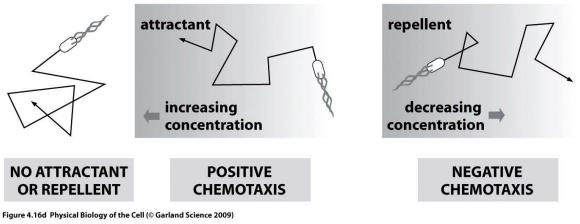

Figure 5.5: Examples of chemotaxis. Figure from Phillips, Kondev and Theriot [34]; used with permission of Garland Science.

5.4 Bacterial Chemotaxis

Chemotaxis refers to the process by which micro-organisms move in response to chemical stimuli. Examples of chemotaxis include the ability of organisms to move in the direction of nutrients or move away from toxins in the environment. Chemotaxis is called *positive chemotaxis* if the motion is in the direction of the stimulus and *negative chemotaxis* if the motion is away from the stimulant, as shown in Figure 5.5. Many chemotaxis mechanisms are stochastic in nature, with biased random motions causing the average behavior to be either positive, negative or neutral (in the absense of stimuli).

In this section we shall look in detail at bacterial chemotaxis, which *E. coli* use to move in the direction of increasing nutrients. The material in this section is based primarily on the work of Barkai and Leibler [8] and Rao, Kirby and Arkin [36].

Control system overview

The chemotaxis system in *E. coli* consists of a sensing system that detects the presence of nutrients, and actuation system that propels the organims in its environment, and control circuitry that determines how the cell should move in the presence of chemicals that stimulate the sensing system. The approximate location of these elements are shown in Figure **??**.

The actuation system in the *E. coli* consists of a set of flagella that can be spun using a flagellar motor embedded in the outer membrane of the cell, as shown in Figure 5.6a. When the flagella all spin in the counter clockwise direction,†, the individual flagella form a bundle and cause the organism to move roughly in a straight line. This behavior if called a "run" motion. Alternatively, if the flagella spin in the clockwise direction, the individual flagella do not form a bundle and the organism "tumbles", causing it to rotate (Figure 5.6b). The selection of the motor direction is controlled by the protein CheY. If phosphorylated CheY binds to the motor complex, the motor spins clockwise, otherwise it spins counter-clockwise.

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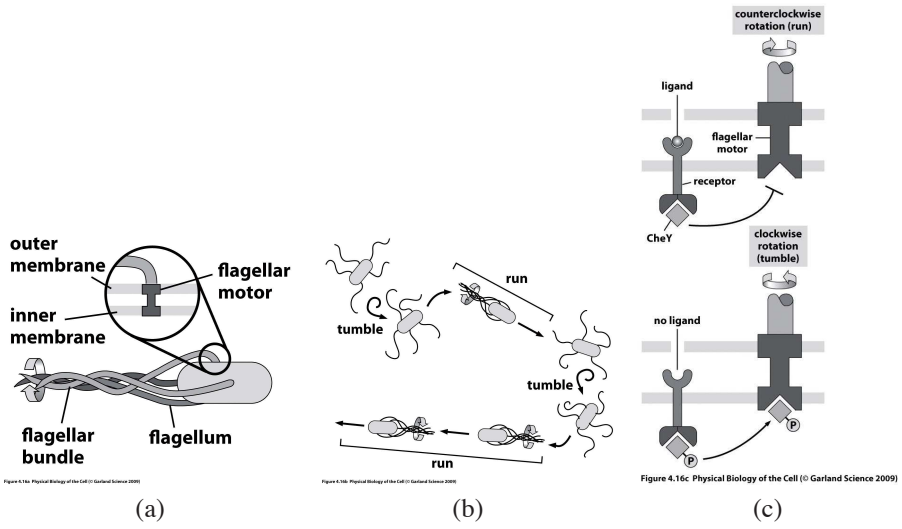
Because of the size of the organism, it is not possible for bacteria to sense gradients across their length. Hence, a more sophisticated strategy is used, in which the organism undergoes a combination of run and tumble motions. The basic idea



(a) (b) (c)

Figure 5.6: Bacterial chemotaxis. Figures from Phillips, Kondev and Theriot [34]; used with permission of Garland Science.

is illustrated in Figure 5.6c: when high concentration of ligand (nutrient) is present, the CheY protein is left unphosphorylated and does not bind to the actuation complex, resulting in a counter-clockwise rotation of the flagellar motor. Conversely, if the ligan is present then the molecular machinery of the cell causes CheY to be phosphorylated and this modifies the flagellar motor dynamics so that a clockwise rotation occurs, leading to a tumble motion. The net effect of this combination of behaviors is that when the organism is travelling through regions of higher nutrient concentration, it continues to move in a straight line for a longer period before tumbling, causing it to move in directions of increasing nutrient concentration.

