Adaptive Ising Model and Bacterial Chemotactic Receptor Network

Yu Shi

Cavendish Laboratory, University of Cambridge, Cambridge CB3 0HE, United Kingdom

Abstract

We present a so-called adaptive Ising model (AIM) to provide a unifying explanation for sensitivity and perfect adaptation in bacterial chemotactic signalling, based on coupling among receptor dimers. In an AIM, an external field, representing ligand binding, is randomly applied to a fraction of spins, representing the states of the receptor dimers, and there is a delayed negative feedback from the spin value on the local field. This model is solved in an adiabatic approach. If the feedback is slow and weak enough, as indeed in chemotactic signalling, the system evolves through quasi-equilibrium states and the “magnetization”, representing the signal, always attenuates towards zero and is always sensitive to a subsequent stimulus.

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As a prototypical system of cell signalling, bacterial chemotaxis is extensively studied in biology. A bacterium, such as *Escherichia coli*, swims under the control of several flagellar motors. When the motors rotate counterclockwise, the bacterium runs forward; when the motors rotate clockwise, it tumbles. The motors switch between these two modes of rotation with the probability ratio determined, through a signalling pathway, by the change of the concentration of the ambient chemical. Therefore the bacterium performs a biased random walk towards higher concentration of an attractant or lower concentration of a repellent. The signalling pathway (Fig. 1) is as follows [1]. The chemoeffector molecule ligands bind to transmembrane receptor dimers, which are coupled by two proteins CheW to two cytoplasmic histidine kinases CheA. CheA is autophosphorylated with the rate greatly enhanced by the receptor, hence attractant binding causes the receptor dimer to undergo a conformational change which leads to a decrease of autophosphorylation rate of CheA. CheA transfers phosphorylation group to two regulators CheB and CheY. Phospho-CheY directly modulates the motors. On the other hand, Phospho-CheB mediates demethylation of the receptor, while another regulator CheR promotes methylation. Attractant binding also makes the receptor a better substrate for CheR. Since methylation increases the autophosphorylation rate of CheA, Phospho-CheB and CheR provide a negative feedback. The basic structure of the information loop is: the ligand binding is the input, the activity change of CheA is the output, and there is a negative feedback from the output on the input.

A crucial feature of chemotaxis is its sensitivity: as little as a single molecule can trigger a detectable motor response [2]. Another crucial feature is adaptation: after an initial sensitive response, the tumbling rate returns to the pre-stimulus level. A noteworthy fact is that there are about 2000 chemotactic receptor dimers clustering at a pole of the cell, furnishing a detecting “nose”. Is the sensitivity enhanced by clustering [3]? The possibility that ligand binding of one receptor can change the activities of more receptors was considered [4]. A biological principle may be formulated: *An attribute that exists most probably confers advantages over possible alternatives, especially if the latter have some apparent merit* [5]. This principle and various experimental findings led to a cooperative model based on coupling among receptor dimers [6]. This model is equivalent to an Ising model in a bimodally distributed field, and provides an arbitrarily sensitive initial response, by choosing an appropriate value of a parameter comparing the coupling with the noise. In this theoretical framework, adaptation is achieved by a counteracting effect due to the negative feedback and mapping to an opposite induced field in the Ising model. The theoretical results are in good agreement with, say, a recent experiment [6].

More investigations need to be made on adaptation and its relation with sensitivity. Especially it is important to explain why the adaptation is always perfect, i.e. the activity always returns to the pre-stimulus level precisely [7]; recent experiments showed that this perfectness of adaptation is robust though other properties, such as the time needed to complete the adaptation, vary with conditions [8].

In this letter, to improve the previous approach, we present a so-called adaptive Ising model (AIM), in which there is a negative feedback from the magnetization on the field. *With large separation of time scales*, there exists quasi-equilibrium, which is temporally local, i.e. on a short time scale. On a long time scale, however, the system evolves, with the existence of a dynamical attractor corresponding to a fixed pre-stimulus activity and is sensitive to the subsequent stimulus. Thus we obtain a natural explanation for why the adaptation is
always perfect, and show that not only the sensitive signal, but also the effective adaptation, is very likely a manifestation of the coupling among receptor dimers. Therefore sensitivity and adaptation are two sides of the same coin. Our model is above the level of molecular details, hence it is generic for signalling networks with similar conditions. Furthermore, the feedback from the information output on the input is a general way to preserve sensitivity.

