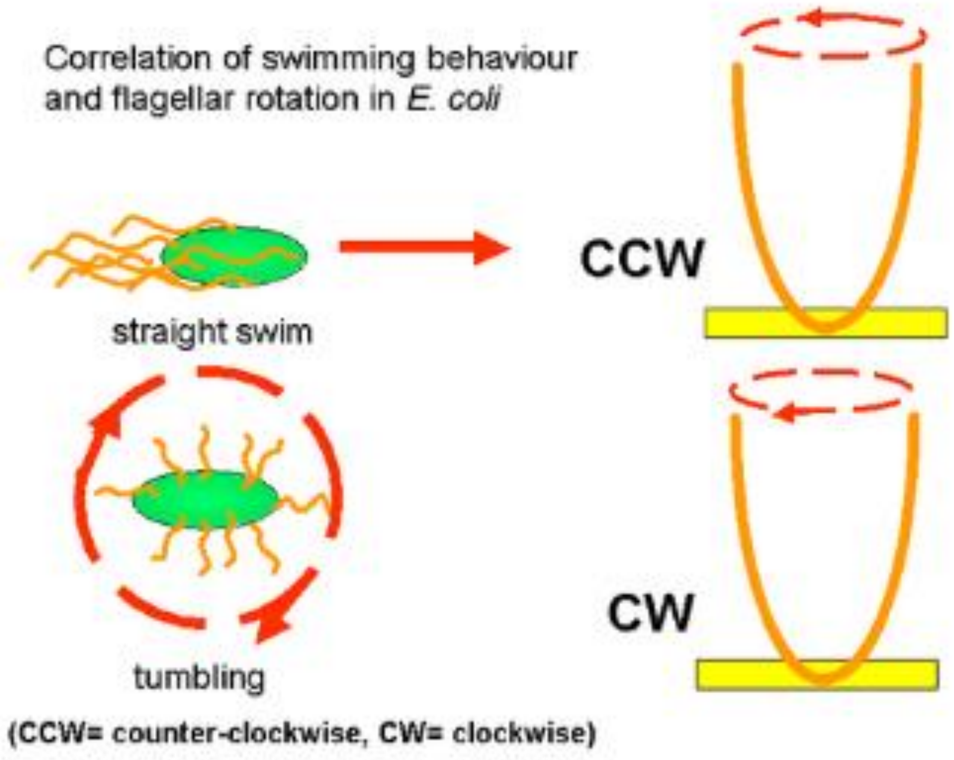
Signalling for Bacterial Chemotaxis

Bacterial chemotaxis

- Bacterial chemotaxis is a process where bacteria move directionally in response to chemical stimuli in their environment.
- Such behavior enables them to navigate toward favorable conditions, such as areas rich in nutrients, and away from toxic substances.
- The mechanism involves receptor proteins on the bacterial surface detecting chemical signals, which then trigger changes in the rotation of their flagella, resulting in movement.
- This sophisticated navigation system is crucial for bacterial survival, adaptation, and pathogenicity, allowing them to effectively respond to environmental changes and optimize their living conditions.
- Understanding bacterial chemotaxis provides insights into microbial behavior and potential therapeutic targets.
- *Positive* chemotaxis occurs if the movement is toward a higher concentration of the chemical in question; *negative* chemotaxis if the movement is in the opposite direction.
- Chemically prompted kinesis (randomly directed or nondirectional) can be called chemokinesis.

Bacterial chemotaxis

- Some bacteria, such as *E. coli*, have several flagella per cell (4–10 typically). These can rotate in two ways:
    - Counter-clockwise rotation aligns the flagella into a single rotating bundle, causing the bacterium to swim in a straight line; and
    - Clockwise rotation breaks the flagella bundle apart such that each flagellum points in a different direction, causing the bacterium to tumble in place.
- The overall movement of a bacterium is the result of alternating tumble and swim phases, called [run-and-tumble motion].
- As a result, the trajectory of a bacterium swimming in a uniform environment will form a biased [random walk] with relatively straight swims interrupted by random tumbles that reorient the bacterium.
- By repeatedly evaluating their course, and adjusting if they are moving in the wrong direction, bacteria can direct their random walk motion toward favorable locations.



- In the presence of a chemical gradient bacteria will chemotax, or direct their overall motion based on the gradient.
- If the bacterium senses that it is moving in the correct direction (toward attractant/away from repellent), it will keep swimming in a straight line for a longer time before tumbling; however, if it is moving in the wrong direction, it will tumble sooner.
- Peritrichous bacteria such as *Escherichia coli* use temporal sensing to decide whether their situation is improving or not, and in this way, find the location with the highest concentration of attractant, detecting even small differences in concentration.
- *Salmonella typhimurium* can also behave in this way, and also lophotrichous flagellated bacteria such as *Pseudomonas putida*, can actively influence the angular change between their swimming phases.
- As a result the swimming direction is biased in the direction of a better environmental condition for the bacteria.

