Bacterial Information Processing: Is It Cognition?

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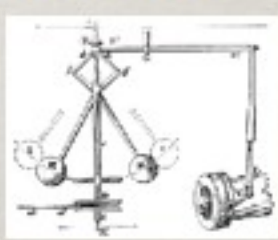
Bacteriologists are Invoking the Language of Cognition

- Shapiro (2007): "the term cognitive refers to processes of acquiring and organizing sensory inputs so that they can serve as guides to successful action. The cognitive approach emphasizes the role of information gathering in regulating cellular function."
- Cognition in a social context: "As a member of a complex superorganism—the colony—each unit (bacteria) must possess the ability to sense and communicate with the other units comprising the collective and perform its task within a distribution of tasks. Bacterial communication thus entails collective sensing and cooperativity. The fundamental (primitive) elements of cognition in such systems include interpretation of (chemical) messages, distinction between internal and external information, and some self vs. non-self distinction (peers and cheaters)." (Ben Jacob, Shapira, and Tauber, 2006).

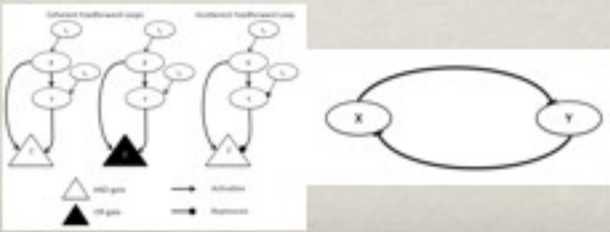
What is Required for Information Processing/Cognition

- Representations that carry information in formats that can be employed for further processing and ultimately to regulate behavior
- Operations that use those representations to regulate other operations (including behavior activities of the organism)
- Information processing is characteristically performed in control systems, even very simple ones such as the governor for the steam engine invented by James Watt



How Do Bacteria Compute?

- Regulatory networks
  - Gene regulatory networks through which expression of different genes is regulated (e.g., by an activator binding to the promoter of the gene)
  - Protein interaction networks through which proteins bind with each other, altering their capacity to bind with other molecules, including DNA, and their enzymatic activity
- Motifs: Starting with the efforts in the late 1990s of Uri Alon and his collaborators, researchers have identified a number of basic modes of organization used to process information in gene, protein, and neural networks



Outline

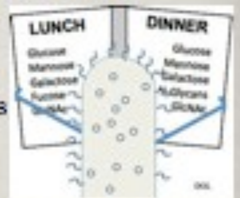
1. **Regulating Metabolism: The lac operon**
2. Regulating Behavior: Chemotaxis
3. Organisms Regulating Their Own Genes
   1. Genome Repair
   2. Natural Genetic Engineering
   3. Lateral Gene Transfer
   4. Circadian Timing
4. Coordinating Social Behavior: Quorum Sensing
5. Conclusion: Are Bacteria Cognitive?

Necessary Capacities of Living Organisms

- Self maintenance
  - Organisms persist as organized systems in the face of the tendency of physical processes to produce equilibrium (death)
    - Requires procuring energy from the environment (engine) and deploying it in the maintenance of the living system (pump)
- Self maintenance often requires self repair--rebuilding the organisms' own structures
- Importance of the boundary (membrane, skin)
  - By generating a different environment inside than outside the cell it creates the conditions for needed chemical reactions
  - By regulating the what molecules are are brought into or expelled from the internal environment the cell can regulate its chemical reactions

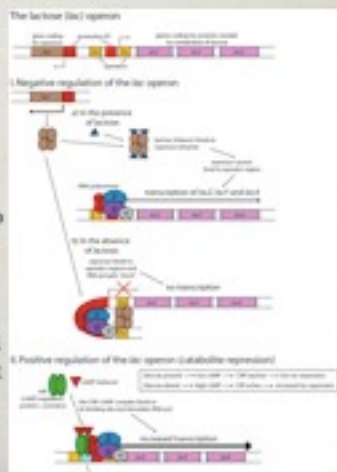
Regulating Life's Machinery

- In his dissertation Monod (1942) showed that *E. coli* showed preferences between sugars and would consume all of a preferred sugar (simpler to digest) before consuming any of the less preferred, more complex sugars
  - Somehow, bacteria recognize and alter their metabolism when different sugars are present
- The quest for the mechanism led to the discovery of the *lac operon* that employs the following logic in regulating the lactose metabolism system:
  - Transcribe and translate the genes needed for metabolizing lactose only when glucose is not present and lactose is present



