complexity. Surely, this is a fruitful area for future research.

I shall stop here, omitting descriptions of bonding in large polyhedral borane anions and other related compounds. Also, polyhedral rearrangements, hydrogen atom tautomerism, and particularly the use of bonding theory in bringing some degree of order to chemical transformations of the boranes have been omitted. Attention has thus been concentrated on those aspects of chemical bonding which have been especially illuminated by the molecular and crystal structures that we and others have studied over these many years.

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48. It remains to give credit where it really belongs, to my research associates: graduate students, undergraduates, postdoctoral fellows, and other colleagues who have coauthored nearly all of these studies. For the figures of this manuscript, and of the lecture, I thank Jean Evans. I am most grateful to the Office of Naval Research which supported this research during the period from 1948 to 1976, a remarkably long time. I am most aware of the great influence of Linus Pauling on my whole scientific career. Finally, this manuscript is dedicated to the memory of my sister, Helen Porter Lipscomb, composer, teacher, and performer.

A Response Regulator Model in a Simple Sensory System

Bacterial behavior can provide insight into the molecular aspects of more complex behavioral systems.

D. E. Koshland, Jr.

A modern molecular biologist might paraphrase the poet Pope by saying, "The proper study of mankind is the bacterium." Similarities in metabolic pathways, adenosine triphosphate as a central energy source, and the genetic code which transcend species suggest that there are universal biological principles. The word "behavior" on the other hand is usually used to describe phenomena in higher differentiated species, and words like judgment, memory, choice, and discrimination seem inappropriate when applied to organisms at the lower end of the phylogenetic tree. Yet biologists have recognized that the study of behavior applies even to the simplest species (*1*, *2*). Hence, the molecular mechanisms involved in bacterial behavior may provide insight into the behavior of more complex organisms.

Sensory and neural processes are in a sense the ultimate regulatory mechanism, the refinement of "feedback" and "feedforward" information-processing to the most advanced level. It seems of interest, therefore, to examine sensory systems, to determine, on the one hand, if known processes are utilized to provide their regulation and, on the other, if any new principles or new combinations of principles are revealed. In this article, the behavioral response of bacteria is analyzed in terms of a response regulator model which may be useful in explaining regulation and behavior in more complex organisms.

The author is professor of biochemistry at the University of California, Berkeley 94720. This article is adapted from the text of the Earl A. Sutherland Memorial Lecture, delivered by the author at the University of Miami, Miami, Florida.

Some Features of Sensory Systems

In looking for a unity in sensory systems, it would be unwise to expect that precisely the same chemicals would be used in all species. Many neurotransmitters are known in the brain and yet surprisingly similar synaptic actions can be triggered by all of them. Likewise, the detailed "wiring diagrams" for neural systems may be characteristic of the species and even of the individual. Nevertheless there are common factors in signaling systems, a schematic outline of which is shown in Fig. 1. In this scheme, an external event activates the sensory system through a receptor that is specific for a very limited number of modalities, such as a few chemicals, some wavelengths of light, and the like. The initial receptor signal proceeds through a signal-processing system which then generates a behavioral response.

The generalized scheme of Fig. 1 applies to the human brain as well as to lesser but nevertheless "sophisticated" organisms such as the lobster. It applies also to the bacterium. In bacterial chemotaxis, receptors on the periphery of the organism receive stimuli from the environment, a central processing machinery interprets the signals, and there is a motor response that controls behavior. The behavioral response allows the bacteria to migrate up a gradient of attractant (usually a nutrient) or down a gradient of repellant (usually an indicator of toxic conditions). The processing program is, of course, far less complex than that of higher species but the analogies are extensive and quite surprising.

Engelmann (*3*) and Pfeffer (*4*) discovered the phenomenon of bacterial chemotaxis in the 1880's. By inserting a capillary containing a solution of attractant into a suspension of bacteria, they showed that bacteria would swim into the capillary in numbers far greater than a random distribution would predict. Adler and his co-workers greatly advanced our understanding of bacterial chemotaxis in a series of studies (*5, 6*) that established among other things (i) that attractants need not be metabolized, (ii) that specific chemoreceptors were present for each attractant, and (iii) that genetic mutations could not only damage responses to individual chemicals ("specific receptor mutants") but also responses to all chemicals ("generally non-chemotactic mutants"). Because this work as well as that of a number of laboratories has been summarized in recent reviews (*5–9*), I shall concentrate here on certain aspects that help to clarify the sensory processes and relate them to regulatory systems in general.

Mechanism of Bacterial Sensing

It seems extraordinary that an organism approximately 2 micrometers in length can sense a chemical gradient at all. Yet it was found that the bacteria can detect a gradient which yields a difference in concentration of attractant over the length of its body of only 1 part in 10^4, a formidable analytical problem (*10*). Two general detection mechanisms seemed possible on the basis of known mechanisms in other living systems: (i) a simultaneous comparison of the concentrations of chemoeffector impinging on receptors at the "head" and "tail" of the bacterium and (ii) a comparison over a time interval of the sensors in the bacterium moving through space.

