical reaction, one obtains
\[
\prod_{c,w} a_{ij} a_{ji}^0 / \prod_{c,w} a_{ij} a_{ji}^0 = e^{ART}. \tag{13}
\]

Hence a description of a given cycle in terms of first-order and pseudo-first-order rate constants with assigned values immediately gives the affinity of the overall chemical reaction. Note that setting the concentration of ligand, \(L\) (Fig. 1), to zero gives rise to a constrained equilibrium (7) in case iii.

**Exact Adaptation**

Segel and co-workers (1-3) assume that the response to a signal is a function of the "activity" per mole of the receptor \(B\), defined as follows:
\[
B = \sum_{i=1}^{4} a_i p_i, \tag{14}
\]

where \(p_i\) is the probability of the \(i\)th state and \(a_i\) is a weighting factor associated with it. Whenever \(B\) has a fixed value \(B_0\) for all steady states of the receptor, irrespective of ligand concentrations, we have exact adaptation. Hence, for the stationary state, remembering that \(\Sigma p_i = 1\),
\[
B_0 = \sum_{i=1}^{4} a_i p_i, \quad \text{or} \quad \sum_{i=1}^{4} a_i p_i = 0, \tag{15}
\]

where \(a_i = a_i - B_0\). Segel et al. have shown that a set of positive weighting factors \(a_i\) can be found (see appendix 3 of ref. 2) and have used two methods, one extended and the other brief, to derive relations between the weighting factors and the rate constants. The brief method essentially expresses the fact that at steady state the net transitional flux in each branch of a given cycle is constant, constituting \(J\), the cycle flux per receptor molecule (4):
From Eqs. 15 and 16 it follows that

\[ \alpha_{14}p_1 \left( \frac{a_1}{a_{14}} + \frac{a_4}{a_{41}} \right) + \alpha_{23}p_3 \left( \frac{a_2}{a_{23}} + \frac{a_3}{a_{32}} \right) + J \left( \frac{a_2}{a_{23}} + \frac{a_4}{a_{43}} \right) = 0. \]  

This condition was obtained by Segel et al. (2). It is worth noting that from considerations of symmetry an additional condition can be found:

\[ \alpha_{12}p_1 \left( \frac{a_1}{a_{12}} + \frac{a_2}{a_{21}} \right) + \alpha_{43}p_4 \left( \frac{a_3}{a_{34}} + \frac{a_4}{a_{43}} \right) - J \left( \frac{a_3}{a_{32}} + \frac{a_4}{a_{43}} \right) = 0. \]

For relations 17 and 18 to be valid under all conditions, each term must be identically zero. For kinetic schemes whose only steady states are equilibrium states, the third term in each relation is zero since \( J \) is zero, and hence each relation yields two conditions between the four weighting factors. This applies to cases \( i \) and \( ii \) discussed above. For kinetic schemes whose steady states are nonequilibrium states, \( J \) does not vanish, and hence each relation yields three conditions. This applies to case \( iii \). It also applies to case \( iv \) under the conditions considered by Segel et al. (2)—i.e., far from equilibrium when the clockwise-directed reactions in cycles \( a \) and \( b \) (Fig. 2) can be neglected. In this case \( \beta_i = 0, \beta_i' = 0 \), and Eq. 16 refers to transitions between states 1 and 2 and states 3 and 4. For transitions between states 1 and 4 and states 2 and 3 the corresponding relation is

\[ J = \beta_{32}p_2 - \beta_{32}p_3 = \beta_{14}p_4 - \beta_{14}p_1, \]  

and Eq. 17 must be replaced by

\[ \beta_{14}p_1 \left( \frac{a_1}{a_{14}} + \frac{a_4}{a_{41}} \right) + \beta_{23}p_3 \left( \frac{a_2}{a_{23}} + \frac{a_3}{a_{32}} \right) + J \left( \frac{a_2}{a_{23}} + \frac{a_4}{a_{43}} \right) = 0. \]  

Eq. 18 comprises rate constants pertinent to ligand-binding transitions only and thus yields conditions dependent on ligand concentrations, although independent of external chemical reactant concentrations. Accordingly only the conditions that can be derived from Eqs. 17 or 17a can be relevant. But in most cases we are then still faced with the problem of external chemical reactant concentrations. If these vary, we cannot have exact adaptation.