Lac Operon

- Transcription of the genes required for metabolizing lactose (*lacZ*, *lacY*, and *lacA*) is regulated by a promoter site
- When lactose is not present, LacI, synthesized from a site upstream, binds to the promoter site and blocks transcription
- But when lactose is present, it binds to LacI, disinhibiting transcription of the lactose genes
- However, transcription remains weak when cAMP is in low concentration, indicating glucose is being metabolized
- When cAMP is in high concentration, it together with CRP binds to the promoter, resulting in high transcription of lactose genes



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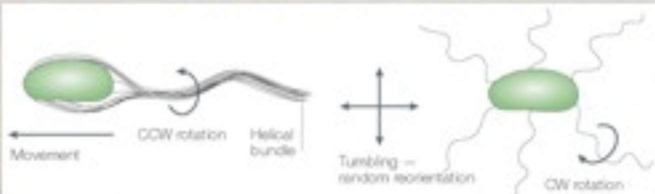
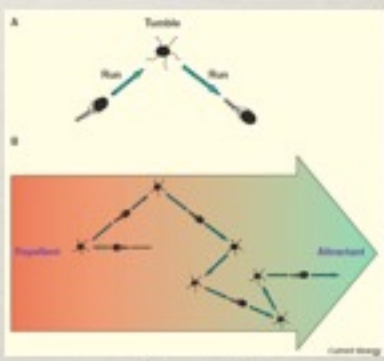
Moving About with a Flagellum

- Bacteria such as *E. coli* have a complex motor--flagellum--that enables them to move about their environment
  - Running behavior when each filament rotates counter clockwise, causing the individual filaments to form a bundle
  - Tumbling episodes occur when one or more filaments rotates clockwise
    - Tumbling episodes last about 0.1 seconds and reorient the bacterium on average about 60°
- Bacteria move so as to procure food and avoid toxins
  - Challenge: how to use such a mechanism to achieve these goals?



Controlling Flagellar Navigation: Chemotaxis

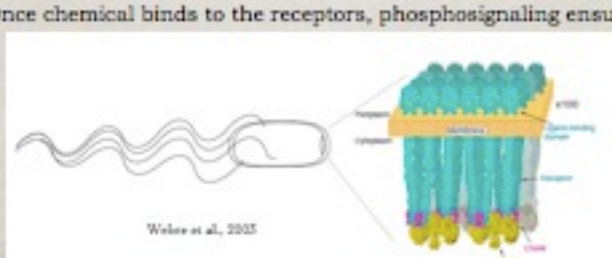
- Strategy: prolong runs when moving toward food or away from toxin
- Needs a sensory system
  - Example: sense glucose gradient
- Used not just for glucose gradients: find nutrients more generally, avoid toxic chemicals, respond to pH, light, temperature, electricity, or magnetism
- Also used to regulate symbiotic or pathogenetic interactions with other organisms



Webre et al., 2003

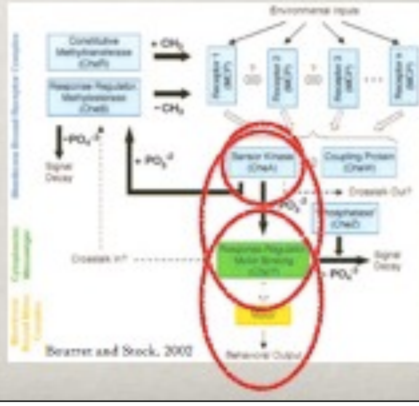
Sensing the Environment

- What a bacterium needs is information about whether the concentration of a substance is increasing or decreasing
  - Since bacteria are too short to directly detect gradients, they must compare concentrations over time
    - If the gradient is changing in the desired direction, increase probability of flagellum action
- *E. coli* has five types of receptors (transmembrane proteins), although other species have as many as 40
  - Once chemical binds to the receptors, phosphosignaling ensues



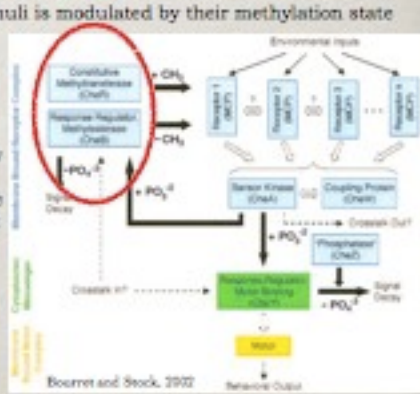
Processing Sensory Information

- The receptors (methylated chemotaxis proteins) share a signaling domain that phosphorylates or dephosphorylates the sensor kinase CheA
- CheA is a kinase that phosphorylates response regulator CheY
- CheY diffuses through the cytoplasm and when phosphorylated is able to bind to FliM, a flagellum protein that causes the motor to rotate clockwise (tumble)
  - Otherwise the motor rotates counterclockwise