Under the assumption of high gain limit, the state of the receptor dimer, characterized as \( V_i \), can be either of two values, \( V^0 \) and \( V^1 \), corresponding to the higher and lower rates of CheA autophosphorylation, respectively. As in the neural network \([9]\), we assume Mc Culloch-Pitts behavior for \( V_i \), i.e., in the absence of noise, \( V_i = \psi(\sum_j T_{ij} V_j + H_i - U_i) \), where \( \psi(x) = V^1 \) if \( x > 0 \) while \( \psi(x) = V^0 \) if \( x \leq 0 \), \( U_i \) is a threshold value, \( T_{ij} \) describes coupling between neighbouring receptor dimers, \( H_i \) is the effect of ligand binding and methylation level change. With \( T_{ij} = T_{ji} \) and \( T_{ii} = 0 \), there exists a Hamiltonian which determines the equilibrium state. One may use the spin representation \( S_i = 2(V_i - V^0)/\Delta V - 1 \), where \( \Delta V = V^1 - V^0 \). Defining \( J = J_{ij} = T_{ij} \Delta V^2/4 \) and \( B_i = H_i \Delta V/2 \), assuming that the “magnetization” is zero at the paramagnetic phase for \( c = 0 \), and taking into account the time-dependence of \( B_i \), we obtain the Hamiltonian

\[
\mathcal{H}(t) = -\sum_{\langle ij \rangle} J_{ij} S_i S_j - \sum_i B_i(t) S_i,
\]

where \( \langle ij \rangle \) denotes nearest neighbouring pairs. \( J_{ij} = J > 0 \) is a constant. An essential element of AIM is a negative feedback on \( B_i \):

\[
\frac{dB_i(t)}{dt} = -\sigma S_i(t - t_r),
\]

where \( \sigma > 0 \), \( t_r \) is the retard time of feedback. This is not an arbitrary assumption put in by hand, but is a close representation of the experimental finding that, in the chemotactic signalling pathway, the state of CheA, through CheB and CheR, causes an opposite effect on its state later on \([1]\). The initial condition is that \( B_i(t_0) \) is bimodally distributed between \( B \) and 0,

\[
p[B_i(t_0)] = c\delta[B_i(t = t_0) - B] + (1 - c)\delta[B_i(t_0)].
\]

Here \( B_i = B \) if the receptor dimer \( i \) is bound to ligand, otherwise \( B_i = 0 \). \( B > 0 \) for attractant binding while \( B < 0 \) for repellent binding. \( c \) is the the fraction of the receptor dimers with ligand bound, determined by the ambient concentration of the chemical. In other words, \( B_i(t) \) is superposed by two parts. One part is the externally applied field \( B_i(t_0)\theta(t - t_0) \), where \( \theta(x) = 0 \) if \( x < 0 \) while \( \theta(x) = 1 \) if \( x \geq 0 \). Another part is an induced field, denoted as \( M_i(t) \), with \( dM_i(t)/dt = -\sigma S_i(t - t_r) \). Note that we have assumed that the randomness is quenched, representing that ligand binding is so strong that debinding happens on a very long time scale \([10]\).

Generally, AIM defines a non-equilibrium model. However, the large separation of time scales holds in the current problem: ligand binding and conformation change occur within only millisecond, demethylation reactions take about 0.1 seconds, while time needed to complete the adaptation, which is associated with the slow modulation of methylation level, is on the scale of minutes \([1]\). This situation validates an adiabatic approximation. Roughly speaking, the demethylation reaction time plus the time for the transfer of phosphorylation
number of the receptor dimers with state $V$
distributes between 0 and $B$
The average function $m$ is the average of $S$ is the average of $\langle S_i \rangle(\tau)$. On the long time scale, $m(\tau)$ depends on $\tau$ because of the feedback on $B_i$. $m(\tau)$ is a measure of the signal. Usually the signal is characterized by the change of the magnetization.