That the bacteria use the latter alternative was demonstrated by Macnab and

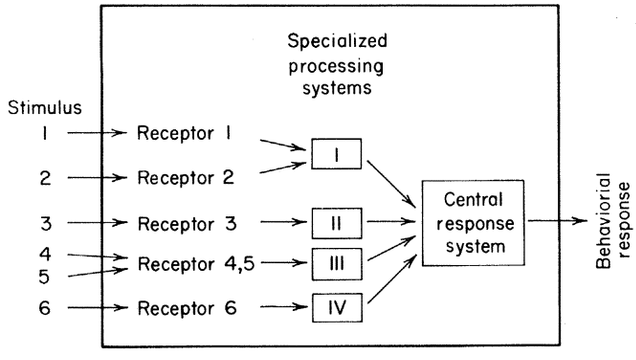
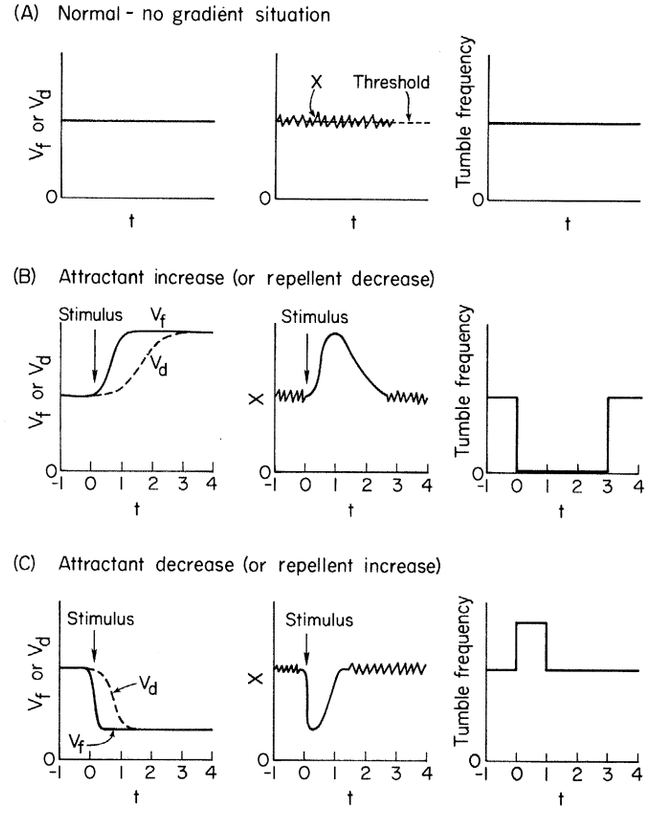


Fig. 1 (left). A generalized scheme of a signaling system. Stimuli 1, 2, 3, and so forth, represent chemicals, sound, light, and so forth, which act to modify receptor proteins which are designed to be specific for one or more stimuli. Receptors 4 and 5 are used to illustrate a receptor that can be stimulated by stimuli 4 and 5. The receptor transmits the signal to a specialized processing system, which is then transmitted to a central response system. Receptors 1 and 2 are seen to act at the same specialized processing system I. The processed signal then generates a motor response to result in a behavioral pattern. Fig. 2 (right). Response of wild-type bacterium to attractants and repellents, as explained by a response (tumble) regulator model. The variation over time for the enzyme activities, the level of tumble regulator and the tumbling frequency is shown for three situations. (A) in absence of a gradient, $V_f=V_d$ are constant over time, and X (the tumble regulator) concentration varies around threshold in a Poissonian manner. The tumble frequency remains essentially constant. (B) Sudden increase in attractant increases rate of V_f faster than V_d leading to transient increase in concentration of X and transient decrease in tumbling frequency. Repellent decrease gives the same effect. (C) Sudden decrease in repellent decreases rate of V_f more rapidly than V_d leading to decrease in concentration of X and transient increase in tumbling frequency.



Koshland (*11*) using an apparatus designed to generate temporal rather than spatial gradients. First, the motility behavior of *Salmonella typhimurium* and *Escherichia coli* was shown to be the same at different absolute concentrations of attractant. Then the bacteria were subjected to a sudden change in concentration and examined immediately after the mixing process was complete. If the sensing mechanism utilized an instantaneous comparison between attractant concentrations at its head and tail, the bacteria after mixing would sense only a uniform distribution of attractant and should, therefore, behave as though they were in a "no gradient" situation. If, however, the sensing mechanism compares concentrations over time, a sudden decrease in concentration should generate responses of the type observed in swimming down a gradient.

The latter was precisely what occurred (*11*). The bacterial tumbling increased dramatically if the concentration of attractant were decreased suddenly (simulating swimming down a gradient). Bacterial tumbling was suppressed ("smooth swimming") if the concentration was increased. No change in tumbling pattern was observed if the concentration was kept constant (the control). When the swimming pattern was recorded over a longer time interval, the patterns observed immediately after mixing gradually returned to normal—precisely the adaptation expected in a temporal process as the "memory" of the stimulus faded over time. Similar responses were observed for repellents, except that a repellent decrease caused smooth swimming and a repellent increase caused tumbling (*12*). These experiments eliminated the instantaneous comparison mechanism and indicated that bacteria have a rudimentary "memory" which is utilized to direct migration.

The Control of Migration

These stopped-flow experiments also showed that alteration in tumbling frequency is the mechanism by which bacteria control migration (*11*). Berg and Brown demonstrated (*13*) independently that bacteria migrate by altering their tumbling frequency with the use of an elegant tracking system which followed the bacteria in three-dimensional space. Their tracking experiments also established that the bacteria follow a random walk behavior and that the tumbling pattern is asymmetric; that is, tumbling suppression is quantitatively more important than tumbling enhancement in real space gradients (*13*).

The bacterium has thus reduced a complex problem in three-dimensional migration to a very simple on-off device. It senses whether it is going in a favorable direction and suppresses tumbling or in an unfavorable direction and activates tumbling. By taking giant steps in the right direction and small steps in the wrong direction, it biases its walk very effectively in the direction which aids its survival.

Useful Memory

We used the term "bacterial memory" to describe the behavior pattern of the bacteria because it involves a time-dependent comparison of past and present. It is certainly not long-term memory in the sense of higher species; but it is no less real or useful to the bacterium than the memory of humans is to their behavior.

To decide how long a useful memory should be for a bacterium, it is important to remember that (i) the bacteria move in a random walk manner and (ii) they are very small. A long memory would mean that the bacterium could utilize gradient information over long distances of motion—that is, many body lengths—and hence reduce its analytical problem. However, a long memory would increase the probability that information might be processed after a change in direction. A brief memory span, therefore, would offer a high correlation between gradient information and direction of motion, but it would be of little help in analytical accuracy. A long memory span would offer an advantage in analytical accuracy, but there would be lower correlation with direction of motion. To optimize their sensory system, bacteria might be expected to have an intermediate memory span, and that is indeed what is observed (*14*). The effective memory span for the bacterium swimming in a gradient is approximately the time it takes for a bacterium to swim 20 to 100 body lengths. The "memory" thereby reduces the analytical problem from detecting one part in 10^4 to one part in 10^2 to 10^3, a more reasonable but still formidable analytical challenge.

