1) CheW is a docking protein
2) CheA is an autophosphorilating kinase (wasteful cycle)
3) CheA-P passes P to CheY and CheB
4) CheY-P diffuses, binds to the motor, CCW → CW. (~ 0.1 sec)
5) CheZ dephosphorilates CheY-P
6) Methylation increases ability to phosphorilate CheA
7) CheR transfers methyl groups to the receptor
8) CheB-P demethylates the receptor (~ 10 sec – 10 min)

MCP = methyl-accepting chemotactic protein

Conformational change

control of Flagellar Motor

4 methylation sites at each α-helix; 8 - total
An idea: CheR methylates only inactive receptor; CheB de-methyl only active receptor. This is the so called *robust* model.

Exact adaptation!
M(t) (methylated, inactive)

I(t) (not methylated, rA inactive)

A(t) (methylated, active)

\[ x = A, \quad y = M + A, \quad k = r + d + a \]

\[ \frac{dx}{dt} = ay - kx \]

\[ \frac{dy}{dt} = m - rx \]

\[ \frac{dM}{dt} = m + (dA - aM) \]

\[ \frac{dA}{dt} = -rA + (aM - dA) \]
\[
\begin{align*}
\frac{dy}{dt} &= m - rx, \quad m - rx = 0, \quad x = m/r \\
\frac{dx}{dt} &= ay - kx, \quad ay - kx = 0, \quad y = kx / a = \left(1 + \frac{d + r}{a(s)}\right)x
\end{align*}
\]

\[
x = \frac{m}{r}, \quad y = \left(1 + \frac{d + r}{a(s)}\right)m/r
\]

Exact adaptation:
steady state number of active receptors, 
\(x(A)\), d.n. depend on the signal \(s\), while the number of methylated receptors, 
\(y\), depends on \(s\).
Why is adaptation needed? For time $\sim 1/r$, the cell has memory: it compares the conditions at $\sim t-1/r$ with the current situation at $t$. Swimming up the gradient:

\begin{align*}
\frac{dy}{dt} &= m - rx, \quad a = a_0 - gt, \quad d >> a_0 >> m, r \\
\frac{dx}{dt} &= ay - kx, \quad k = r + d + a \approx d \\
\frac{dy}{dt} &= m - rx, \quad a_0 >> gt, \quad d/a_0 >> r \\
\frac{dx}{dt} &= (a_0 - gt)y - dx, \\
x &\approx \frac{m}{r} - \delta, \quad \frac{dy}{dt} \approx r\delta, \quad y \approx \frac{dm}{a_0r} + r\delta t, \\
\delta &\approx \frac{mg}{a_0r}, \quad y \approx \frac{dm}{a_0r} + \frac{mg}{a_0} t
\end{align*}

$r$ has to be small – memory has to be long. But not too long!
Another problem: hydrodynamics (it takes a while for chemicals to diffuse to the cell surface through the boundary layer).

The devil was always in the detail. But as we accumulate more and more quantitative data on living cells, those diabolical details become increasingly finicky and numerical. Small differences that we would have cheerfully disregarded a decade ago as being due to “experimental error” or “differences in technique” suddenly become crucial – the nub of debate if not controversy. Sometime, even, they reveal cracks in the smooth surface of current dogma and hint at unexplored levels beneath.

*Dennis Bray, 2002*
Attractant, $s$

$$s = s_0 e^{\lambda t}$$

Tumbling bias

$$s + R \underset{k_-}{\overset{k_+}{\longleftrightarrow}} R^*$$

$$\frac{dR^*}{dr} = -k_- R^* + k_+ s R = 0, \quad k_- R^* = k_+ s (\bar{R} - R^*), \quad R^* = \frac{k_+ s \bar{R}}{k_- + k_+ s}$$

$$\frac{\bar{R}}{R} = \frac{s}{K_D + s}, \quad K_D = \frac{k_-}{k_+} \quad \text{(Michaelis-Menten kinetics)}$$

Bias $\sim \frac{d}{dt} \left( \frac{R^*}{\bar{R}} \right) = \frac{K_D}{(K_D + s)^2} \frac{ds}{dt} = \frac{K_D s}{(K_D + s)^2} \left( \frac{1}{s} \frac{ds}{dt} \right) = \frac{K_D s}{(K_D + s)^2} \frac{d}{dt} (\ln s) = \frac{\lambda K_D s}{(K_D + s)^2}$
\[ \frac{\partial R_+}{\partial t} + v \frac{\partial R_+}{\partial x} = + \left( k_- R_-^* - k_+ sR_+ \right) + \left( \sigma^- R_- - \sigma^+ R_+ \right) \]

\[ \frac{\partial R^*}{\partial t} + v \frac{\partial R^*}{\partial x} = - \left( k_- R_-^* - k_+ sR_+ \right) + \left( \sigma^- R_- - \sigma^+ R_+ \right) \]

\[ \frac{\partial R_-}{\partial t} - v \frac{\partial R_-}{\partial x} = + \left( k_- R_-^* - k_+ sR_+ \right) - \left( \sigma^- R_- - \sigma^+ R_+ \right) \]

\[ \frac{\partial R^*}{\partial t} - v \frac{\partial R^*}{\partial x} = - \left( k_- R_-^* - k_+ sR_+ \right) - \left( \sigma^- R_- - \sigma^+ R_+ \right) \]

\[ \sigma^- = \sigma_0, \quad \sigma^+ = \sigma_0 - \kappa v \frac{\partial}{\partial x} \left( \frac{R^*_+}{R_+ + R^*_+} \right), \quad s(x) = s + \varepsilon g x \]

\[ \varepsilon \ll 1: \text{signal changes in space slowly compared to the mean run length} \]

\[ R_+ + R_-^* = b_+, R^- + R^*_+ = b_- \]

\[ b = b_+ + b_-, J = v \left( b_+ - b_- \right) \]

\[ \frac{\partial b}{\partial t} = - \frac{\partial J}{\partial x} \]

\[ \frac{\partial}{\partial t} \left( \frac{J}{v} \right) + \frac{J}{v} \left( \sigma_+ + \sigma_- \right) = -v \frac{\partial b}{\partial x} - b \left( \sigma_+ - \sigma_- \right) \]
$X = \varepsilon x, T = \varepsilon^2 t$ - “large” spatial scale and “slow” time scale

$b_+ - b_- = \varepsilon j, J = \varepsilon v j,$

$\sigma^+ = \sigma_0 + 2\varepsilon a, a = \frac{1}{2} \frac{\partial}{\partial X} \left( \frac{R^*_+}{R_+ + R^*_+} (\varepsilon = 0) \right)$

$\sigma^+ = \sigma_0 + 2\varepsilon a, a = \frac{\kappa}{2} \frac{\partial}{\partial X} \left( \frac{R^*_+}{R_+ + R^*_+} (\varepsilon = 0) \right)$

$\varepsilon^2 \frac{\partial}{\partial T} (\varepsilon j) + \varepsilon \frac{\partial}{\partial X} (\varepsilon v b) = -b (2\varepsilon a) - \varepsilon j (2\sigma_0)$

$j = -\frac{a}{\sigma_0} b - \frac{\partial}{\partial X} \left( \frac{v}{2\sigma_0} b \right)$

What happens in steep and noisy gradients is still an open problem