Hence we may solve our problem by using coarse-graining, replacing the above Hamiltonian with a temporally coarse grained one

$$\mathcal{H}(\tau) = - \sum_{(ij)} J_{ij} S_i S_j - \sum_i B_i(\tau) S_i,$$

where $\tau$ is the coarse grained and discretized time defined as $\tau = \text{int}(t/t_r)$. Here the function $\text{int}(x)$ is the greatest integer less than or equal to $x$. $\mathcal{H}(\tau)$ determines, through equilibrium statistical mechanics, the coarse grained instantaneous state characterized by the magnetization per spin, $m(\tau)$, which is the value of each $S_i(\tau)$. Note that $S_i(\tau) = m(\tau)$ is the average of $S_i(t)$ over the time period from $(\tau - 1)T$ to $\tau T$, equal to the ensemble average $\langle S_i \rangle(\tau)$. On the long time scale, $m(\tau)$ depends on $\tau$ because of the feedback on $B_i$. $m(\tau)$ is a measure of the signal. Usually the signal is characterized by the change of the number of the receptor dimers with state $V^0$, the average of which is $m/2$.

On the coarse grained time scale, the initial condition becomes that $B_i(\tau_0)$ bimodally distributes between 0 and $B$, i.e. $p[B_i(\tau_0)] = c\delta[B_i(\tau = \tau_0) - B] + (1-c)\delta[B_i(\tau_0)]$, where $\tau_0 = \text{int}(t_0/t_r)$. The feedback equation becomes $B_i(\tau) = B_i(\tau - 1) - \sigma m(\tau - 1)$, or equivalently, $M(\tau) = M(\tau - 1) - \sigma m(\tau - 1)$, which implies

$$M(\tau) = M(\tau_0) - \sigma \sum_{\tau_0}^{\tau - 1} m(k).$$

On the coarse grained time scale, the induced field is the same for different spins, therefore the subscript $i$ has been omitted.

Under the adiabatic approximation, we apply mean field theory for each instant $\tau$ to obtain:

$$m(\tau) = \frac{2c}{1 + \exp[-2\beta(\nu Jm(\tau) + M(\tau) + B)]} + \frac{2(1-c)}{1 + \exp[-2\beta(\nu Jm(\tau) + M(\tau))]} - 1,$$

where $M(\tau)$ is given by (3), $\beta = 1/k_B T$, $\nu$ is the number of nearest neighbors.

One may observe that $m = 0$ is a fixed point of Eq. (6): if $m(\tau - 1) = 0$, then $m(\tau) = m(\tau - 1) = 0$. Moreover, if $\sigma/\nu J$ is small enough, $m(\tau)$ does not change the sign while its magnitude decreases towards 0 [11]. Therefore $m = 0$ is an attractor of the evolution of the magnetization.

In the original Ising model with $c = 0$, there are two phases, ferromagnetic and paramagnetic, depending on $\beta \nu J$. For AIM, however, as an interesting consequence of the feedback, $m(c = 0)$ is always zero: suppose $m(c = 0)$ is nonzero initially, the feedback automatically causes it to attenuate to zero. Therefore, we always have $m(\tau < \tau_0) = 0$, and thus $M(\tau_0) = 0$. Consequently

$$m(\tau \geq \tau_0) = \frac{2c}{1 + \exp[-2\beta(\nu Jm(\tau - \theta(\tau - \tau_0) - 1)\sigma \sum_{k = \tau_0}^{\tau - 1} m(k) + B)]}$$

$$+ \frac{2(1-c)}{1 + \exp[-2\beta(\nu Jm(\tau - \theta(\tau - \tau_0) - 1)\sigma \sum_{k = \tau_0}^{\tau - 1} m(k))]} - 1.$$
Thus when a “field” is applied, i.e. ligands are bound to the receptor dimers, randomly but with a certain occupancy \( c \), there is an initial change of magnetization from 0 to \( m(\tau_0) \), depending on \( c \). This initial response can be arbitrarily sensitive, as seen from \( \partial m(\tau_0)/\partial c \) with \( c \to 0 \), given by Eq. (10) of Ref. 5. However, due to the negative feedback of the output (magnetization) on the input (field) at each spin, the magnetization always attenuates towards zero. Practically, the adaptation is completed when the difference between \( m(\tau) \) and zero is below the detectable threshold of the motors.

