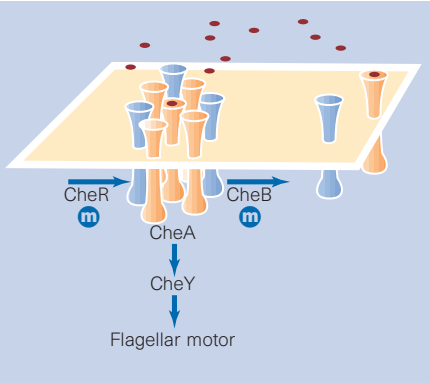

Figure 1 **The chemotactic network. Attractant or repellent molecules bind to the chemotactic receptors that span the bacterial membrane, and induce a conformation change (shown here as a change from blue to orange). This is translated into a change in swimming behaviour through modification of the activity of an intracellular kinase, CheA. CheA modifies a messenger protein, CheY, which binds to the flagellar motor and induces tumbling. Adaptation involves reversible methylation (m) of the receptors by opposing enzymes CheR and CheB (an enzyme activated by CheA). Bray *et al.*[1] propose that the ligand-induced activity change of the receptor propagates in a cluster of neighbouring receptors, a process that amplifies the signal and may account for the high gain of the chemotactic response. The authors suggest that, to preserve the dynamic range, both clusters and single receptors coexist on the cell membrane.**

direction of motion is chosen. To achieve chemotaxis, a bacterium that is moving in a favourable direction along a chemical gradient suppresses tumbling events, and thus migrates, on average, towards attractant and away from repellent. Although tumbling frequency is modulated by changes in chemical concentrations, its steady-state value is independent of the concentration itself. This property is called exact adaptation. Among other effects, it is believed that adaptation allows bacteria to respond to gradients over a wide range of background chemical levels.

The biochemical network that mediates the chemotactic response is relatively simple[8]. Sensory receptors modulate the activity of an associated kinase that phosphorylates a messenger protein, which, by interacting with flagellar motors, induces tumbling (Fig. 1). Binding of an attractant, such as aspartate, to the receptor suppresses tumbling by inhibiting the kinase activity. Adaptation is brought about by a feedback mechanism involving reversible methylation of the receptors.

The efficiency of the chemotactic response is evident in its high sensitivity — binding of attractant to less than 1% of the receptors is sufficient to induce measurable changes in the tumbling frequency[1,9]. This sensitivity is also remarkable in view of the low abundance of some receptors that function through the same phosphorylation cascade. For instance, addition of ribose can suppress tumbling completely, even though only a small fraction of all receptors is sensitive to ribose[1]. The origin of this high sensitivity, or gain, remains unknown and it is perhaps one of the most striking aspects of the chemotactic response. In fact, none of the quantitative models of the chemotactic network[10–13] has accounted for the observed gain, although they have successfully explained several aspects of the response, including adaptation. This is particularly distressing in view of experiments that quantitatively measured the interaction between the messenger proteins and the flagellar motor and found a relatively low degree of cooperativity (ref. 14, and U. Alon *et al.*, personal communication).

What, then, is the origin of the reported high sensitivity of the chemotactic response? There are several ways in which the observed gain might be generated by signal processing within the biochemical network. It could simply result from an as yet unidentified, highly cooperative protein–protein interaction, or from network amplification processes such as those observed in other phosphorylation cascades. Such mechanisms operate downstream of the receptor–ligand binding and amplify the signalling activity of the receptors. High sensitivity then requires the steady-state activity of the receptor to be adjusted with the 'edge of sensitivity' of the amplifying process.

Bray and collaborators[1] consider a different type of mechanism, where the high gain is the result of interactions between receptors. Here, the ligand-induced change in conformation, which is responsible for the transmission of the tumble signal to the motor, can spread between receptors. Such 'infection' amplifies the effect of ligand binding, and may account for the observed gain. In principle, this mechanism does not restrict the level of receptor signalling activity, as this activity is now the output of the amplification process. Bray *et al.* demonstrate, however, that whereas a high degree of receptor 'infection' increases the gain of the system, it also severely reduces the dynamic range, because the receptors will already be saturated at low chemical concentrations. Such an apparent incompatibility between high sensitivity and wide dynamic range is a general problem for many sensory systems; the solution is indeed provided through adaptation.

Bray *et al.* propose the existence of an additional form of adaptation in bacterial chemotaxis: that the degree of receptor clustering depends on the concentration of ligand. Although the detailed molecular mechanism that accounts for such adaptation needs to be elucidated, the proposed dependence fits in well with observations on receptor function in other systems[2–4]. If confirmed by biochemi-

100 YEARS AGO

The theory of the origin of sleep which has gained the widest credence is the one that attributes it to anaemia of the brain. ... It has been supposed, but without sufficient evidence to justify the supposition, that this anaemia of the brain is the cause and not the sequence of sleep. The idea behind this supposition has been that, as the day draws to an end, the circulatory mechanism becomes fatigued, the vasomotor centre exhausted, the tone of the blood vessels deficient, and the energy of the heart diminished, and thus is the circulation to the cerebral arteries lessened. ... The alternative theories, which have been suggested to account for the onset of sleep, may be classed as chemical and histological. ... It is held possible that the dendrites or branching processes of nerve cells are contractile, and that they, by pulling themselves apart, break the association pathways which are formed by the interlacing or synapses of the dendrites in the brain. Ramón y Cajal, on the other hand, believes that the neuroglia cells are contractile, and may expand so as to interpose their branches as insulating material between the synapses formed by the dendrites of nerve cells.

From *Nature* 5 May 1898.

50 YEARS AGO

As I look at a living organism, I see reminders of many questions that need to be answered. Not all these questions are obviously important, nor would their answers be useful – but we want them answered. Thomas Wright in 1601 said, "Nothing is so curious and thirsty after knowledge of dark and obscure matters as the nature of man" – of scientific men especially, he might have said. What is skin, fingernail? How do fingernails grow? How do I feel things? How are nerves built and how do they function? How do I see things? ... The basic answers to all these questions are not to be found in books. Even though Chaucer said

For out of olde feldes, as men seith,
Cometh al this newe corn fro yeer to yere;
And out of old bokes, in good feith,
Cometh al this newe science that men lere,

he was before long corrected by Francis Bacon: "Books must follow sciences, and not sciences books". – Linus Pauling

From *Nature* 8 May 1948.