### Table 1. Notation for and values of rate constants

<table>
<thead>
<tr>
<th>Source</th>
<th>First-order or/pseudo-first-order rate constants</th>
<th>Dissociation constants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Segel and co-workers (1–3)</td>
<td>( k_1 )</td>
<td>( K_k )</td>
</tr>
<tr>
<td>Cases ( i-iii )</td>
<td>( \alpha_{14} ) ( \alpha_{41} ) ( \alpha_{23} ) ( \alpha_{32} ) ( k_{-2} )</td>
<td>( K_k ) ( K_D )</td>
</tr>
<tr>
<td>Case ( iv )</td>
<td>( \beta_{14} ) ( \beta_{41} ) ( \beta_{23} ) ( \beta_{32} )</td>
<td>( K_k ) ( K_D )</td>
</tr>
<tr>
<td>Methylation (1)(</td>
<td>)</td>
<td>0.276</td>
</tr>
<tr>
<td>Phosphorylation (9)(</td>
<td>)</td>
<td>0.012</td>
</tr>
</tbody>
</table>

*Values for rate constants are given in \( \text{min}^{-1} \).

\( K_k = K_D \) was assumed (1).

\( K_D \) is a dissociation constant for ATP and can be from Table 2.

### Biological Relevance of the Different Cases

Adaptation in bacterial systems is known to involve \( S \)-adenosymelithione-dependent methylation and demethylation of the receptor molecules, each catalyzed by a different enzyme (chemotactic methyltransferase and chemotactic methyltransferase) (8). This may be true of higher organisms as well (8), but it is generally considered that in these cases phosphorylation and demethylation may be involved (2, 9) although conformational changes cannot be excluded (9). Clearly cases \( i \) and \( ii \) can then be eliminated for methylation–demethylation systems.

In two experimental systems—i.e., Dictyostelium and Escherichia coli—sufficient data are available to have enabled Devreotes and co-workers (1, 9) to estimate values for the rate constants as summarized in Table 1. [This table also relates the notation of Segel and co-workers (1–3) to that used in this paper.] From these rate constants, it is possible to calculate reaction affinities according to Eq. 13. For case \( iii \) we obtain, with the aid of Eq. 6,

\[ A = RT \ln[(K_{D2a2a4})/(K_{R2a2a4})]. \]  

This equation also holds for cases \( i \) and \( ii \), but is then trivial since \( A \) is always zero (cf. Eqs. 7 and 8). Substituting the values from Table 1 into Eq. 20 yields an affinity of 6.8 kJ/mol for methylation and 10.4 kJ/mol for phosphorylation at 22°C. From this one can immediately conclude (4) that in any stationary state, irrespective of ligand concentration, the cycle in Fig. 1a runs counterclockwise. In view of the energetics of \( S \)-adenosymelithione and ATP, the most likely reactions involved are those of RL with \( S \)-adenosymelithione or, in the case of phosphorylation, RL with ATP and D with water.

For case \( iv \) we obtain from Eq. 13, rewritten in terms of cycles \( a \) and \( b \) (see Fig. 2b),

\[ A = RT \ln[(\beta_{14}\beta_{23})/(\beta_{41}\beta_{32})]. \]  

Here it is seen that values for the rate constants in the denominators are missing from Table 1. These are the quantities assumed by Segel et al. (2) to be negligibly small. This assumption imposes a lower bound on the value of \( A \). Let us suppose, for example, that \( \beta_i/\beta_i' = \beta_j/\beta_j' = f \). Then we find that when \( f = 10^{-3}, 10^{-4}, \) or \( 10^{-5} \), \( A = 33.9, 45.2, \) or 56.5 kJ/mol, respectively, at 22°C. To obtain such large affinities, it is clear from Eq. 12 that only reactions with large equilibrium constants are feasible, otherwise unrealistically large or small concentrations of external reactants would be needed. Phosphorylation with ATP would satisfy this criterion, and so in all probability would methylation since the formation of \( S \)-adenosymelithione involves splitting ATP completely into pyrophosphate and phosphate.
Table 2. Turnover rates for methylation and phosphorylation at different ligand concentrations