Response Regulator

It is necessary to try to explain the bacterial memory in chemical terms. The elements of a rudimentary model are shown in scheme 1 and the application to the gradient responses of a wild-type bacteria is shown in Fig. 2.

$$W \xrightarrow{V_f} X \xrightarrow{V_d} Y \qquad (1)$$

(Response regulator)

In this model X represents a response regulator (a tumble regulator in the bacterial system) which operates somewhat like a thermostat to activate or suppress the response. The regulator is formed from W at a rate designated by V_f and decomposed at a rate indicated by V_d. Either or both of these steps can be modified by signals from receptors. For illustrative purposes, we assume that the response regulator suppresses tumbling when it rises above the threshold and increases tumbling when it falls below the threshold (*7, 11, 15*).

A bacterium moving up a gradient of attractant would initially increase V_f more than V_d (possibly because V_f responds more rapidly to the change in chemoeffector concentration) and thus lead to an increased level of the tumble regulator. This would suppress tumbling for an interval but if no further stimulus were encountered, the decomposition rate (V_d) which would be a function of (X) would increase until X returns to its former level. On going down a gradient the inverse would occur. The level of X would be momentarily depressed, and tumbling would be increased. Although the details of the system are yet to be fully uncovered, the features that emerge from the experiments are (i) there is some entity whose level regulates tumbling, (ii) the formation and decomposition of this regulator are under the influence of stimuli so that the level can be perturbed in gradients, and (iii) the bacterial "memory" is a function of the time-dependent characteristics of this response regulator. The tumble regulator could be a small molecule, a membrane potential, or a macromolecular complex.

This simple model allowed an explanation of a number of observed phenomena and led to several predictions which have been verified. Some of these are illustrated in Fig. 3. For example, the explanation of nonchemotactic mutant behavior became clear. If modification of tumbling frequency was essential to the behavior pattern, mutants that tumbled all the time or not at all could obviously not follow a gradient (Fig. 3, A and B). The nonchemotactic mutants (*5*) observed so far all follow one of these two patterns. Moreover, constantly tumbling mutants might be able to exhibit smooth

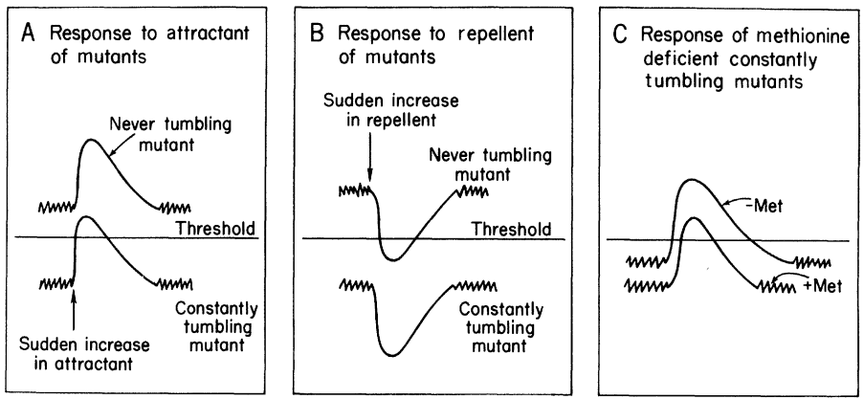


Fig. 3. The tumble regulator model applied to mutants and methionine deprivation. (A) A constantly tumbling mutant has the level of tumble regulator below the threshold in the absence of a gradient, leading to constant tumbling. Stimulus with an attractant can raise the tumble regulator for a brief period above the threshold, after which it returns, in the absence of a further stimulus, to constant tumbling patterns. A smooth-swimming nonchemotactic mutant has a tumble regulator level above the threshold at all times. An increase in attractant can further increase the level of X but does not change the behavioral pattern. (B) A smooth-swimming nonchemotactic mutant has a tumble regulator level above threshold. When treated with a sudden increase in repellent, the tumble regulator level is lowered to give a momentary tumbling response. Same treatment of a constantly tumbling mutant would have no observable behavioral effect. (C) Methionine auxotroph transduced into constant tumbling mutant shows tumbling, demonstrating that methionine is not essential for tumbling. However, the rate of return after stimulus is decreased in the absence of methionine, suggesting that methionine has a role in the kinetics of tumble regulator formation (a decrease in V_d or an increase in V_f) (45).

swimming if given large enough increases in attractant stimulus (Fig. 3A). This was demonstrated (*16*). Likewise, smooth-swimming mutants should be induced to tumble by a strong repellent stimulus and this also has been shown (Fig. 3B) (*16*).

The tumble regulator model also readily explains how the bacterium optimizes its useful memory. When the bacterium starts up a gradient of attractant it immediately begins producing higher levels of tumble regulator and hence increases its probability of traveling a longer than normal distance. When a bacterium heads in the wrong direction it starts reducing the level of tumble regulator and shortening the average path length in that direction.

The "memory span" is controlled by the pool level of the tumble regulator and the rate constants of the processes V_f and V_d in scheme 1. By appropriate adjustment of these values, the pool level can be kept close to threshold in shallow gradients, thus maximizing sensitivity to a change in direction. Artificially high gradients can generate a longer memory span. Moreover, a low threshold for X could explain the asymmetry observed in the gradient responses.

Quantification of the Stimulus Response

The quantification of the tumble frequency response was carried out (*17*) by the procedure illustrated in Fig. 4. The use of this "tumble frequency assay" revealed a number of the relationships between stimuli and responses: (i) The response is proportional to the change in receptor occupancy (*17, 18*). (ii) The responses of different stimuli are in most cases additive algebraically, that is, a negative response of decreasing attractant gradient or increasing repellent gradient offsets a positive response of an increasing attractant gradient or decreasing repellent gradient (*12, 17, 19*). (iii) The response is quantitatively predictable from the binding affinity of the purified receptor isolated from the periplasm (*17, 18*). (iv) A roughly additive relationship is observed for responses to stimuli provided by carbohydrates (*17*), amino acids (*17*), light (*20*), repellents (*12, 19*), and metal ions (*21*); thus all these stimuli may eventually be processed through a common sensory system. (V) In some cases the responses are not strictly additive, and potentiation effects have been observed (*22*).