Detecting a Gradient

- To detect a gradient, the bacterium must alter the response of its sensors depending on its recent experience
- Ability of receptors to respond to stimuli is modulated by their methylation state
  - Constitutively methylated by CheR
  - Demethylated by CheB when it is phosphorylated by the sensory kinase CheA
    - The methylation process is slow relative to response regulator response, thereby rendering the receptors' sensitivity dependent on previous stimuli (memory)
- Concentrations of stimuli may vary over five orders of magnitude
  - As a result of a non-linear response function (due to a Hill coefficient of 10 or more), the response behaves in accord with Weber's Law

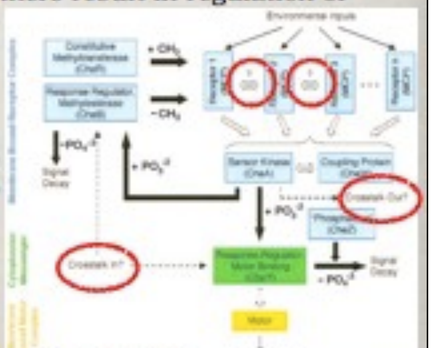


Complexity of the Sensory System

- Approximately 10,000 MCPs are clustered in an assembly at one pole of the cell.
- There are four methylation sites on each MCP, resulting in 16 possible methylation states
  - This generates the potential for huge variability in the responses of individual bacteria
- Stock and colleagues have dubbed the receptor assembly and response regulator a *nanobrain*.

Coordinating Responses

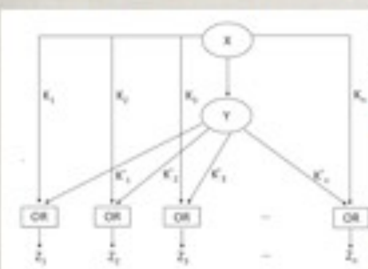
- Remember, motor activity is not the only output of the chemotaxis system (many others result in regulation of gene expression)
  - Note the question marks in the diagram
  - There is suggestive evidence of crosstalk, i.e., integration of information between different sensor kinases that may affect the response regulators as well as the methylation of the receptors

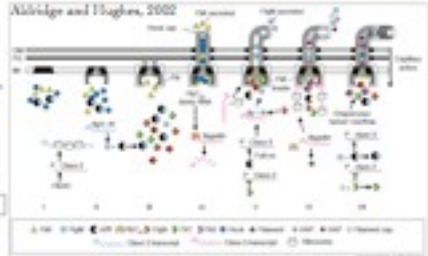


Bourret and Stock, 2002

Construction of the Flagellum

- Constructing the flagellum is itself a complex engineering task
  - Built from the membrane out with many different kinds of components
  - Since it is materially and energetically costly to build, a control mechanism is employed that generates each components just when needed and then shuts down
    - A modification of the feedforward loop identified by Alon





Aldridge and Hughes, 2002

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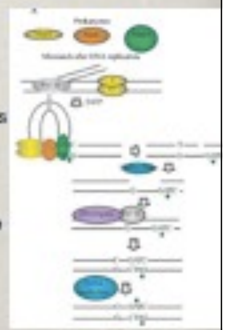
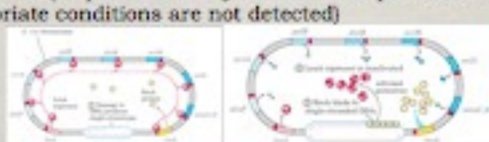
Achieving Reliable Replication Via Error Prone Operations

- *E. coli* duplicates its 4.6 million base-pair genome in 40 minutes, but makes about one mistake for every 100,000 nucleotides
- Reliable transmission thus requires error correction
- Two error detection and correction systems in DNA replication
  - Exonuclease proofreading:
    - When an incorrect nucleotide is incorporated, mispairing distorts the structure of the growing double helix
    - The polymerase senses the distortion and interrupts polymerization while the incorrect base is removed
  - Methyl-directed mismatch repair:
    - MutS binds to distorted regions of the double helix
    - MutL recognizes the bound MutS and connects it to MutH
    - MutH differentiates the newly formed strand and cleaves it, allowing other proteins to excise and replace the strand

