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Heightened sensitivity of a lattice of membrane receptors

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ABSTRACT **Receptor proteins in both eukaryotic and prokaryotic cells have been found to form two-dimensional clusters in the plasma membrane. In this study, we examine the proposition that such clusters might show coordinated responses because of the spread of conformational states from one receptor to its neighbors. A Monte Carlo simulation was developed in which receptors flipped in probabilistic fashion between an active and an inactive state. Conformational energies depended on (*i*) ligand binding, (*ii*) a chemical modification of the receptor conferring adaptation, and (*iii*) the activity of neighboring receptors. Rate constants were based on data from known biological receptors, especially the bacterial Tar receptor, and on theoretical constraints derived from an analogous Ising model. The simulated system showed a greatly enhanced sensitivity to external signals compared with a corresponding set of uncoupled receptors and was operational over a much wider range of ambient concentrations. These and other properties should make a lattice of conformationally coupled receptors ideally suited to act as a "nose" by which a cell can detect and respond to extracellular stimuli.**

Sensory systems commonly possess the ability to detect a relative change in the strength of a stimulus over a wide range of intensities. A familiar example is our visual system, which is capable of rendering good contrast, almost independently of the brightness of an image (1). This capacity is also expected to be advantageous in the detection of molecular signals by cells. For instance, a bacterium moving in a diffusive gradient of nutrient typically encounters, in a given interval of time, a change in concentration that is proportional to the ambient level. Thus, the ability to detect and respond to relative changes of concentration (2, 3) would be a good strategy for chemotaxis. What design principles might have been adopted by cells, during evolution, to acquire such an advantage? It has long been recognized that adaptation of individual receptor molecules is an important part of the solution (4). Not only does such an adaptation provide a method of temporal comparison, it also maintains the signal generated by the detection apparatus at a level best suited to the response machinery (5). But adaptation alone is not sufficient to provide a low threshold of response. Here, we examine the proposition that conformation-dependent cooperative interactions between receptors play an equally important role by enhancing the sensitivity.

The idea that arrays of membrane proteins might propagate conformational changes was proposed as long ago as 1967. In the wake of findings showing that many enzymes and other proteins undergo concerted changes in their conformation, Changeux *et al*. (6) speculated that a similar mechanism would be expected to occur in two-dimensional arrays of allosteric proteins embedded in a lipid bilayer. Their analysis indicated that arrays of membrane receptors could show highly sensitive "all-or-none" responses to the binding of ligands, which would be modulated by the strength of coupling between individual receptor molecules. However, subsequent experimental work showed that the excitability of neuronal membranes had a different molecular basis and provided no evidence for a spread of conformations in the well characterized arrays of nicotinic acetylcholine receptors in fish electric organs or vertebrate muscle (7, 8).

Recent studies of the chemotaxis of bacteria led to a renewed interest in the idea of conformational spread. Bacteria such as *Escherichia coli* have a combination of high sensitivity and a wide range of responses to attractants such as aspartate that cannot easily be reproduced in conventional simulations (9). Because the chemotactic receptors have been shown to exist in clusters at one end of the cell (10), the proposal was made that they could generate the required sensitivity and range by propagating conformations from one receptor to the next (11). Statistical-mechanical analysis of a two-dimensional array of chemotactic receptors with equations derived for an Ising model indicated that the required cooperative properties could be produced simply from nearest-neighbor interactions (12).

In the work described in this paper, we have investigated the performance of an array of coupled receptors in greater detail by using a molecularly based Monte Carlo simulation. The simulation is an implementation of the model proposed in ref. 12, and the numerical solution highlights features that were less apparent in the approximate (mean-field) analytical treatment. Receptors were assigned two conformational states and changed this conformation in response to the binding of ligand and a reversible chemical modification (adaptation)—properties that are common to many eukaryotic and prokaryotic receptors. In addition, the conformational state of each receptor in the simulation was assumed to be influenced by the state of its four nearest neighbors: the basic postulate of the idea of conformational spread. We find that this third rule confers a remarkable set of properties to the simulated receptor array.

METHODS

We use a square array of 50 × 50 receptors with toroidal coordinates to avoid boundary effects. Each receptor exists in either an active ("1") or an inactive ("0") conformational state and can flip from one to the other. Receptors may also bind ligand molecules, present in the extracellular fluid at concentration c, and undergo a covalent modification (such as methylation or phosphorylation) that adapts their response. A separate record is kept of the conformational state, ligand occupancy, and state of adaptation of each receptor.