Receptor Competition in the Signaling System

In examining the way receptors can interact, several possibilities could be envisioned. The receptor may be an enzyme that is induced by its chemoeffector into an active state. If the receptor is not itself an enzyme, it could interact with another component to activate the signaling system. The receptor could be permanently associated with this component, associate with it for activation, or dissociate from it for activation. Evidence for or against these hypotheses (*23*) have, for experimental reasons, been difficult to obtain in mammalian systems so that the bacterial system with its combination of purified receptor proteins, receptor mutants, and quantitative behavioral assay was utilized (*24*).

The mechanism illustrated in Fig. 5 was indicated by the following experimental evidence. First, the galactose-binding protein of *Salmonella* was isolated and found to bind galactose tightly, but ribose not at all (*24*). The ribose-binding protein was also purified and found to bind ribose tightly and galactose not at all (*25*). Yet ribose inhibits galactose taxis and galactose inhibits ribose taxis (*24*). Second, a mutant that lacked the ribose binding protein entirely was available (*25*); and, if the mechanism of Fig. 5 is correct, this mutant should show no inhibition of galactose taxis by ribose. This was found to be the case (*24*). Third, ribose and galactose must induce conformational changes in their chemoreceptors since there was no evidence that the uncomplexed receptors compete with each other. Evidence was obtained for induced conformational changes in the galactose receptor (*26, 27*) and the ribose receptor (*28*). Fourth, in *Escherichia coli* (*29*) and *Salmonella* (*30*), mutants exist which fail to respond to either ribose or galactose but do respond to other chemoattractants. The mutant from *Salmonella*, moreover, was shown to contain the normal amounts of the ribose-binding protein and the galactose-binding protein (*30*). Thus, the alternative of a double mutant lacking both receptors was eliminated. A similar elimination of two functions by a single mutant has been shown in histidine and arginine transport (*31*).

The model to explain all these observations (Fig. 5) suggests that induced association of proteins can be an important feature of a signaling system. It provides a mechanism for competition between receptors, and it represents a specialized or focused processing prior to the central processing in contrast to a parallel system in which all stimuli proceed directly to the central system (*24*).

The advantages of such a mechanism, particularly in a sensory system, are several. First, there is an economy and simplicity in a common response. In the chemotaxis case, a rough additivity in the signals generated by attractants and repellents indicates a common pool of a

response regulator that can integrate a variety of stimuli. Cyclic adenylate obviously provides a similar integrating function in hormonal systems. Second, the mechanism provides a focusing of stimuli, which has added control benefits. In this case, an organism saturated with a good carbon source (for example, ribose) would not respond to an added superfluous carbon source (for example, galactose), but it could still respond to a nitrogen source. In higher species such as man, a number of different sensory phenomena feed into a common brain, but separate, focused pathways prevent saturation of one system (for example, the visual) from desensitizing a second (for example, the auditory) system. If we are blinded we still hear. Third, an interaction system of the type shown in Fig. 5 provides a maximum of sensitivity with a maximum of control. In most cases, an organism is subject to one stimulus at a time and at low levels. Hence, maximum sensitivity is achieved by a tight binding of chemoeffector to an excess of receptor with subsequent attraction of the chemoeffector to the signaling component molecules. If enough component I molecules for every receptor were present, however, the occasional situation in which the organism is bombarded by many stimuli could result in overstimulation and metabolic breakdown. The focused pathways limit maximum response while maintaining sensitivity to small stimuli.

The advantage of using a protein competition for focusing such a system can be explained in terms of specificity. About 20 receptors have been identified in *E. coli* (*6*) and an equivalent number has been identified in other species (*32*). Each has a limited range of compounds that bind to it. The galactose receptor mentioned above binds glucose and galactose tightly and binds arabinose, lactose, and fucose weakly; but it does not bind ribose and allose at all (*26, 33–35*). The ribose receptor binds ribose strongly and allose weakly, but it does not bind galactose (*25*). Since these are typical protein specificities, one might ask how a sensory system could obtain the advantages of focusing while still achieving discrimination between similarly structured chemical compounds. In the case of galactose and glucose, conventional competition at a single receptor site is possible because these two compounds differ only by inversion at a single carbon atom. Thus, the active site can be made to bind both galactose and glucose and exclude many saccharides that differ only slightly in structure. However, it would be extremely difficult to design a site that could bind ribose and galactose but exclude compounds such as fucose and arabinose. In that case, receptor competition provides an answer. The binding sites are tailored for the chemoeffector, and the "adapter end" of the protein receptor is tailored to bind with the next component of the signaling system.