Note that in Ref. 4, it had to set that \( \beta \nu J \leq 1 \), i.e. the system should be in the paramagnetic phase when there is no ligand binding. With the feedback naturally integrated to the model in an \textit{ab initial} way, this constraint becomes unnecessary, and thus the model becomes more robust.

To obtain some analytical sense, consider high temperature limit \( \beta \to 0 \). In this case, \( m(\tau_0) = c \beta B/(1-\beta \nu J) \). A simple calculation based on Eq. \( \hat{\text{6}} \) reveals that \( m(\tau_0 + \Delta \tau) = [1 - \beta \sigma/(1 - \beta \nu J)]^{\Delta \tau} m(\tau_0) \). When \( \beta \sigma < 1 - \beta \nu J \), \( m(\tau) \) attenuates towards zero exponentially. For generic values of the parameters, the solution can only be obtained numerically, as shown in Fig. 2. Note that the effective parameters are \( \beta \nu J \), \( \beta B \), \( \beta \sigma \), and \( c \). Comparing plots for different values of parameters, one can observe that the speed of attenuation of \( m(\tau) \) increases with \( \beta \sigma \) and with \( \beta \nu J \), while decreases with \( c \). It increases with \( \beta B \), but when \( \beta B \) is large enough, \( m(\tau) \) becomes independent of the exact value of \( \beta B \), as indicated by the results for \( \beta B = 1, 10 \) with \( \beta \nu J = 0.5 \). On a log-log scale (not shown), the plots are generally convex, indicating that the attenuation is in general more rapid than exponential decay, due to the larger \( \beta \nu J \).

After the adaptation is completed, if there is a further change in the chemoeffector concentration, the occupancy changes from \( c \) to \( c' \) at \( \tau_0' \), then \( m(t \geq \tau_0') \) is given by Eq. \( \hat{\text{6}} \) with \( c \) updated with \( c + c' \). Because \( m(\tau_0' - 1) = 0 \), \( M(\tau_0' - 1) \) is given by

\[
0 = \frac{2c}{1 + \exp[-2\beta(\tau_0' - 1) + B]} + \frac{2(1-c)}{1 + \exp[-2\beta \tau_0' - 1]} - 1.
\]

Hence,

\[
m(\tau \geq \tau_0') = \frac{2(c+c')}{1+\exp[-2\beta(\nu J m(\tau) - \sigma \sum_{k=0}^{\tau_0'} m(k) + M(\tau_0'-1) + B)]} + \frac{2(1-c-c')}{1+\exp[-2\beta(\nu J m(\tau) - \sigma \sum_{k=\tau_0'}^{\tau_0'} m(k) + M(\tau_0'-1)]} - 1
\]

which is largely determined by \( c' \) since the effect of \( c \) is counteracted by \( M(\tau_0') \). \( m(\tau > \tau_0') \) attenuates towards zero, repeating the dynamics of Eq. \( \hat{\text{6}} \). \( \partial m(\tau_0')/\partial c' \) with \( c' \to 0 \), approximately equal to \( \partial m(\tau_0)/\partial c \) with \( c \to 0 \), can be arbitrarily large if the latter can. Therefore our adaptation mechanism not only brings the signal to the pre-stimulus level, but also preserves the sensitivity, as required by chemotaxis.

Therefore we have explained why perfect adaptation can always be achieved in chemotaxis: a fixed pre-stimulus activity is a dynamical attractor. The variation of the values of the parameters, under a basic requirement that \( \sigma \) is sufficiently small, only affect the time needed to achieve perfect adaptation. Thus our result is fully consistent with the experiments.