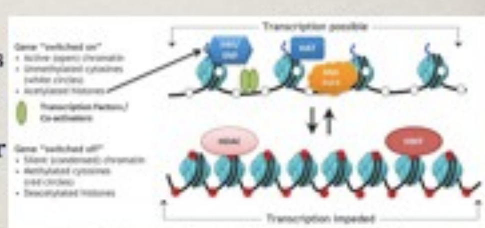


DNA Damage Repair and the SOS Response

- Two-step process
  - Detection of characteristic features of UV damage and excision of the damaged strand
  - Mutagenic process in which error-prone DNA polymerases are created to create new mutations
- Synthesis of proteins that promote homologous recombination, halt cell division, alter cell metabolism, inhibit normal DNA replication, and stimulate exit from the SOS state
  - Ex: Single stranded DNA is detected by RecA, LexA repressor is deactivated, and cell division is halted by SulA through action at a checkpoint (step in the cell cycle where the process can be stopped if appropriate conditions are not detected)



Chromatin Remodeling



http://en.wikipedia.org/wiki/File:Luong_LD_SA_F2.jpg

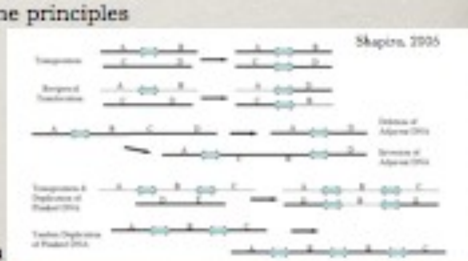
- One mechanism by which gene activity is regulated is through the modification of chromatin that either opens up the structure to allow transcription factors to bind to the DNA or close it up so as to block access
- Although most studied in eukaryotes, examples are increasingly being identified in bacteria

Natural Genetic Engineering

- Traditional view (Crick's central dogma)--genome is a read-only memory
  - Modified only by random (non-directed) processes of mutation and recombination
- Ironically, the very study that pointed to DNA as the genetic material (Avery et al., 1944) showed the ability of bacteria to incorporate and express exogenous DNA
- Evidence is increasing that the genome is a read-write system
  - Writing employs proteins that cut, unwind, polymerize, anneal, and spice DNA strands
- Moreover, these processes are under the control of the organism, not random events
- Shapiro (1992) labeled these processes "natural genetic engineering"

DNA Units for Engineering

- Designers do not start from scratch for each project
  - Rather, they adapt designs previously developed
  - This process is aided by developing modules that can easily be employed (and perhaps modified) within new designs
- Biology has adopted the same principles
  - DNA transposons and cassettes--defined DNA segments--are units that can be moved between sites
    - Target sites often selected by recognition proteins
    - Movement is often from sites where the genes are silenced to ones where they are expressed expressed or vice versa

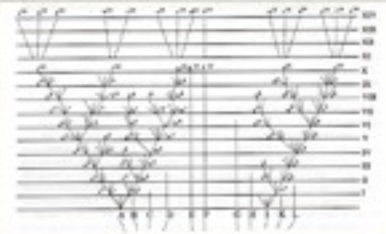


"The war against infectious diseases has been won" (U.S. Surgeon General, 1967)

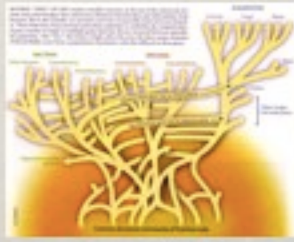
- But someone forgot to tell the bacteria!
  - They have continually found ways to resist our drugs
- The idea was that through normal processes of evolution, bacteria could not produce mutations that could be selected for fast enough to prevent their decimation
- But bacteria employed a different strategy—acquiring transmissible genomic elements (plasmids) that inactivated antibiotics, pumped antibiotic out of the cell, or altered their metabolic targets
  - Horizontal or lateral gene transfer between different lineages (including different orders of life)
  - Integration (via integrons that insert cassettes) and engineering of transferred DNA (e.g., DNA transposition and site-specific recombination)

Lateral Gene Transfer

- The traditional view is that organisms inherit their genes from their parents
  - Foundation for the tree of life metaphor
- The discovery that genes can transfer between organisms has "uprooted the tree of life"