At any instant, the probabilities of a given receptor being in the active or in the inactive state depend on the difference in energy $\Delta E = E_1 - E_0$ of the two conformations. For simplicity, we assume that ΔE is zero for an isolated, "virgin" (unoccupied

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and unmodified) receptor so that it is equally likely to be active or inactive. In a cluster, the energy difference is altered by the sum of contributions from (*i*) ligand binding, (*ii*) adaptive modification of the receptor, and (*iii*) the four nearest neighbors because of conformational coupling (Fig. 1*A*). Ligand binding changes the energy of the active conformation, relative to the inactive one, by E_L. Owing to thermodynamic constraints, E_L is related to the ratio of the dissociation constants (K_d) of the ligand from the two states: $K_d^1/K_d^0 = \exp(-E_L/kT)$, where k is the Boltzmann constant and T is the absolute temperature. We used values of E_L/kT between 0 and 8, chosen to be positive so that the activity diminishes when additional ligand binds. The adaptation modification has the converse effect to ligand association, such that the energy change E_M has an opposite sign. For simplicity, we assign it the same magnitude as E_L. This assignment ensures that a receptor that has both bound ligand and adapted will behave like a virgin receptor. The coupling between receptors is assumed to be caused by a short-range interaction that depends on only the conformational state. For each neighbor that has the same conformation, the energy of a receptor is reduced by E_J; for each neighbor in the alternative conformation, the energy is increased by E_J. The value $E_J/kT = 0.4$ used was chosen to be close to the critical coupling parameter of the two-dimensional Ising model (ref. 13; see Fig. 1*B*).

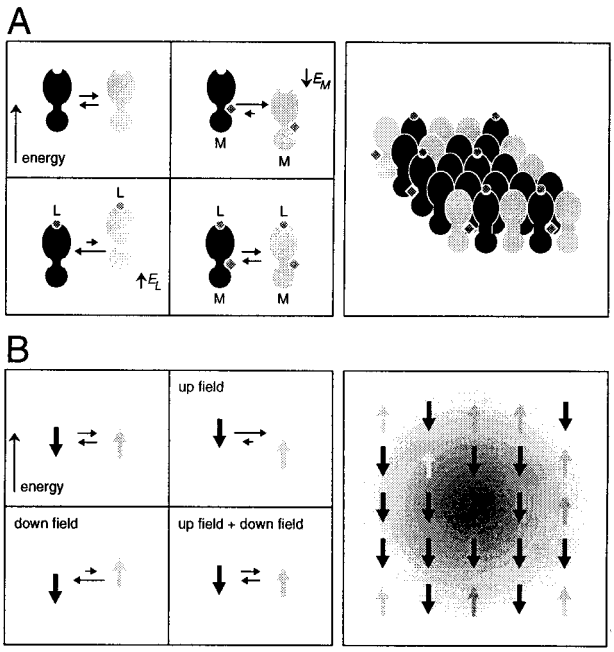

FIG. 1. (*A*) Representation of the relative energies of the two conformational states of a receptor. The active (gray) and inactive (black) states of a virgin, isolated receptor have the same energy. Ligand binding (L) lowers the energy of the inactive state, and methylation (M) reduces the energy of the active state. When a receptor is part of a cluster, it also interacts with its four nearest neighbors; its energy is lowered by each adjacent receptor in the same conformational state and raised by each adjacent receptor in the alternative state. (*B*) This picture is analogous to the Ising model of a ferromagnet. An isolated magnetic spin is equally likely to point up (gray) or down (black). However, when a magnetic field is applied, the spin tends to point in the direction of the field (because it then has a lower energy). A ferromagnet is a lattice of coupled spins. In the Ising model, a cooperative interaction between adjacent spins lowers each of their energies when both spins have the same sign. Consequently, neighboring spins tend to align with one another. The magnetic properties of the array of spins depend on the magnitude of the coupling energy. Above a critical value, a high proportion of the spins all point in the same direction, and the array is ferromagnetic. Below the critical value, the array is paramagnetic (i.e., it is magnetized only when an external field is applied). Close to (but below) the critical point, the propagation of nearest-neighbor interactions causes one spin to influence other spins over a wide range (depicted by the shaded area). Then, a weak external field gives rise to a strong magnetization. In the receptor cluster, by analogy, a small change in the amount of bound ligand generates a big response.