Recent experimental analyses of the aspartate receptor revealed that attractant binding induces a displacement of one of four helices, each two of which constitute a subunit of
a receptor dimer [12]. Therefore $V_i$ may be identified as the position of the mobile helix $[13]$. $V^0$ is the original position of the helix, corresponding to the higher rate of CheA autophosphorylation. $V^1$ is down towards the cytoplasm, corresponding to the lower rate of CheA autophosphorylation. Thus $H$ is the force generated by ligand binding. $2B = H\Delta V$ is the shift of energy difference between the two conformations due to free energy exchange with the bound ligand, or the work done by the generated force. One may find that $4J/\Delta V$ is the force due to the activity change of one nearest neighbour. $2M_i(t)/\Delta V$ is the force due to feedback, and thus should be opposite to the force generated by ligand binding.

In the high temperature limit, when $\Delta \tau = -\ln2/\ln[1 - \beta\sigma/(1 - \beta\nu J)]$, $m(\tau_0 + \Delta \tau) = m(\tau_0)/2$. Assuming $1/\beta \approx 4pN \cdot nm$, $\beta\nu J \approx 0.5$ [5], and that the time needed to complete adaptation be 1 minute, i.e. $\Delta \tau \approx 600$, we may estimate that $\sigma \approx 0.002pN \cdot nm$. Because the formula is for high temperature limit, the real value of $\sigma$ is smaller for the assumed values of the parameter values. Experimentally, by measuring $\beta$, $\nu J$, $B$ and the adaptation time, $\sigma$ can be determined. On the other hand, $\sigma$ can also be determined through $\sigma = -[M_i(t) - M_i(t_0)]/\int_{t_0}^{t} S_i(t - t_r)dt = [M(\tau_0) - M(\tau)]/\sum_{\tau'=\tau_0}^{\tau-1} m(\tau')$. By comparing the results obtained in different ways, the model may be tested or refined.

Eq. (4) implies that the feedback is assumed to be local. This is because we preserve the assumption that there exists a feedback loop for each receptor dimer although we consider coupling between the states of neighbouring dimers. However, one may make a straightforward extension to include the neighbouring states in the feedback equation, without changing the qualitative physics. Furthermore, this makes no change in the temporally coarse grained feedback equation, or in the sense of (spatial) renormalization group. Therefore the large separation of time scales, which validates coarse graining, makes the essential mechanism not so much dependent on the microscopic details. This is also an aspect of robustness.

Finally, it is interesting to note that in the case of bacterial chemotaxis, the clustering of receptors exists prior to a stimulus, while in many other cell signalling processes, the receptors diffuse on the membrane and the clustering appears as a response to the stimulus. One may make a generalization of our model to a sort of combination of Ising and lattice gas models to address such a case, as will be described in a forthcoming paper.

To summarize, an adaptive Ising model is proposed to combine cooperativity and negative feedback. It is applied to the receptor network of bacterial chemotactic signalling and explains the perfect adaptation as a dynamical attractor. Both the signal magnitude and the sensitivity of response are adapted. The large separation of time scales leads up to the solution by using adiabatic approximation. The change of parameter values, under a basic requirement that the feedback effect is sufficiently weak, only changes the time needed to complete adaptation, without affecting its perfectness. Hence the robustness of perfect adaptation is explained. This work shows that coupling among receptor dimers gives rise to a unifying description of both sensitivity and effective adaptation. We anticipate further experimental and theoretical investigations. Cooperativity in cell signalling is likely a new playground of statistical mechanics. Combining cooperativity and feedback, and preserving sensitivity, the idea of AIM may be useful for a variety of problems.

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FIGURES

FIG. 1. A schematic illustration of the chemotactic signalling pathway of one receptor dimer. Around 2000 receptor dimers constitute a network.