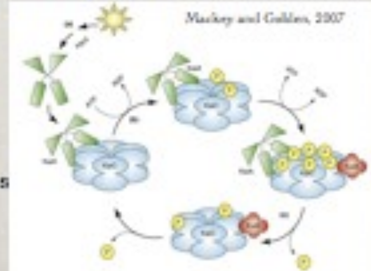


Darwin, 1859, Chapter 4



Regulating Timing of Gene Transcription

- Initially it was not clear why organisms that live less than 24 hours needed to know what time of day it was
- In the late 1990s, however, circadian rhythms were found in cyanobacteria
  - And their utility was also discovered: they allow for segregation of biochemically incompatible operations (those dependent on oxygen and those to which oxygen is a poison)
- Initially the mechanism was assumed to operate in the same manner as those in eukaryotes via a transcription-translation feedback loop
  - But without genes, the Kai proteins suffice for generating circadian oscillations via a phosphorylation-dephosphorylation mechanism



Mackey and Golden, 2007

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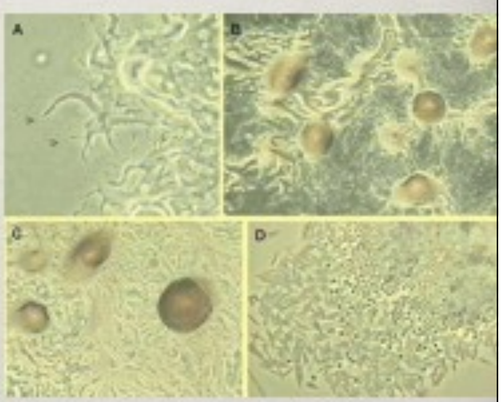
Colony Formation and Behavior

- Bacteria have largely been construed as solitary organisms--even in colonies, each bacterium was assumed to behave solely as an individual, not as part of a collective
  - But this was an artifact of the techniques employed for studying their behavior
- Many species of bacteria self-organize into structured colonies containing from a million to a billion bacteria
  - In these colonies, different bacteria perform different tasks
- Behaviors of individuals such as sporulation depends on integration of information about external conditions, population structure, and internal physiology

Myxobacteria: Exemplar of Social Bacteria

- Soil dwelling bacteria
- A. The edge of a colony of Myxococcus growing on an agar plate, showing slime tracks and a few outlying vegetative cells (arrowheads).
- B, C. Aggregation of vegetative cells to produce fruiting bodies just behind the colony margin shown in A. Figure B shows clearly that the cells are heaped on top of one another near the bases of the fruiting bodies; most of the slime tracks further away from these points contain few or no cells.
- D. Part of a small fruiting body crushed by an overlying cover-clip. The elongated vegetative cells (bottom, left) were near the base of the fruiting body, the fully differentiated myxospores dark spherical bodies) were near the apex of the fruiting body, and cells in the centre of the fruiting body (top right) were in different stages of transition into myxospores.

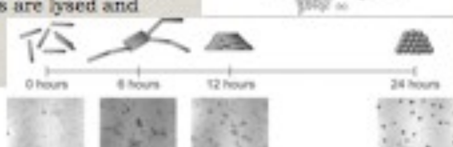


- From http://archive.bio.ed.ac.uk/jdeacon/microbes/myxococ.htm

Myxococcus xanthus

- (a-d) Bacteria emerge from spores when nutrients are available and form a swarm
- (e-f) While food is available, swarms move as predatory collectives gliding over solid surfaces, communally generating extracellular enzymes to lyse and consume prey
  - The bacteria move by pulling themselves with pili and pushing themselves with slime nozzles
  - Every 8-9 minutes they disassemble the pili and reassemble them on the other end
- (g-i) When food is scarce, bacteria begin stress response that involves generating waves, streaming into aggregates (where many cells are lysed and consumed), building a mound, and then creating spores

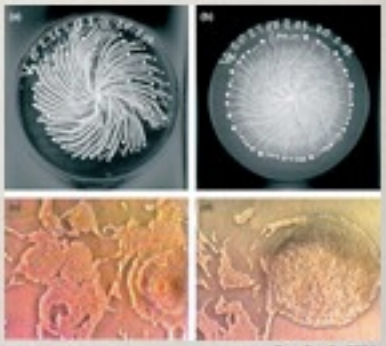
Wu et al., 2011



Tseng et al., 2006

Complex Community Organization

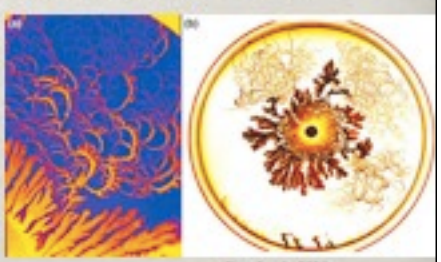
- *Paenibacillus vortex* generates complex community organization involving vortices in which tens to millions of bacteria swim around a common center
  - Vortices expand through active cell division
  - Vortices move outward as a unit, but leave a trail of motile but not dividing cells
  - Dynamics of vortices involve attraction and repulsion of cells, merging and splitting of vortices
  - Individual bacteria adapt their behavior to their situation--requires information
    - Especially true in the formation of new vortices
      - These form in the trail behind a vortex when a signal initiates increased production of lubricating liquid and rapid movement until an eddy forms, leading to a new vortex