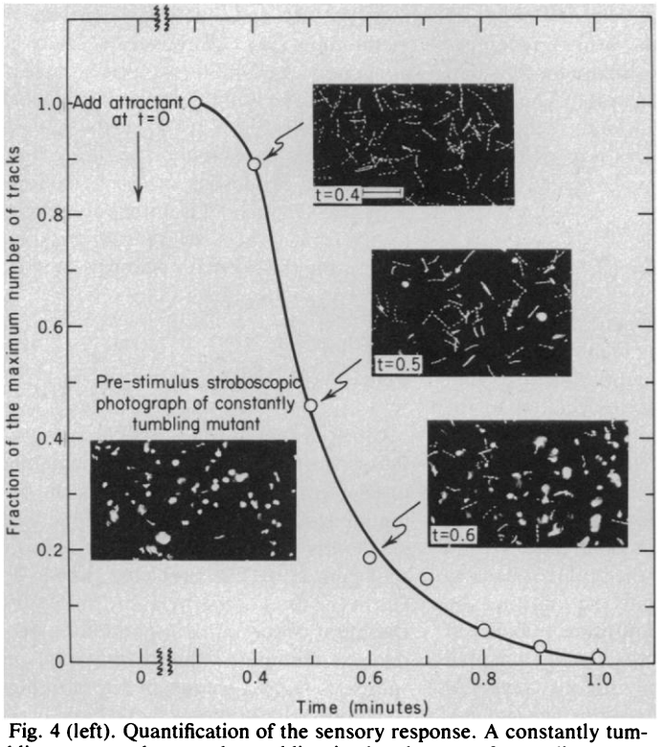


Fig. 4 (left). Quantification of the sensory response. A constantly tumbling mutant shows only tumbling in the absence of a gradient (prestimulus). If an attractant (serine) is added rapidly at time zero, all the bacteria swim smoothly. As time passes, more and more bacteria revert to tumbling. Quantification is achieved by counting tracks in exposures of the microscopic observation chamber subjected to four stroboscopic flashes per 0.8 second. Datum points for prestimulus, 0.4 minute, 0.5 minute, and 0.6 minute are shown for illustrative purposes. The splotches of light indicate a bacterium tumbling over and over in the same position. The dotted path indicates the smooth-swimming bacterial path.

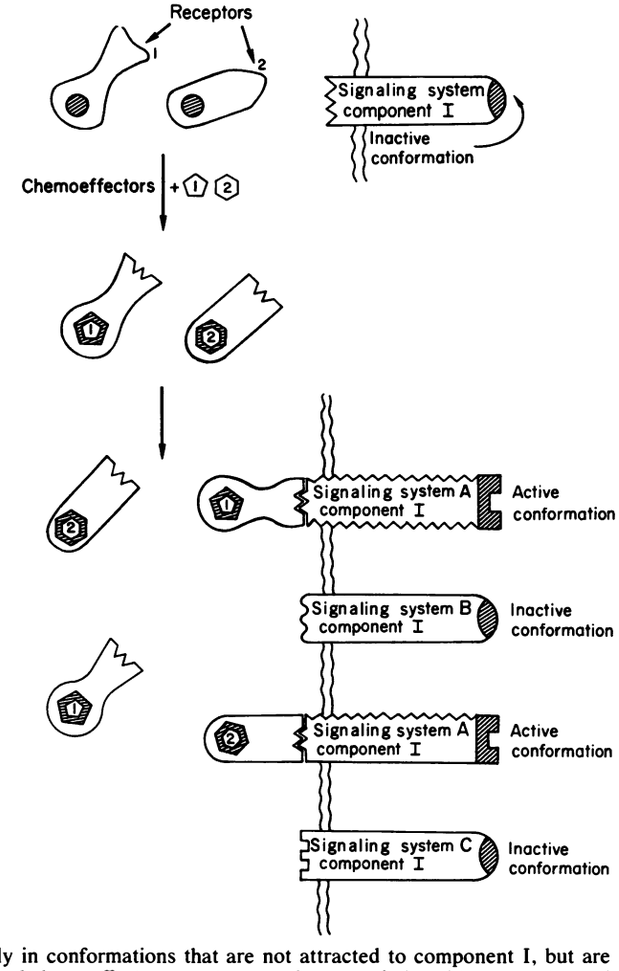


Fig. 5 (right). Floating receptor model. Receptors are initially in conformations that are not attracted to component I, but are induced into new conformations by the chemoeffectors. As a result, individual chemoeffector receptor complexes are induced to encounter and associate with the first component of the signaling system. If one binds there, it induces a conformation change, which activates the signaling system and begins a signal that can be amplified in a cascade process. If two receptor-chemoeffector complexes compete for the same site, one stimulus can diminish or completely block another.

Chemotaxis and Pain

As more and more receptor proteins are identified, an interesting generalization appears to be emerging, namely, that a common feature of receptor proteins is that they have more than one function. The galactose-binding protein was found to be the chemoreceptor for galactose chemotaxis (*34*), ribose-binding protein for ribose chemotaxis (*25*), and the maltose-binding protein for maltose chemotaxis (*36*). The binding proteins also serve as part of the transport system for those compounds (*25, 34, 35*). The glucose receptor for chemotaxis (*37*) is part of the phosphotransferase transport system (*38*). A blue light effect that disturbed the sensory system could be identified with a perturbation of the electron-transport system (*20, 39*). The oxygen, nitrate, and fumarate receptors are identified with the enzymes involved in electron transport (*40*). The Mg,Ca-dependent adenosine triphosphatase is a chemotaxis receptor for divalent cations (*21*).

These results suggest two intriguing possibilities. The first is that a single subunit is used for multiple purposes. Suggestions have been made that this may also be the case in other systems (*41*). The second possibility is that there is a common feedback mechanism to alert the central processing system of perturbations in key components of the system.

Chemotaxis in bacteria and the pain-pleasure signaling system in higher species seem particularly analogous. Chemotaxis is a survival device to impel bacteria away from noxious conditions or toward favorable conditions. Various stimuli such as nutrient levels, oxygen supply, temperature deviations, *p*H deviations, and toxic substances generate chemotactic signals. Pain and pleasure are similarly used as indicators of dangerous deviations or optimal functioning in higher systems. Both serve as surveillance systems to maintain physiological normality.

Genetic Dissection of the Sensory System

One of the main advantages of using bacteria for any study is the ease of obtaining mutants. In the *E. coli* system, Adler and co-workers showed three separate complementation groups (genes *cheA*, *cheB*, *cheC*) for generally nonchemotactic mutants whose genes mapped near the flagella region (*42*), and recently Parkinson has found a fourth (*cheD*) (*43*). In *Salmonella*, using some of the same and some different techniques, my co-workers and I have found nine such complementation groups, six of which (*cheP*, *cheQ*, *cheR*, *cheT*, *cheW*, and *cheX*) map at the end of the flagella region, two (*cheU* and *cheV*) are coincidentally mapped with flagella genes, *flaQ* and *fla*AII, and one (*cheS*) has not yet been mapped (*44, 45*). In the *E. coli* system, Simon has shown that *cheC* maps coincidentally with *flaA* (*46*). The finding of a coincidence between flagella mutants and chemotactic mutants suggest that these loci may code for flagella proteins that receive the final signal of the sensory system to control the flagellar response. Since all of the generally nonchemotactic mutants eliminate chemotaxis toward all chemoeffectors, the mutations appear to affect the central processing machinery of the sensory system and hence can be utilized to delineate this system. One such gene product has been identified (*47*) and has already been useful in clarifying the system (see below). Moreover, the number of genes offers some view of the complexity of the total system. About 9 to 12 genes for the central processing system and about 25 to 30 genes for the various receptors seems a reasonable estimate for the complete chemotactic apparatus. That represents a complexity which seems decipherable with the tools now at our disposal.