Adaptation is presumed to be exact so that the steady-state activity A_0 (average fraction of active receptors) is independent of the ligand concentration c. Precise adaptation can be accomplished if the modification and demodification reactions are mediated by enzymes that bind at very different rates to the active and inactive states of the receptor (14). In general, the value of A_0 depends on the modification kinetics. We chose rates that give $A_0 = 0.5$, because this value is the base level that permits maximal variation of the activity (either up or down) when the ligand concentration is altered. In this case, the fraction of adapted receptors P_M is equal to the ligand occupancy P_L in the adapted system.[‖]

Receptors were assigned initial ligand occupancy and adaptation states randomly, with probabilities calculated from the value of the ambient ligand concentration. Equilibration was then performed by selecting receptors at random and flipping their conformation with a probability dependent on ΔE, according to the Metropolis algorithm (15). The average rate of equilibration per receptor was set at 10 μs, a typical value for the change in conformation of many proteins (16). Ligand binding and adaptation reactions were also performed on randomly selected receptors. These occurred at a slower rate than the conformational changes. Ligand molecules bound to the receptor at a diffusion-limited rate, $10^9\ M^{-1}\cdot s^{-1}$, and dissociated at a conformation-dependent rate, calculated with the assumption that the concentration $c_{0.5} = \sqrt{(K_d^0 K_d^1)}$, which gives 50% occupancy of the adapted cluster, is 1 μM. Adaptation occurred even more slowly, with a modification rate of 0.1 s^{-1} per receptor (based on the estimated rate of the methylating enzyme CheR in the bacterial chemotaxis system; ref. 17).

RESULTS

Patterns of Activity. To examine the changes in receptor activity caused by conformational spread alone, we ran a series of simulations in which designated receptors were fixed in either the ligand-bound or the adapted state (Fig. 2*A*). After equilibration, an instantaneous snapshot of an array of receptors reveals irregular patterns of active and inactive conformations (Fig. 2*B*). These patterns are transient and rapidly changing, being formed and lost on a time scale of tens of microseconds because of coupling between neighboring receptors. However, if the activity levels of individual receptors are averaged over a series of time steps, then more regular patterns emerge. Averages taken over 100 iterations—corresponding to a biological time of 1 ms—reveal patches of inactivity centered around ligand binding sites and patches of active receptors centered around adapted receptors (Fig. 2*C*). The patches of active receptors become progressively smoother in outline as the averages are taken over longer periods (Fig. 2*D*).

In a normal, unconstrained simulation, the patterns are more complicated (Fig. 2*E*). Fluctuations in the activity caused by conformational changes, ligand binding, and the reactions of adaptation each have a characteristic correlation time (approximately 10 ms, 1 ms, and 10 s, respectively); on these time scales, the fluctuations from each source are apparent in the patterns of activity.[**]

[§]When $E_J \neq 0$, this equality is only approximate, because the coupling induces a correlation in the location of bound ligands, whereas adapted receptors are positioned randomly.

[**]Correlation time τ of a fluctuating signal S defined as $\langle S(t)S(t+\tau)\rangle \approx \exp(-t/\tau)$, for $t \gg \tau$. For times shorter than the correlation time, the signal is noisy; over longer intervals, the fluctuations are averaged out.