Ben Jacob, 2004

Transitioning Between Morphotypes

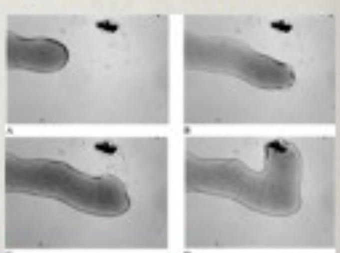
- *Paenibacillus dedritoformis* exhibit two morphotypes: branching and chiral
  - Harder surfaces require more bacteria are needed to produce lubricant, resulting in branching morphotype
  - On softer surfaces, they develop the chiral morphotype that expands faster and, by curling back, takes advantage of food sources left behind
    - This involves suppression of division and elongation, replacing run/tumble movement with back and forth movement (a)
      - This depends on signaling, especially among newly chiral cells
    - In (b) starting population in atypical soft condition, can result in initial abnormal chiral pattern, switch to branching pattern, and finally a synchronized switch to the chiral pattern

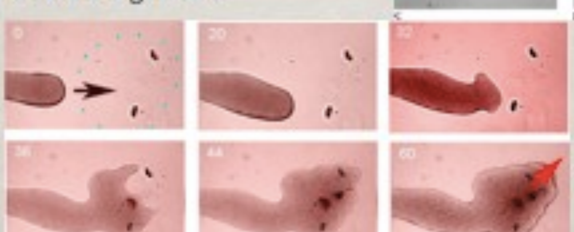


Ben Jacob, 2004

Complex Community Behavior

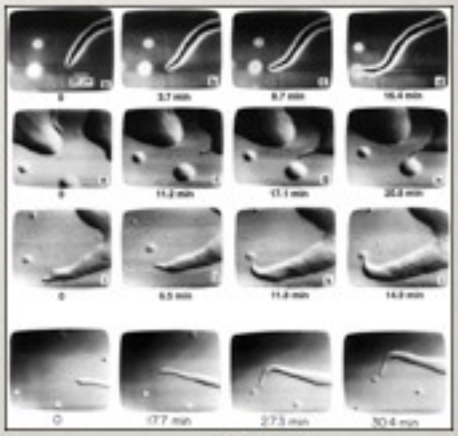
- Moving branch of *Paenibacillus vortex* colony when extracellular material from multiple washings (containing both food and signaling molecules) is placed near the moving tip
  - Collective response due to coordination of responses of individual organisms





Mysterious Motion of Myxococcus xanthus

- Tactic movement of swarms of Myxococcus xanthus toward clumps of Micrococcus luteus.
- Bottom row: tactic movement toward 5-m polystyrene latex beads
- Somehow they perceive objects at a distance without apparently relying on chemical sensors



Dworkin, 1983

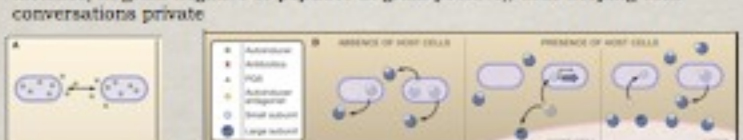
Learning From Experience

- Antibiotic co-trimazole suppresses cell reproduction in *Paenibacillus vortex* colony
  - The bacteria respond by intensifying chemotactic attraction to form larger vortices and increasing repulsive chemotactic responses to signals from bacteria behind the vortex
    - Effect is to move the bacteria away from the locus of the antibiotic
- New colony from original shows better response (learning) when the antibiotic is present
  - This learning is erased if intermediate populations grow in normal conditions