Adaptation in Bacteria

The responses of bacteria show some of the characteristics identified with desensitization and potentiation in higher species. The response is related to the change in the receptor-chemoeffector complex (ΔRC), not the absolute level of RC. Thus a temporal increase in chemoeffector concentration from C_1 to C_2 causes a change in tumbling pattern for a brief interval, which then relaxes back to normal motility despite the fact that the chemoeffector concentration remains at C_2. This means the system has adapted to an increased continuous level of chemoeffector. The system has not become desensitized to all stimulants since it will respond to other stimuli, for example, a change in concentration of another attractant or even a further increase in concentration of the same attractant from C_2 to C_3. Adaptation in higher species is, of course, commonplace (*48*) (such as to loud noises, to the clothes we wear) and desensitization is observed in stimuli at the molecular level [such as cholinergic synapses (*49, 50*) or the visual system (*51*)].

A mutant bacterium, SL4041, has also been shown (*22*) to undergo potentiation. In this mutant, prior incubation with serine can increase a response to a subsequent aspartate gradient by 260-fold and to a ribose gradient, 110-fold. Furthermore, ribose can potentiate the response of serine and of aspartate in the same manner, by factors of 12- and 20-fold, respectively. Every attractant does not potentiate every other attractant, however, particularly if the two attractants compete for the same receptor. These results are analogous to potentiation in higher systems where stimulation in one sensory system can enhance (potentiate) the responses in another system of the same species (*48*).

The response regulator model not only explains adaptation but provides some limitations on behavior. Since the enzymes maintaining the steady level of the response regulator are involved in the recovery from a stimulus, it would be expected that conditions which modified the normal tumble frequency would usually alter the adaptation phenomena also. That was found to be true for some mutants (*6, 8*) and bacteria deprived of methionine (*16*). Moreover, a study in nongenetic variability showed a correlation between tumbling and recovery from stimuli (*52*). This suggests that adaptation is a phenomenon resulting from the kinetic properties of the behavioral response system and is intimately related to the rate processes of the enzymes generating the normal responses to stimuli.

Role of Methylation

Clues in regard to the biochemistry of the processing machinery are beginning to emerge. The role of a membrane potential is suggestive (*53*) and a blue light effect has been identified with a flavin spectrum (*39*). The best clue, however, lies in the area of methylation. Adler and Dahl first observed that methionine deprivation eliminated the chemotactic response (*54*), and studies in our laboratory showed that this was caused by an alteration of the relative rate constants of the tumble regulator system (Fig. 3C) (*16*). This was followed by findings that the methionine effect was actually a requirement for *S*-adenosylmethionine (*55*), that a protein in the membrane is methylated (*56*), and that a methylating enzyme can be identified with the *cheR* gene product (*47*). These findings lead to the further modification of the response regulator model to some scheme in which methylation of the proteins in-

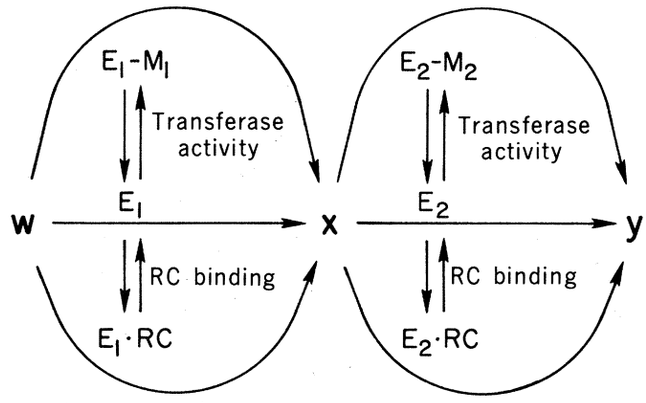


Fig. 6. More general response regulator model. Paths for formation and decomposition of X, the response regulator, can be altered by covalent modification as well as binding to a chemoeffector-receptor complex (RC). Covalent modification to form E_1-M_1 and E_2-M_2, for example, a methylated or a phosphorylated or adenylated protein, can either increase or decrease the rate constant, or increase or decrease the binding constant of RC to E_1 or E_2. Hence, added controls with different time constants are introduced.

volved in V_f or V_d in scheme 1 is a necessary feature of a correctly operating sensory system (Fig. 6). Methylation is not essential for tumbling as shown by the induction of tumbling in a *cheR* mutant by a phenol gradient (*47*). Hence it must be related to maintaining the level of tumble regulator, that is, in the initial response and the adaptation phenomena.

These findings are of particular interest since the methylase acts on carboxyl groups (*57*), and a similar enzyme has been found in the adrenal medulla by Axelrod and co-workers (*58*). Methylation of catecholamines is also important in desensitization of that system.

An interesting insight into cellular organization is given by the facts that the methylase is a cytoplasmic enzyme, that the methylated protein is a membrane-bound protein, and that several receptors are in the periplasm. Thus, the membrane serves as the organizing boundary which is acted on from both sides.