A simple model for the molecular control system that regulates chemotaxis is shown in Figure 5.7. We start with the basic sensing and actuation mechanism. A membrane bound receptor MCP serves as a signal transducing element from the ligand outside the cell and the cytoplasm. Two proteins, CheW and CheA, form a complex with MCP when a ligand is bound to the receptor†. When bound to the complex, CheA serves as kinase for two additional proteins, CheB and CheY. The phosphorylated form of CheY then binds to the motor complex, causing clockwise rotation of the motor. **RMM**: check

Several other elements are contained in the chemotaxis control circuit. The most important of these are implemented by the proteins CheR and CheB, both of which affect the receptor complex. [**?**], which is constitutively produced in the cell, methylates the receptor complex at a number of different methylation sites. Conversely, the phosphorylated form of CheB demethylates the receptor complex. The methylation patterns of the receptor complex affect the activity of CheA, the kinase for

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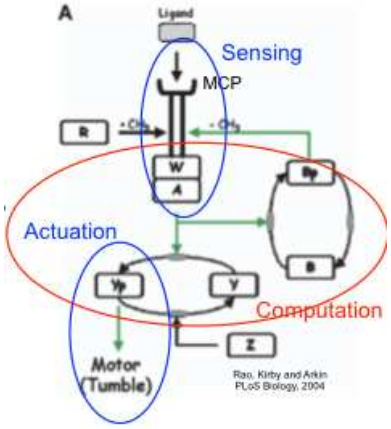

Figure 5.7: Control system for chemotaxis. Figure from Rao *et al*. [36] (Figure 1A).

both CheY and CheB. The more methylated the complex, the more active CheA is. We see that the combination of CheA, CheB and the methylation of the receptor complex forms a negative feedback loop: if the receptor is active, then CheA phosphorylates CheB, which in turn demethylates the receptor complex, making it less active. As we shall see when we investigate the detailed dynamics, this feedback loop corresponds to an integral feedback law. This integral action allows the cell to adjust to different levels of ligand concentration, so that the behavior of the system is invariant to the absolute nutrient levels (this is explained in more detail below).

Modeling

The detailed reactions that implement chemotaxis are illustrated in Figure **??**. Letting T represent the receptor complex and T^A represent the active form (described in more detailed form below), the basic reactions can be written as

$$T^A + A \rightleftharpoons T^A{:}A \longrightarrow A^p + T^A \qquad A^p + P \rightleftharpoons A^p{:}P \longrightarrow A + P$$
$$A^p + B \rightleftharpoons A^p{:}B \longrightarrow A^p + B^p \qquad B^p + P \rightleftharpoons B^p{:}P \longrightarrow B + P$$
$$A^p + Y \rightleftharpoons A^p{:}Y \longrightarrow A^p + Y^p \qquad Y^p + Z \rightleftharpoons Y^p{:}P \longrightarrow Y + P$$

where CheA, CheB, CheY and CheZ are written simply as A, B, Y and Z for simplicity and *P* is a non-specific phosphotase. We see that these are basically three phosphorylation/dephosphorylation reactions that are linked together.

The description of the methylation of the receptor complex is a bit more complicated. Each receptor complex can have multiple methyl groups attached and the activity of the receptor complex depends on the amount of methylation and whether a ligand is attached to the receptor site. To capture this, we use the set of reactions that are illustrated in Figure 5.9. In this diagram, T_i^s represents a receptor that has

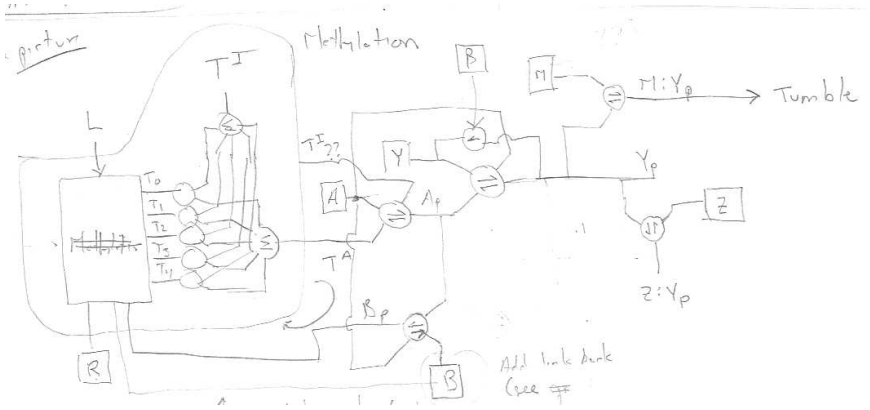

Figure 5.8: Circuit diagram for chemotaxis.

s methylation sites filled) and ligand state i (which can be either u if unoccupied or o if occupied). We let M represent the maximum number of methylation sites.