Ben-Jacob et al., 2009

Quorum Sensing

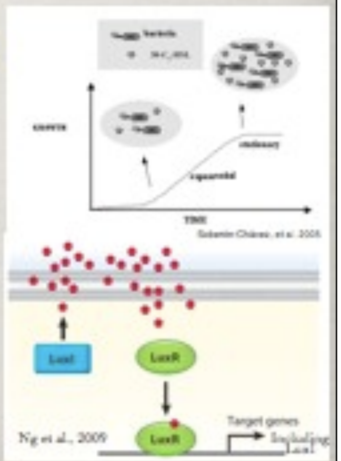
- All of these social activities require some mode of communication between bacteria
  - The most basic and first studied form of such communication is *quorum sensing*
    - Used to determine when a bacterium is part of a population and should perform those activities that only make sense when performed by a large number of individuals (e.g., producing toxins or emitting light)
- Quorum sensing is widespread both within and between bacterial species and between bacteria and eukaryotic hosts
  - Results in altered behavior depending on the number or species present
  - Figures in biofilm formation, swimming, bioluminescence, virulence factor secretion, antibiotic synthesis, and stress responses including sporulation
- Different species produce and detect different molecules (AHLs [Acyl homoserine lactones] in gram negative or peptides in gram positive), thus keeping their conversations private



Bassler and Losick, 2006

Quorum Sensing in Typical Gram Negative Bacteria--Vibrio Fischeri

- *Vibrio Fischeri* colonize the light organ of the squid *Euprymna scolopes*, which uses the bacterial generated light to mask its shadow, while providing an environment rich in nutrients to the bacteria
  - LuxI in individual *V. fischeri* synthesizes Acyl homoserine lactone [AHL] which disperse into the environment where it is picked up by other *V. fischeri*
  - In the recipient bacteria it binds to LuxR and bound LuxR binds to DNA at *lux*-boxes, activating transcription of genes involved in bioluminescence and *luxI*



Soberón-Chávez, et al. 2005

Ng et al., 2009

Vibrio harveyi Quorum Sensing

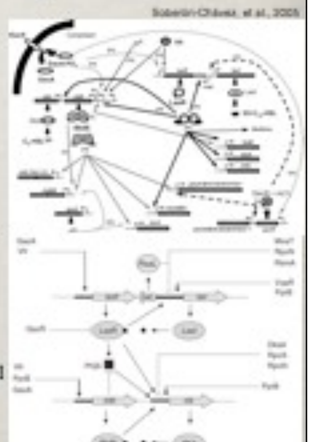
- Gram positive bacteria use peptides as autoinducers
  - Peptides are impermeable to membranes, requiring receptors on the membrane
- Although gram negative, *Vibrio harveyi* exhibits features of gram positive quorum sensing. It is a free living marine bacterium that is a pathogen to many marine organisms
  - Uses quorum sensing to activate bioluminescence and metalloprotease production and repress type III secreition
- It produces and detects three autoinducers (AI—chemical signaling molecules):
  - HAI-1, produced only by *V. Harveyi*
  - CAI-1, produced by other *Vibrio* species
  - AI-2, produced by many bacterial species
- Channeled through a common phosphorelay
  - At low AI concentrations, the three receptors--LuxN (AI-1), LuxPQ (AI-2), and CqsS (CAI-1) function as kinases
    - Through a phosphorylation pathway they together inhibit LuxR, the master quorum-sensing transcriptional regulator
  - At high concentrations, receptors switch to being phosphatases, drain phosphate from LuxU or LuxO, and remove inhibition on LuxR


Waters et al., 2005

More than Density Dependent Quorum Sensing

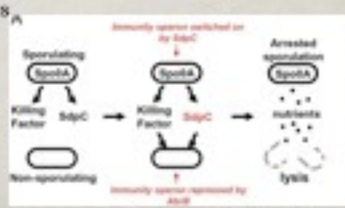
- Complex network in *Pseudomonas aeruginosa*
  - Three response elements (LasR, RhlR, QscR), each with different effects
  - Depending on whether it is bound to C_4-HSL, RhlR acts as either activator or inhibitor
- Many factors, carrying different information about cell conditions (growth phase, alarmones, environmental signals, etc.) influence the transcription of the response elements including:
  - the cAMP receptor regulatory protein Vfr, the stationary-phase sigma factor RpoS, the alternative sigma factor RpoN, the stringent response protein RelA, two LuxR homologues (QscR and VqsR), the posttranscriptional regulators RsmA and DksA, the transcriptional regulatory proteins RsaL and MvaT, and the global two-component regulatory system GacA-GacS