A Generalized Model and the Hierarchy of Values

From the experimental findings and theoretical analysis, a rough general scheme for the bacterial sensory system can be devised (Fig. 7). Examination of Fig. 6 reveals how a sensory system can develop a hierarchy of values by simple manipulation of basic chemical and enzymological principles. First, the specificity of the receptor establishes an initial discrimination. Some compounds are bound tightly, some weakly, and some not at all. The tightly bound compounds will be detected in low concentrations and will displace more weakly bound molecules when both are present together. The more weakly bound molecules can be effective at high concentrations in the absence of competitors. Thus, a relation between optimal metabolites or stimuli and those that are recorded only in adverse circumstances is developed. Chemicals that are not wanted as stimuli are not bound at any physiological level. Second, the number of receptor molecules present provides a second weighting factor. Some, such as the serine receptor, are produced constitutively. Some such as the ribose and nitrate receptors are induced (*2*). The organism does not respond to ribose or nitrate gradients unless the appropriate receptors are generated by appropriate growth conditions. Thus some responses are innate; some are modified by environmental growth conditions. Third, the affinity of the receptor for the next component in the signaling system can provide a further value hierarchy. Fourth, competition between receptors provides an additional hierarchal complexity and it can utilize, for example, affinity constants and numbers. Normally grown *S. typhimurium* have ten times as many ribose receptors as galactose receptors, and, as a result, ribose can completely inhibit galactose taxis; but galactose can inhibit ribose taxis only slightly. In *E. coli* the numbers of galactose receptors are higher and allow significant galactose inhibition of ribose taxis. Fifth, the time characteristics of the system can be modulated by covalent modifications such as methylation. This not only provides fine tuning but also an "override" mechanism. The absence of *S*-adenosylmethionine causes the bacterium to swim without tumbling, thus in effect ignoring attractant gradients. Swimming in straight lines is the best way to leave an area, and hence an appropriate response if the absence of *S*-adenosylmethionine indicates a threatening condition for the survival of the bacterium.

Bacterial Behavior and Higher Neural Processes

The words "choice," "discrimination," "memory," "learning," "instinct," "judgment," and "adaptation" are words we normally identify with higher neural processes. Yet, in a sense, a bacterium can be said to have each of these properties.

Bacteria show choice in going up a gradient or down, depending on whether it is to them favorable or unfavorable. They can discriminate between closely similar chemical compounds. They utilize a memory to direct their sensory response and their memory time is selected to be of optimal "usefulness" for the bacteria. It can learn to respond to ribose by being grown in a medium that induces ribose receptors and can respond to serine instinctively because serine receptors are produced constitutively. It can analyze opposing stimuli from repellents and attractants and show judgment by moving in the most favorable direction. It can respond to a change in stimulus but adapt or desensitize itself to an incessant repetition of the same stimulus. It has focused pathways analogous to the specialized auditory and visual systems of higher species.

It is apparent that the words in quotation marks are used with quite different connotations by psychologists or neurobiologists studying higher species, and there are real differences. The brain has a "wiring diagram" and hence a capacity for spatial organization not comparable in a unicellular organism. The replication of bacteria takes minutes to hours and hence the long-term memory of higher species would be useless to it. Nevertheless, it would be unwise to conclude that the analogies are only semantic since there seem to be underlying relationships in molecular mechanism and biological function. For example, learning in higher species involves long-term events and complex interactions but certainly induced enzyme formation must be considered as one of the more likely molecular devices for fixing some neuronal connections and eliminating others. The difference between instinct and learning then becomes a matter of time

scale, not of principle, and may be fundamentally analogous to the difference between constitutive and induced receptors in a single cell.

Choice may seem a peculiar word to apply to a bacterium that has a preprogrammed sensory system mandating its movement up some types of gradients, but many psychologists point out that we delude ourselves in regard to our freedom of choice, and certainly many personality traits appear to be hereditary. Judgment involves weighing alternatives, undoubtedly involving integration of signals from various excitatory and inhibitory neurons in the brain. Is it different in principle from the simple algebraic integration of repellent and attractant stimuli or is it a balancing of many neurons, analogous to the bacterial balancing of chemoreceptor complexes? And perhaps integration of stimuli at a single neuron involves a pool level of a response regulator controlled very similarly to the tumble regulator of the bacterium. Memory in higher species is divided into short-term and long-term memory to optimize usefulness, possibly in the same way that a short memory is optimal for a bacterium. Finally, the ability of *S*-adenosylmethionine depletion to override the normal sensory responses to nutrients is not dissimilar to the mechanisms which hormones can utilize in mammalian systems. In each case, one type of signal, working through covalent modification, is made more important than weaker normal stimuli in a hierarchy of values. Thus, it is quite possible to explain the processes of higher neuronal systems by extensions of the principles outlined here. The number of units will be larger but the control on the action of an individual unit may be highly analogous.

An example may be helpful. It is frequently stated that it would be desirable to obtain an opiate that was not addictive or did not induce tolerance of higher and higher doses. If neuronal receptors involve mechanisms similar to those described for the action of the methylase (*51*), that goal may be impossible. Any agonist which induces the increase in the neuronal response (the level of X) would inevitably activate the methyltransferase to diminish that response (Fig. 6). Tolerance would be caused by induced higher levels of methyltransferase activity as a means of opposing the consequences of repeated stimuli, but such higher levels would inevitably alter the normal steady state level of response regulator. This follows from the correlation of adaptation to the normal response discussed above. Hence tolerance to a drug may be inevitably linked to the agonist properties of the drug. A careful balancing of rate constants might allow enhancement of the stimulus while minimizing addiction, but it would be impossible to disengage one completely from the other.

A long-term memory can be hypothesized from the molecular events described so far. A weak stimulus could activate the rise and fall of a response regulator in neuron 1. If the signal failed to exceed a certain threshold, it would decay back to normal levels without any permanent change in neuron 2. If, before it had decayed back to normal, a second stimulus was received by the neuron 1, it might now, by the additive relationships described above, be sufficient to increase the level of the response regulator above the threshold, send a signal to neuron 2, and induce the synthesis of a protein there. Alternatively, the sensitivity of neuron 2 could be potentiated by stimuli from other neurons so that the same weak stimulus would be amplified and generate far higher levels of the response regulator. The first alternative explains repetition of a stimulus to achieve learning; the second explains the existence of previous learning to allow the immediate comprehension of a new fact. We must repeat a telephone number many times to remember it; we need only hear once, "Your doctor wants you to call immediately." It is perhaps significant that cyclic adenosine monophosphate (cyclic AMP), identified with stimulation of protein synthesis (*59*), may also be involved in neuronal stimuli (*60*). Thus a transient change in the level of a response regulator could easily, by inducing protein synthesis, lead to a long-term irreversible change. The potentiation of the bacterial response seems particularly pertinent in this regard. The length of a memory is optimized for the species in which it resides; the principles of memory may be very similar in all species.