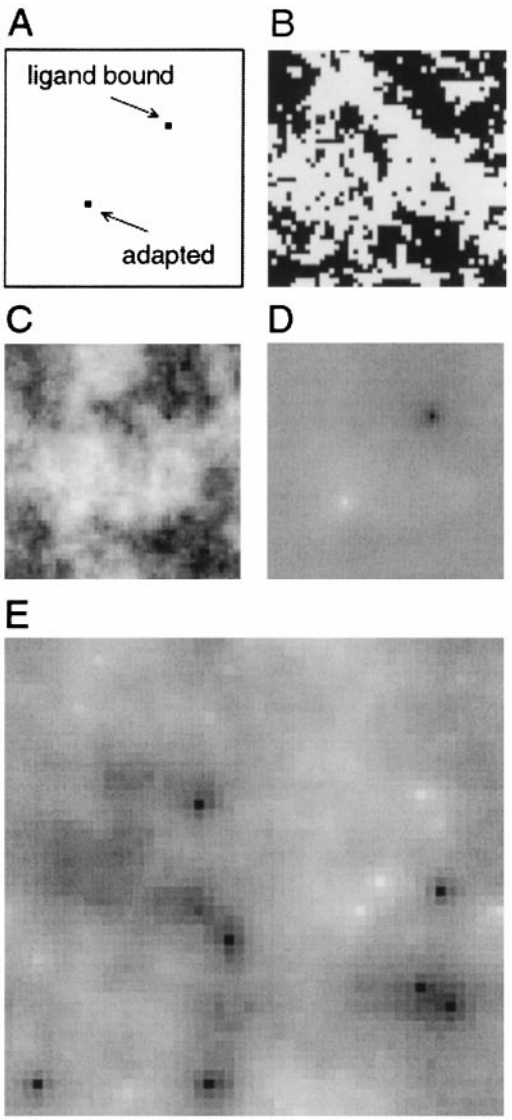

FIG. 2. Patterns of receptor activity in a coupled array. (*A–D*) In this series of simulations, ligand binding and adaptation were disabled so as to reveal the patterns caused by conformational spread alone. (*A*) One receptor in the 50 × 50 array was permanently assigned to the ligand-bound state, and another receptor was assigned to the adapted state. (*B*) The instantaneous pattern of active (white) and inactive (black) receptors is seen in an array after a period of equilibration. (*C*) Average levels of activity taken over 100 individual patterns, corresponding to 1 ms of biological time. Activities are represented by gray levels. (*D*) Receptor activities averaged over 10,000 patterns, equivalent to 0.1 s of biological time (which is a typical response time). The positions of the ligand-bound (black) and adapted (white) receptors are now evident. (*E*) Pattern of activity in an unconstrained array in which ligand binding and adaptation are allowed to proceed at their characteristic rates (ambient concentration $c/c_{0.5} = 0.001$). The pattern shown is an average over 1,000 time steps, equal to 10 ms of biological time. Discrete white patches correspond to the probable location of bound ligand molecules, and black patches correspond to the sites of adaptation.

Signaling Capacity. To examine the signaling capacity of the system, the array was exposed to a step increase in ligand concentration. The stimulus produced a rapid fall in activity, caused by the occupation of receptors, followed by a slower return to the base level, attributable to the adaptation reaction (Fig. 3). The response to a given change in ligand concentration (here, a doubling) is sizeable over a wide range of concentrations. At the extremes of the range, at very high or very low ligand concentrations, the response diminishes in both magnitude and duration and tends to be masked by the background noise, which is augmented.

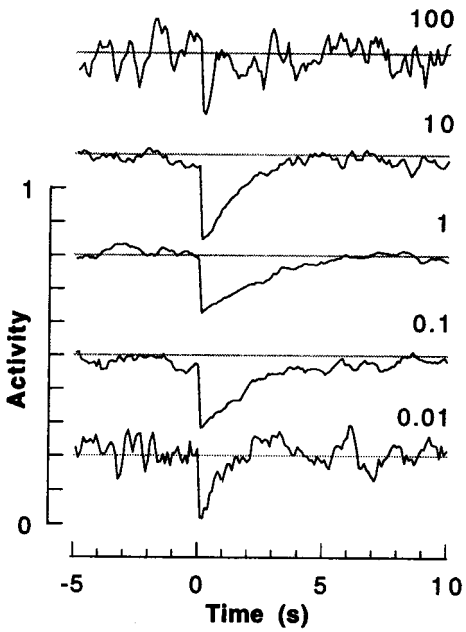

FIG. 3. Changes in array activity produced by a stepwise change in ligand concentration. Each individual trace shows how the activity of the lattice (measured by the average fraction of active receptors during a period of 10,000 time steps or 0.1 s) changes with time. The lattice was equilibrated with ligand at one concentration, and then its activity followed as this concentration was doubled (at time zero). The traces are labeled by the initial value of $c/c_{0.5}$ and have been displaced vertically (the gray lines indicate the average activity of an adapted array, $A_0 = 0.5$).

The lattice of receptors can detect a remarkably constant *relative change in concentration* over a very wide range of ambient concentrations. Its performance is best appreciated by comparing it with an equivalent number of uncoupled receptors (Fig. 4). In response to a doubling of the ligand concentration, the signal decreases by more than 30% over four orders of magnitude. By contrast, an ensemble of independent receptors gives only a 10% decrement over two orders of magnitude.