FIG. 2. Attenuation of $m(\tau)$, the solution of Eq. (7), for different values of parameters. $\tau$ is the coarse grained time, $\tau_0$ is set to 1. To compare the attenuation speed for different values of parameters, we plot $m(\tau)/m(\tau_0)$. The parameters ($\beta\nu J, \beta B, \beta\sigma, c$) for each plot are given on the right upside.
REFERENCES

* Electronic address: ys219@cam.ac.uk

[1] J. Stock and M. Surette, in *Escherichia coli and Salmonella typhimurium: Cellular and Molecular Biology*, ed. F.C. Neidhardt, (ASM, Washington, 1996); J.J. Falke *et al.*, Annu. Rev. Cell Dev. Biol. 13, 457 (1997); D.F. Blair, Annu. Rev. Microbiol. 49, 489 (1995).

[2] S.M. Block, J.E. Segall, and H.C. Berg, J. Bacteriol. 154, 312 (1983); J.E. Segall, S.M. Block, and H.C. Berg, Proc. Natl. Acad. Sci. USA 83, 8987 (1986).

[3] J. S. Parkinson and D. F. Blair, Nature. 259, 1701 (1993).

[4] D. Bray, M.D. Levin, and C.J. Morton-Firth, Nature, 393, 85 (1998).

[5] Y. Shi and T. Duke, Phys. Rev. E 58, 6399 (1998).

[6] R. Jasuja, Y. Lin, D. R. Trenthan and S. Khan, Proc. Natl. Acad. Sci. USA 96, 11346 (1999).

[7] We believe that the perfect adaptation is necessary for chemotactic machinery to work, as an example of perfectness required in many biological processes. Suppose that the adaptation is not perfect, and as a generic case, there is a probability distribution for the difference between the activities after two consecutive adaptations, with mean $\delta$ and variance $\epsilon^2$. Then according to the central limit theorem, after $n$ times of stimulus and adaptation, the activity drifts from the first pre-stimulus one with mean $n\delta$ and variance $n\epsilon^2$. In the life of the bacterium, $n \to \infty$, therefore the activity range of the chemotactic machinery should be infinity, unless both $\delta$ and $\epsilon^2$ are exactly zero, i.e. the adaptation is perfect. The viewpoint of evolution may thus help us to understand why the adaptation has to be perfect. On the other hand, an underlying physical mechanism needs to be found.

[8] U. Alon, M. G. Surette, N. Barkai and S. Leibler, Nature, 397, 168 (1999).

[9] J.J. Hopfield, Proc. Natl. Acad. Sci. USA 81, 3088 (1984).

[10] The time scale of ligand debinding ranges from tens of seconds to tens of minutes, longer than the signalling time scale, i.e. the time scale for achieving the temporally local equilibrium, as discussed below. This quenched disorder model is thus more favorable than a grand canonical ensemble approach, which would treat binding-debinding processes as a part of the process towards an equilibrium. Although we are not sure whether the debinding time scale is always longer than the time to complete the adaptation, this does not matter, because on the coarse grained time scale, Eq. (6) is always valid, independent on which of the receptors are liganded.

[11] A sufficient condition is $\sigma/\nu J < |x_0|/|m_0|$, where $x_0$ is the solution to $0 = \frac{1}{1+\exp[-2\beta(\nu J x + B)]} + \frac{2(1-c)}{1+\exp[-2\beta(\nu J x)]} - 1$. To understand this, consider $m(\tau - 1)$ as the $x$ coordinate of the cross between $y = x$ and $y = f(x)$, while $m(\tau)$ as the $x$ coordinate of the cross between $y = x$ and $y = f[x - \sigma J m(\tau - 1)]$, which is obtained by translating $y = f(x)$ along $x$ direction.

[12] S. Chervitz and J.J. Falke, Proc. Natl. Acad. Sci. USA 93, 2545 (1996); A.G. Hughson and G.L. Hazelbauer, Proc. Natl. Acad. Sci. USA 93, 11546 (1996).

[13] We conjecture that which subunit provides the mobile helix may be random, and that dimerization of receptors might provide a redundancy so that if one subunit is damaged, the other can work as an alternative. The negative cooperativity between the two subunits may be due to an “antiferromagnetic” coupling.