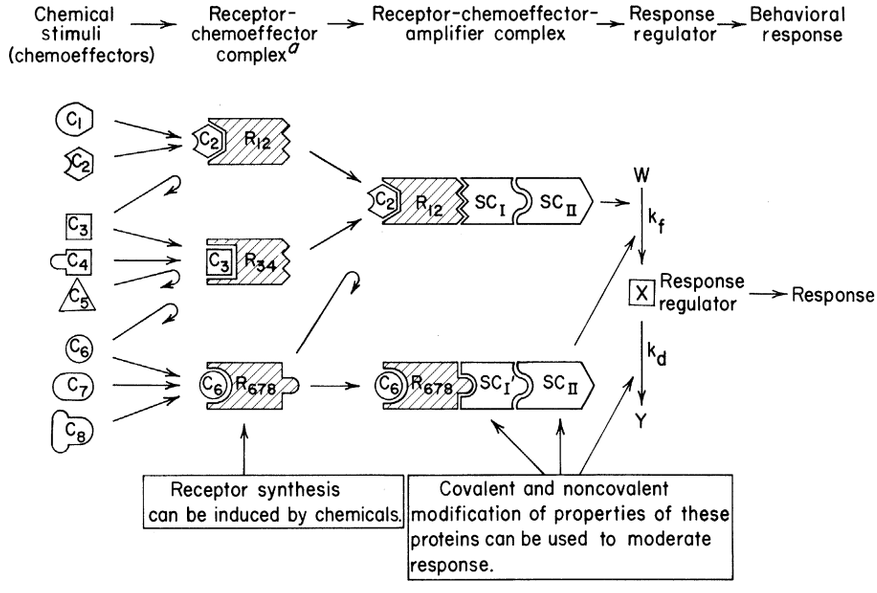


Fig. 7. Schematic representation of general signaling systems. A series of stimuli interact in various ways with individual receptors. Compounds C_1 and C_2 bind to receptor 12, but not to receptors 34 or 678. Compound C_5 binds to no receptors, and hence cannot be detected by the organism. On binding to the receptor, an induced conformation change occurs such that R12 and R34 receptors are attracted to signal components I. This means that the receptor chemoeffector complexes will compete with each other and can limit responses if the number of SCI molecules is significantly smaller than the number of R12 and R34 receptors. Chemoeffectors C_6, C_7, and C_8 are focused through a separate processing machinery via SCI′ by the specificity of R678 for SCI′ and not SCI. Signal components I and I′ can then interact with other signaling components of the general system, which may or may not be similar to each other and are designated by SC_{II}. Ultimately the signal from this system interacts with one of the two steps of the response regulator system, here designated as being formed from W in a k_f step and being decomposed to Y in a step designated k_d. The effects of the two chemoeffectors may be positive or negative, depending on whether they increase or decrease the rates of the k_f or k_d steps. Favorable effects (increase of attractant, decrease of repellent) reinforce each other and are inhibited by unfavorable effects (decrease of attractant or increase of repellent). The level of tumbling regulator then determines the behavioral response in the same way that a thermostat regulates a furnace. The receptor proteins can be induced by chemicals or be constitutive. The properties of the various enzymes and receptors in the system can be altered by covalent or noncovalent modification leading to enhanced or subdued sensory responses. The level of X relative to a threshold controls the sensory response.

Conclusion

The response regulator model shown (Figs. 6 and 7 and scheme 1) involves a combination of well-known mass action phenomena and some new features which may be of widespread utility in regulatory systems. In the first place, overall control is achieved by a response regulator level and a threshold detector. This combination allows not only the level of the response regulator but its time-dependent generation and decay to become vital features of a regulatory process. Thus the "memory" characteristics of each system can be selected for optimization in the same way that the bacterium optimizes its useful memory. A hormonal response regulator, a short-term neuronal memory, long-term memory, and a neuronal action potential would each be examples of systems with needs for quite different time constants which might operate on the same basic principles.

In the second place, a response regulator model allows individual responses to a wide variety of stimuli and yet can integrate these stimuli into a common response output. A number of different receptors, more than 20, in the chemotactic system give an algebraically integrated response. This is achieved not only by the device of "floating receptors," which can be bound to common elements of the sensory system, but more importantly by the systems leading ultimately to an adjustment of the level of a common parameter. Thirdly, the convergence of a wide variety of stimuli to a common response regulator allows the development of a hierarchy of values and interrelationships not available in independent parallel systems. The specificity of the receptors, the affinity constants between protein and ligand, the numbers of receptors, and the competition between receptors provide mechanisms to allow the system to make value judgments between stimuli and to alter their value judgments under changing circumstances. For example, galactose can be detected sensitively when present alone, but it is ignored in the presence of excess ribose. Covalent protein modification can alter the rate constants or inactivate receptors and thus change values. Finally, the response regulators provide a mechanism for increasing sophistication. A unit obeying patterns like those shown in Figs. 6 and 7 can generate a regulator, X, which becomes a stimulus for the receptor in the next unit. Hence the complexity of a neuronal or hormonal or enzymatic network becomes, in principle, a repetition of unitary responses based on the levels of response regulators.

Summary

Bacterial behavior is shown to be modulated through a simple on-off switching device which directs migration toward favorable conditions and away from unfavorable ones. The behavioral response is controlled by a rudimentary memory which allows the bacteria to sense gradients over time. The memory can be explained by a biochemical system involving a response regulator whose level relative to a threshold controls flagellar function. The level of the response regulator is itself controlled by factors such as enzyme levels and environmental stimuli. The molecular basis of the model appears to be relevant to more complex hormonal and neural signaling systems.

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