Mechanism of Bacterial Chemotaxis

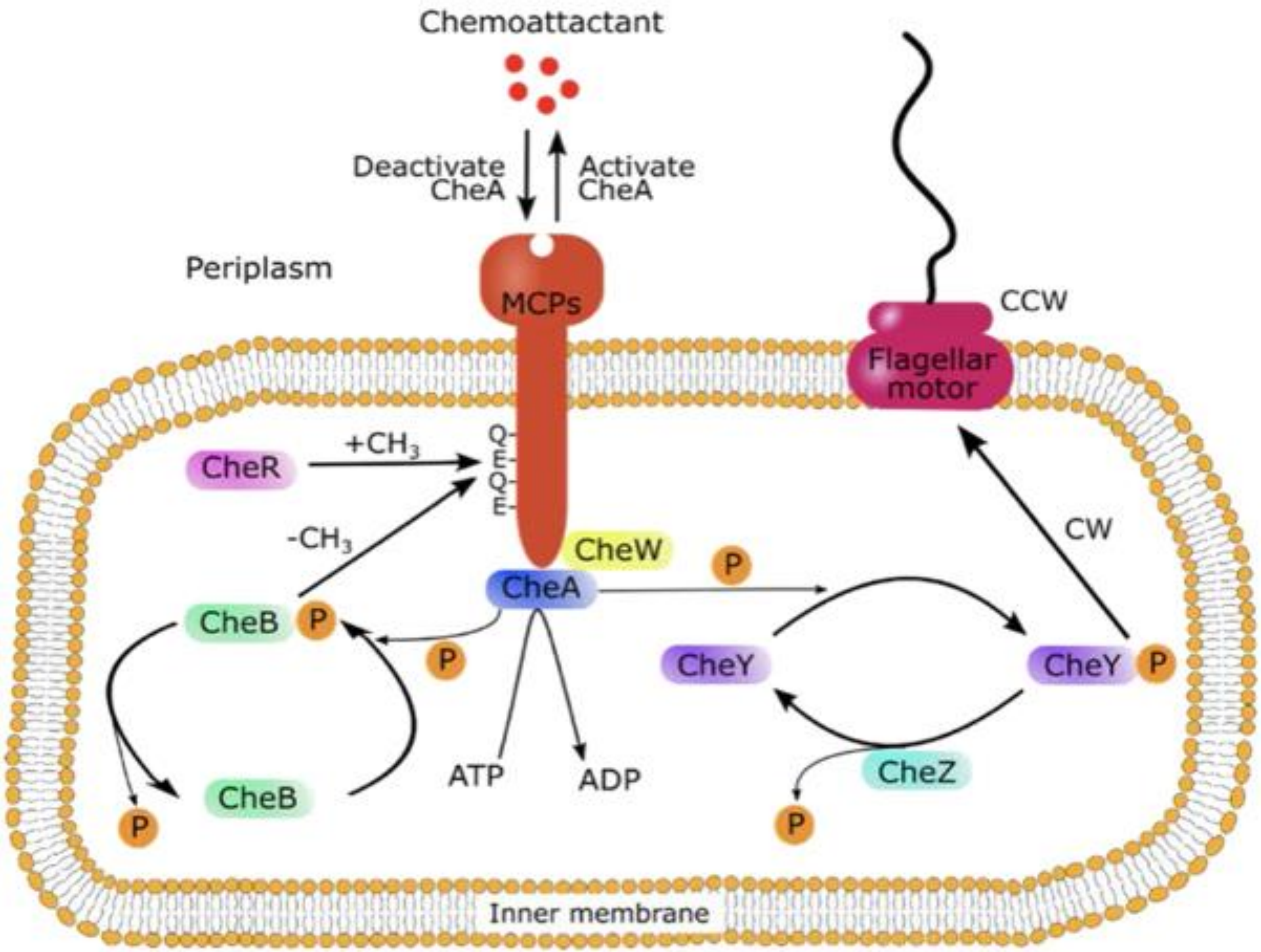
- **Chemical Signal Detection:** Bacteria detect chemical gradients using specialized receptor proteins called chemoreceptors on their cell surface.
- **Signal Transduction Pathway:** Chemoreceptors transmit signals to the inside of the cell, initiating a signal transduction pathway involving a series of proteins and enzymes.
- **Phosphorylation Cascade:** The signal transduction pathway typically involves a phosphorylation cascade, where phosphate groups are transferred between proteins, amplifying the signal.
- **Flagellar Motor Control:** The signal transduction affects the rotation of the bacterial flagella, which act as propellers for movement.
- **Tumbling and Running:** Bacteria alternate between "running" (smooth swimming in a straight line) and "tumbling" (random reorientation), controlled by changes in flagellar rotation.
- **Bias in Movement:** Chemotactic signals bias the frequency of tumbling, allowing bacteria to move more effectively toward attractants or away from repellents.
- **Role of Methyl-Accepting Chemotaxis Proteins (MCPs):** MCPs are key chemoreceptors involved in detecting chemical gradients and initiating the chemotactic response.