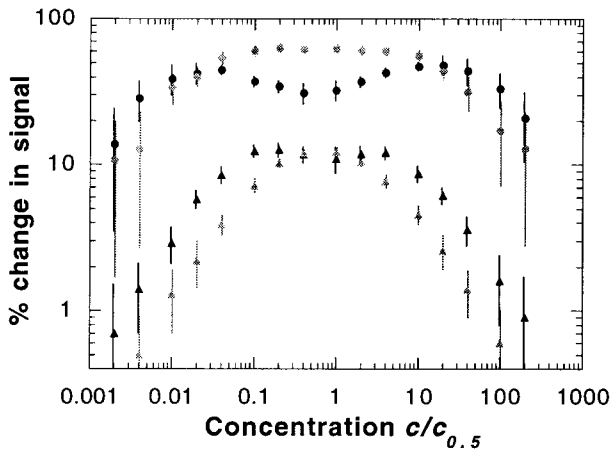

FIG. 4. Response of a receptor array to a step change in concentration. The change in the signal, immediately after the concentration was doubled, is plotted as a function of the initial concentration c. The two pairs of data sets are for a coupled array of receptors with $E_J/kT = 0.4$ (circles) and the same number of independent receptors (triangles). Two values of ligand-binding energy are represented: $E_L/kT = 2$ (gray) and $E_L/kT = 4$ (black). The vertical bars indicate the typical noise in the signal when it is averaged over the response time (0.1 s).

DISCUSSION

Operation of the Receptor Cluster. The combination of sensitivity (which, throughout this paper, we understand to mean sensitivity to a fractional change of ligand concentration) and wide dynamic range derives from the highly nonlinear response of the receptor cluster, which contrasts with the linear behavior of an uncoupled system. For a set of independent receptors, the response is directly proportional to the change in occupancy. In this case, the sensitivity depends on the shape of the ligand-binding curve (P_L vs. c), which, because of the difference in dissociation constants from active and inactive receptors, varies with E_L. As shown in Fig. 5*A*, increasing E_L/kT from 0 to 4 flattens the curve and broadens the range of sensitivity by a modest amount. A further increase of E_L, however, results in a diminution of the sensitivity at ambient concentrations close to $c_{0.5}$. Thus, in the linear system, there is no way of improving the sensitivity at extreme concentrations without adversely affecting the response in the middle of the range.