<table>
<thead>
<tr>
<th>Turnover rates, min⁻¹</th>
<th>Methylation*</th>
<th>Phosphorylation</th>
</tr>
</thead>
<tbody>
<tr>
<td>[L]/K_D</td>
<td>Case iii</td>
<td>Case iv</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0.221</td>
</tr>
<tr>
<td>0.5</td>
<td>0.042</td>
<td>0.185</td>
</tr>
<tr>
<td>1.0</td>
<td>0.058</td>
<td>0.164</td>
</tr>
<tr>
<td>5.0</td>
<td>0.062</td>
<td>0.105</td>
</tr>
<tr>
<td>10.0</td>
<td>0.047</td>
<td>0.081</td>
</tr>
</tbody>
</table>

Turnover rates were calculated by means of Eqs. 22-24 using rate constant values given in Table 1.

*The absolute values of ligand concentration, [L], cannot be computed for this reaction (see Table 1).

Turning now to the flows at steady state, one readily derives the appropriate relations by following the procedure given by Hill (4). Assuming that the transitions associated with binding and release of ligand, L, are much faster than the transitions pertinent to modification of the receptor (2), we find for case iii

\[ J = [L](\alpha_{12}\alpha_{41}/K_R) - (\alpha_{32}\alpha_{14}/K_D))/\Sigma'. \]  \[22\]

where

\[ \Sigma' = \alpha_{14}\alpha_{41} + [L][(\alpha_{12} + \alpha_{41})/K_R] + [(\alpha_{32} + \alpha_{14})/K_D] + [L](\alpha_{32} + \alpha_{14})/(K_RK_D)). \]  \[23\]

For models complying with case iv the general result has been given by Hill (5). In our terms this becomes

\[ J = \beta_{14}\beta_{14} + [L](\beta_{14}\beta_{32}/K_R) + (\beta_{14}\beta_{32}/K_D) + [L]\beta_{32}\beta_{32}/(K_RK_D))/\Sigma''. \]  \[24\]

where \( \Sigma'' \) is obtained by rewriting \( \Sigma' \) in terms of \( \beta_{ij},s \) and \( \beta_{ij}'s \) according to Table 1. Values for the flows per receptor—i.e., the turnover rates—are reported in Table 2 for selected ligand concentrations. It is seen that, when [L] = 0, the turnover rate is zero in case iii and nonzero in case iv.

Affinity Dependence of the Response

We have pointed out above that exact adaptation of case iii–iv models can only be obtained with a particular set of concentrations of the external reactants. This set defines the reference state for which we determine the weighting factors.

Fig. 3. Response of a case iv type receptor to a square wave pulse of ligand concentration. Phosphorylation is assumed, and the time courses of the activity B and the turnover rate J in response to an instantaneous increase in ligand concentration from zero to 3 \( \mu \)M (↑) and back to zero (↓) are shown. The data listed in Table 1 with \( \alpha_{11} = \alpha_{22} = 300 \) min⁻¹ were used for the reference state with affinity \( A_0 \) and the weighting factors \( a_i \) were determined according to Eqs. 15 and 17a such that \( B_0 = 1 \) and \( a_4 = 0 \). For states with different affinities \( A \), the [ATP]-dependent rate constants were calculated from \( \beta_i(A) = \beta_i(A_0)(1 + K'/\exp(A_0/RT))/(1 + K'/\exp(A/RT)) \) \( (ij = 23 \text{ and } 14) \), which is obtained from Eq. 12 written for ATP hydrolysis under the assumption that [ATP] + [ADP] = constant and \([P_i] = constant; K' = K_0/[P].] = 1.5 \times 10^4 \) Simulations were performed as outlined in ref. 7 using the electric network simulation program SPICE. Affinities (in kJ/mol) are \( A_0 = 50 \) (curves 1), \( A = 45 \) (curves 2), and \( A = 42 \) (curves 3).