Signal transduction

- Chemical gradients are sensed through multiple transmembrane receptors, called methyl-accepting chemotaxis proteins (MCPs), which vary in the molecules that they detect.
- Thousands of MCP receptors are known to be encoded across the bacterial kingdom.
- These receptors may bind attractants or repellents directly or indirectly through interaction with proteins of periplasmatic space.
- The signals from these receptors are transmitted across the plasma membrane into the cytosol, where *Che proteins* are activated.
- The Che proteins alter the tumbling frequency, and alter the receptors.

- The study of chemotaxis pathways has historically largely been conducted in the model organism *Escherichia coli*, owing to its relative tractability in terms of the number of signaling components.
- Briefly, the signaling state of a chemoreceptor is altered through the binding of chemoeffectors. The absence of receptor activation results in the autophosphorylation in the histidine kinase, CheA, at a single highly conserved histidine residue.
- CheW is required for the functional coupling between receptors and CheA. Upon activation, CheA transfers a phosphoryl group from bound ATP to the response regulator CheY to conserved aspartate residues, which in turn becomes activated (CheY-P) and can bind to the flagellar motor by interacting with the flagellar switch protein FliM to alter its direction of rotation (inducing a change from counter-clockwise to clockwise rotation of the flagellum. Change in the rotation state of a single flagellum can disrupt the entire flagella bundle and cause a tumble).
- The direction of motor rotation determines whether the cell ‘runs’ (swims straight) or ‘tumbles’ (changes to a new, random direction).
- Thus, by controlling the relative amount of CheY-P through the receptor-mediated regulation of CheA activity, environmental chemical information is coupled to the swimming pattern of the cell.

- The CheA signal is eventually terminated by the removal of phosphate groups from CheY-P by CheZ.
- Additionally, an adaptation system is provided by CheR and CheB, which add and remove methyl groups from glutamate residues on the cytosolic side, respectively, at specific sites on the receptor to tune its response to ligand binding.
- The MCPs no longer respond to the attractant when they are fully methylated; therefore, even though the level of attractant might remain high, the level of CheA-P (and CheB-P) increases and the cell begins to tumble.
- An increase in receptor methylation increases CheA autophosphorylation and vice versa.
- Although CheR is constitutively active, the rate at which CheB removes methyl groups is increased by phosphorylated via CheA, giving rise to a negative feedback loop that resets the pathway to baseline activity.



Chemoattractant
Deactivate CheA
Activate CheA
Periplasm
MCPs
CCW
Flagellar motor
Q-
E-
Q-
E-
CheR
$+CH_3$
$-CH_3$
CheW
CheA
P
CW
CheB
P
P
CheY
CheY
P
CheB
ATP
ADP
CheZ
P
P
Inner membrane

Protein tyrosine phosphatases (PTPs)

- Protein tyrosine phosphatases (PTPs) form a large family of enzymes that serve as key regulatory components in signal transduction pathways.
- Defective or inappropriate regulation of PTP activity leads to aberrant tyrosine phosphorylation, which contributes to the development of many human diseases.
- The human genome encodes approximately 100 phosphatases that belong to the protein tyrosine phosphatase (PTP) superfamily, whose substrates range from proteins to phosphoinositides and mRNAs.
- The hallmark for this superfamily is the active site sequence C(X)5R, also known as the PTP signature motif.
- In addition to controlling the phosphorylation states of protein kinase substrates, PTPs can also directly modulate protein kinase activity.

PTPs are classified based on their structure and catalytic mechanism into the following major groups:

- **Classical PTPs:**
  - Specifically act on phosphotyrosine residues.
  - Include both **receptor-type PTPs** (e.g., CD45, PTPα) and **non-receptor-type PTPs** (e.g., PTP1B, SHP1, SHP2).
  - Receptor-type PTPs have extracellular, transmembrane, and intracellular catalytic domains.
- **Dual-specificity Phosphatases (DSPs):**
  - Can dephosphorylate both phosphotyrosine and phosphoserine/threonine residues.
  - Include MAP kinase phosphatases (MKPs) which regulate MAPK signaling pathways.
- **Low Molecular Weight PTPs:**
  - Smaller enzymes involved in cell signaling and cytoskeletal organization.
- **CDC25 Phosphatases:**
  - Regulate the cell cycle by activating cyclin-dependent kinases (CDKs).

Catlytic Mechanism:

- The **active site** of PTPs contains a highly conserved **Cys-X_5-Arg** motif.
- The cysteine residue acts as a nucleophile that attacks the phosphorus atom of the substrate, forming a phospho-cysteine intermediate.
- Hydrolysis of this intermediate releases free phosphate and regenerates the active enzyme.