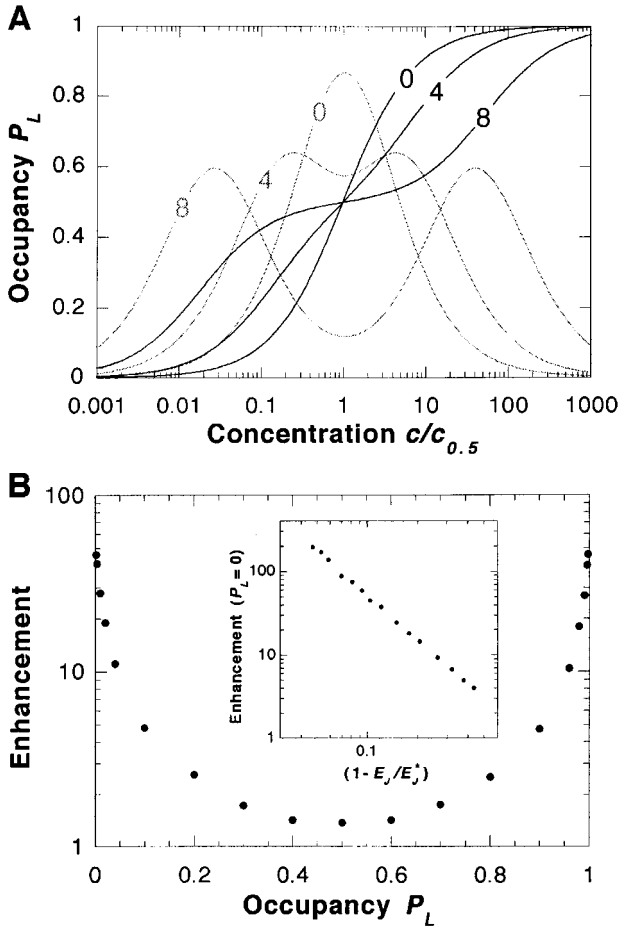

FIG. 5. (*A*) Fraction P_L of receptors occupied by ligand molecules, as a function of the ambient concentration c, for an adapted cluster (black). These binding curves are plotted for $E_J = 0$ and different values of E_L/kT, as marked. The functional form is $P_L = \alpha(\alpha + \beta)/(\alpha^2 + 2\alpha\beta + 1)$, where $\alpha = c/c_{0.5}$ and $\beta = \cosh(E_L/2kT)$. For an uncoupled system, the response to a given fractional change in concentration is proportional to ΔP_L and, thus, to the slope of the binding curve, giving a sensitivity indicated in gray (arbitrary units). (*B*) The enhancement of the response provided by coupling is defined as the average change in the signal generated by an adapted cluster, per additional occupied receptor, relative to the change in the signal produced by the same number of independent, adapted receptors. It is plotted as a function of the initial fraction of ligand-bound receptors P_L. The curve depends only weakly on E_L and is shown here for $E_L/kT = 4$. (*Inset*) Variation of the enhancement (at zero occupancy) with the coupling energy E_J, showing power-law divergence as the critical coupling energy E_J^* is approached.

The coupled system works by greatly enhancing the response to ligand binding at both low and high concentrations, as shown in Fig. 5*B*. To understand how this enhancement is achieved, consider first an array of virgin receptors at zero ambient concentration. If a low concentration of ligand is added, a small number of receptors will bind ligand. This binding will bias the activity of these receptors toward zero and also, through coupling, tend to inactivate other receptors in their immediate vicinity. The realm of influence of these ligand-bound receptors will fluctuate in size because of thermal noise; however, averaged over the duration of ligand occupancy, local patches of low activity will be created (see Fig. 2*C*). The average extent of the conformational spread is given by the correlation length in the equivalent Ising model and can be very large when E_J is close to the critical value of the coupling parameter. The enhancement will therefore be strong.

The diminished level of activity caused by ligand binding will trigger adaptation of individual receptors. In an exactly analogous fashion to that described above for ligand binding, each adapted receptor will nucleate a patch of (in this case) active receptors. As these increase in number, they will limit the extent of neighboring inactive patches (see Fig. 2*E*). The enhancement will therefore fall. Increasing the ligand concentration will cause the number of both ligand-bound and adapted receptors to rise. Because these have opposite effects on the activity, each will limit the influence of the other. The effect of any individual ligand-binding event (that is, the enhancement) will become less and will continue to fall until the concentration of ligand equals $c_{0.5}$.

At or above $c_{0.5}$, another effect becomes important because of the population of receptors that have both bound ligand and have been modified. In this (highly simplified) model, these two influences cancel each other out, such that these receptors have no bias toward either the active or the inactive state and can therefore be easily influenced by the change in conformation of a neighbor. Thus, at ligand concentrations above $c_{0.5}$, the range of conformational spread begins to grow again, and the enhancement rises, reaching a maximum at saturating occupancy.

In summary, through the combined effects of nearest-neighbor coupling and adaptation, the extent of the conformational spread is self-regulated so that the response is boosted significantly only where necessary—at low and at high concentrations. In the middle of the concentration range, the sensitivity is adequate without amplification, and the weak enhancement avoids magnifying the noise unnecessarily.

In addition to ensuring a low threshold for a detectable response, the nonlinear behavior of the receptor cluster serves a second purpose: it permits the system, adapted at a particular ambient concentration, to discriminate between subsequent changes of concentration that differ greatly in magnitude. The enhancement, shown in Fig. 5*B* for limitingly small changes in ligand occupancy ($\Delta P_L \to 0$), declines rapidly as ΔP_L becomes more substantial. As a consequence, the signal does not decrease linearly with the change in occupancy; as shown in Fig. 6, the dependence is closer to logarithmic for strong responses. This slow variation of the signal with the size of the stimulus is advantageous, because it permits the system to respond in an incremental way to a strongly changing concentration, even before the receptors begin to adapt.