Using this notation, the transitions between the states correspond to the reactions shown in Figures 5.7 and 5.8:

$$\begin{aligned} &T_i^x + B^p \rightleftharpoons T_i^x{:}B^p \longrightarrow T_{i-1}^x + B^p && i > 0 \\ &T_i^x + R \rightleftharpoons T_i^x{:}R \longrightarrow T_{i+1}^x + R && i < M \\ &T_i^u + L \rightleftharpoons T_i^o \end{aligned}$$

We now must write reactions for each of the receptor complexes with CheA. Each form of the receptor complex has a different activity level and so the most complete description is to write a separate reaction for each T_i^o and T_i^u species:

$$T_i^x + A \underset{k_i^{r,o}}{\overset{k_i^{f,o}}{\rightleftharpoons}} T_i^x{:}A \xrightarrow{k_i^{c,o}} A^p + T_i^x,$$

where $x \in \{o, u\}$ and $i = 0, \ldots, M$. This reaction replaces the placeholder reaction $T^A + A \rightleftharpoons T^A{:}A \longrightarrow A^p + T^A$ used earlier.

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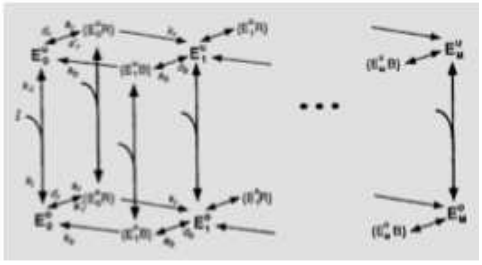

Figure 5.9: Methylation model for chemotaxis. Figure from Barkai and Leibler [8] (Box 1).

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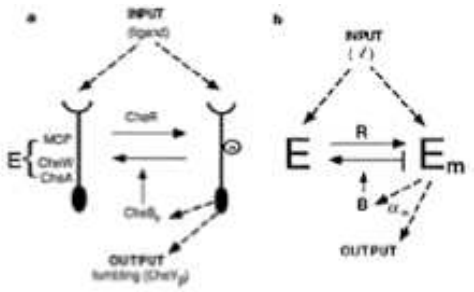


Figure 5.10: Reduced-order model for chemotaxis. Figure from Barkai and Leibler [8] (Figure 1).

RMM Include simulation results on the full model here

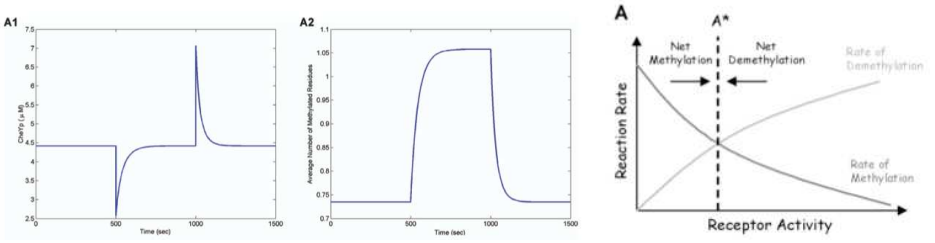
While the equations above give a fairly complete description of the reactions that implement the chemotaxis control circuit, there are still many missing effects.

RMM Summarize some of the main features that are missing.

Reduced-order model

The detailed model described here is sufficiently complicated that it can be difficult to analyze. A much simpler model is possible by simplifying the representation of the receptor complex and its methylation pattern. We can do this by modeling the entire receptor complex as a single species T that exists in an active state T^A and an inactive state T^I. We then keep track of the total methylation M, which is modulated by CheR and CheB, and use this to modulate the amount of active and inactive receptor complex, as shown in Figure 5.10.

RMM Figure out Barkai, Leibler paper and summarize here (including simulations).



(a) (b)

Figure 5.11: Simulation and analysis of reduced-order chemotaxis model. Figure from Rao *et al*. [36] (Figures 4 and 5).

Integral action

Further reading

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