Fig. 4. Response of a case iv type receptor to a square wave pulse of ligand concentration. Methylation is assumed, and the time courses of the activity B, the turnover rate J, and the concentration of S-adenosylmethionine in response to an instantaneous increase in ligand concentration from zero to \( 100 \) \( \mu \)M (↑) and back to zero (↓) are shown. The data listed in Table 1 with \( A_0''/K_R = \alpha_{14} = 0 \) were used for the reference state (curves 1) with a constant concentration of S-adenosylmethionine of 0.1 mM (11) from which \( \beta_i'' \) \( (ij = 23 \text{ and } 14) \) can be determined. Curves 2 and 3 represent starvation of the cells starting at zero time and 30 min, respectively. This causes the decline in S-adenosylmethionine concentration through receptor turnover and an assumed metabolic process with a first-order rate constant of 0.1 min⁻¹; cell volume \( 10^{-12} \) liter. Determination of weighting factors and simulations as indicated in the legend to Fig. 3.
according to Eq. 17. These weighting factors are now taken to be invariant with changes in metabolic state, in line with the suggestions by Segel and co-workers (1–3) that they are binding constants for an effector molecule. Fig. 3 shows the activity $B$ of a case iv type receptor with the corresponding turnover rates in response to a step in the ligand concentration. The modification reaction is phosphorylation, and the response is shown for the reference affinity as well as for two other affinities below the reference. The failure of exact adaptation in the two latter cases is apparent. Note also the changes in response kinetics.

A crucial experiment showing that adaptation–deadaptation in E. coli corresponds to the methylation and demethylation of chemoreceptors makes use of a methionine auxotroph mutant. Adaptation to attractants is found to be methionine dependent, but once a cell has adapted it remains adapted even if methionine is removed; furthermore, deadaptation (i.e., the relaxation to the unstimulated condition after removal of the attractant) can occur in the absence of methionine (10). Fig. 4 shows an attempt to mimic these experiments with a case iv type receptor. The constant S-adenosylmethionine level, which corresponds to a constant affinity, refers to the reference state (unlimited supply of methionine), whereas the other two cases refer to two different experimental protocols involving methionine starvation. It is seen that both adaptation and deadaptation are methionine dependent in the model, in contrast to experimental observation.

Discussion

In treating models conforming to the kinetic scheme of Fig. 1a, Segel et al. (2) omitted to specify the chemistry involved in the transitions between states 1 and 4 and states 2 and 3. Accordingly, these transitions were described only in terms of first-order rate constants, it being unnecessary to identify the pseudo-first-order rate constants. The “principle of microscopic reversibility” was then formulated as $K_{p}k_{-1}k_{2} = K_{h}k_{1}k_{-2}$ (see equations 4 and 28 of ref. 2) and used to discriminate between cases where the constraint applies and those where it “need not be imposed on the constants” (2). Aside from the fact that this constraint arises more correctly from detailed balancing, it is merely a criterion for distinguishing between equilibrium and nonequilibrium stationary states. [The notions of microscopic reversibility and detailed balancing are frequently confused. We discuss (12) this issue in some detail elsewhere.] Using Table 1 it is readily seen that the condition corresponds to $A = 0$ in Eq. 20 and thus represents equilibrium.

Another consequence of choosing pseudo-first-order and first-order rate constants without referring to chemistry is that a predetermined affinity is imposed on the system. Obviously the value imposed should be within physiological limits. In this respect the 10.4 kJ/mol obtained for phosphorylation according to case iii would appear to be unreasonably low, thus ruling out this case. A similar argument can be made for the 6.8 kJ/mol obtained for methylation according to case iii. However, this argument does not apply to the lower limits estimated for case iv.

Nonzero values of the affinity in general imply nonzero values of the flows. Again these values must be within physiological limits—i.e., the consumption of metabolites such as S-adenosylmethionine or ATP by the receptors must not exceed the rate at which they can be replenished. One can estimate the rate of production of S-adenosylmethionine from data presented by Aswad and Koshland (figure 3 in ref. 11), whereupon it is seen that the values given in Table 2 are at most 3% of this rate. Similarly we can estimate the capacity of cells to synthesize ATP from the data for oxygen consumption compiled by Altman and Dittmer (13) and find the values in Table 2 to lie between 0.1% and 1.5% of the estimated rate. In these estimates we have assumed 2500 and 10,000 receptors per cell for E. coli (14) and Dictyostelium (9), respectively.

As seen above, it is unlikely that receptor turnover per se would affect cellular metabolite levels. However, other processes, in particular energy-consuming processes that may be stimulated by receptor activity, may well alter metabolite concentrations significantly. In view of these effects modulation of the enzymes catalyzing the chemical modification of the receptor during adaptation as suggested by Ordal (8) may constitute an attractive alternative model.

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