Influence of Parameters. To what extent do the responses of a receptor array depend on the energies of receptor coupling and ligand binding? The coupling energy E_J is closely defined by the criteria of the Ising model. Values above the critical value E_J^* (which, for the two-dimensional square lattice, is given by $E_J^*/kT = 0.44$) result in clusters in which almost all of the receptors are locked in one of the two conformations. This "all-or-none" response, which might be advantageous in other situations, is deleterious in this case, because it prevents adaptation. Below the critical value, the influence of a single ligand-bound receptor in

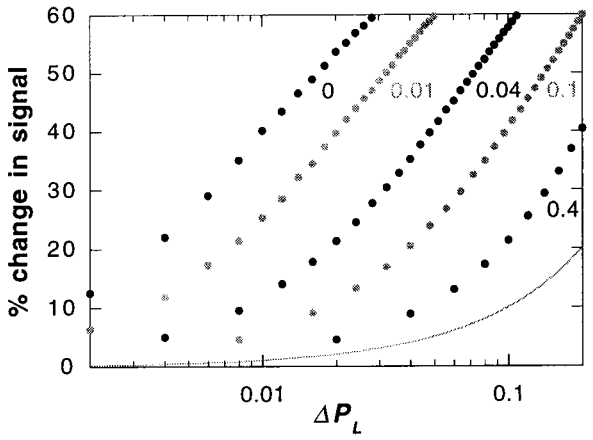

FIG. 6. Relative change in the signal as a function of the change in ligand occupancy ΔP_L. The different data sets are for clusters that were initially adapted at different ambient concentrations and are labeled by the initial fraction of ligand-bound receptors P_L. For comparison, the gray curve indicates the linear response of an uncoupled set of receptors (which is independent of the initial value of P_L).

an otherwise virgin array extends over the correlation length ξ of the two-dimensional Ising model, and the enhancement is proportional to the area ξ^2. Because ξ grows indefinitely as the critical condition is approached, $\xi \approx (1 - E_J/E_J^*)^{-1}$ (13);†† strong enhancement requires E_J to be close to E_J^* (Fig. 5*B Inset*). Thus, effective amplification of the response demands quite accurate specification of the coupling energy, which suggests that the receptors need to be arranged in a well ordered lattice.

By contrast, the energy change associated with ligand binding, E_L, provides a wide range of options. For $E_L/kT < 1$, the system progressively loses responsiveness to ligand binding, and the signaling capacity is diminished across the entire range of concentrations. When $E_L/kT > 4$, the difference in the dissociation constants of the active and inactive conformations becomes important. The effect is to reduce sensitivity in the middle range of concentrations. Background noise also increases, because the strong binding of ligand to inactive receptors leads to long residence times that limit the amount of averaging that can be done. From the standpoint of signaling efficiency, therefore, we conclude that E_L has a fairly broad range of optimal values: sensitivity is highest and most uniform over a wide range of concentrations when $1 < E_L/kT < 4$.

What is the effect of breaking the simplifying assumptions we made about the symmetries of the system? The receptor cluster still has a much better signaling capacity than a set of uncoupled receptors, but its performance is degraded in some aspects. For example, if the magnitudes of E_M and E_L differ substantially, the cluster fails to respond sensitively (and if $|E_M| < |E_L|$, the cluster fails to adapt exactly) at high concentrations; partial degradation of the response also occurs if $A_0 \neq 0.5$ or if $\Delta E \neq 0$ for an isolated, virgin receptor. We conclude that the symmetries are not essential to the cluster's operation but do optimize its effectiveness.

Experimental Support. There is no direct evidence for the propagation of conformational states of the kind envisaged here. However, there is support for individual aspects of our model. Some receptors have been found to exist in stable two-dimensional aggregates, for example chemotactic receptors in coliform bacteria (10), neurotransmitter receptors in synapses (7, 8), and the integrin molecules at focal adhesions (19). Furthermore, other kinds of receptors seem to associate into clusters in the course of signaling, such as T cell receptors (20) and tyrosine-kinase-linked receptors (21). Specific instances in which the activity of an activated or ligand-bound receptor passes to its neighbor have been documented for receptors for T cell superantigens (22) and the ryanodine receptors of skeletal muscle (23).

Many of the requirements for our model seem to be in place. Given the remarkable improvement in detection capacity provided by the simple coupling of individual signaling elements, this solution could well have been favored during evolution. Moreover, the underlying mechanism by which sensitivity is enhanced by cooperative interactions, tuned close to criticality, is quite general. Thus, this mechanism is not restricted to molecular receptors in which the coupling is between nearest neighbors and of thermodynamic origin but might also be relevant to larger scale systems, such as those involved in neural signaling.

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††Note that the reduction of the enhancement when the occupancy is close to neither 0 nor 1 is caused by a shift of the critical point. The lattice of unmodified receptors is, in effect, *diluted* by the modified receptors: this dilution raises the critical coupling energy so that the system moves further from the critical point (18).