Soberón-Chávez, et al. 2005


Venturi et al., 2006

Coordinated Cannibalism

- Sporulation is a last ditch response
  - When nutrient levels are low, *Bacillus subtilis* forestalls fully committing to sporulation through cannibalism whereby some individuals are sacrificed to feed the others
- When a condition of limited nutrients is detected, in about half the cells Spo0A is activated via a bistable switch involving a positive feedback loop between the gene for Spo0A and genes for proteins that govern its phosphorylation
  - Spo0A-ON cells produce and export a peptide-antibiotic-like killing factor that kills Spo0A-OFF siblings, liberating nutrients that delays final commitment to sporulation in ON cells
  - ON cells also generate a pump that transports the killing factor out of themselves
- Only when no other nutrients are found before all OFF siblings have been sacrificed does sporulation become irreversible

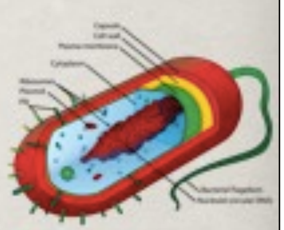


Ellermeier et al., 2006

Aggressive Communication

- In their interactions with eukaryotic cells, bacteria carry out actions that interfere with signaling systems in those cells
  - *Agrobacterium* transfer T-DNA that encodes plant hormones that redirect growth and produce compounds only metabolized by *Agrobacterium*
  - Mammalian pathogenic bacteria inject proteins that
    - interrupt signal transduction and the cytoskeleton of host cells
      - Turning on programmed cell death in lymphocytes
      - Permiting bacterial migration between cells

Conclusion: Are Bacteria Cognitive?



- While relatively simple organisms, bacteria exhibit a variety of behaviors, both individually and collectively
- Performing these activities appropriately to maintain the bacteria requires gathering and processing information about both the internal and external environments
  - This often requires storing information and performing relatively complex integration of information from different sources
- Is this sufficient to treat them as cognitive?
  - If not, what more is required? And Why?

Conclusion: Are Bacteria Cognitive?

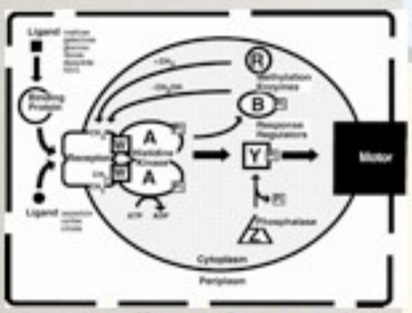
- What is gained by viewing bacteria as cognitive?
  - The value of finding the phylogenetic roots of cognitive abilities
    - Evolution tends to conserve successful traits, replicating them and adapting them to new uses
      - The strategies employed by bacteria are still used by eukaryotic cells and multicellular organisms
    - These traits are often easiest to understand in their earliest development
      - Descent with modification often involves adding complexity, making the basic design less apparent
    - The shortcomings of early evolved traits are also most apparent, focusing attention on what the challenges were that subsequent organisms overcame

Extras

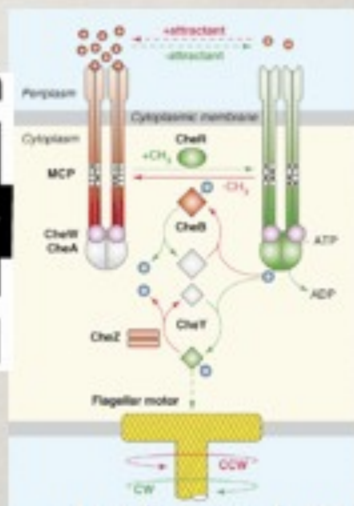
Natural Genetic Engineering Requires Selective Control

- Although the idea of targeting changes in the genome was rejected by orthodox Darwinism, the required mechanisms are widely available
  - DNA-DNA homology or RNA-DNA homology
  - Sequence specific or structure specific binding of proteins to DNA
  - Protein-protein interactions
  - Protein recognition of specific chromatin configurations
- A variety of environmental conditions determine whether natural genetic engineering occurs
  - Under starvation, transposon mediated events increase from <1 in 10^{10} bacteria to >1 in 10^{5}
- Transcription factors
- Two-component signaling networks

- Movement of genes may be under the organism's own control
  - Stress conditions can lead to movement of transposable elements



Falke et al (1997)



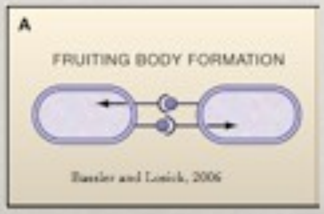
Hazelbauer et al., 2008)

- Paenibacillus vortex: Vortices, consisting of tens to millions of bacteria swarming around collectively around a common center at ~10 microns/sec, grow and move outwards
  - Leave behind a trail of motile [...]
  replicating bacteria
- Communication via attractive [...]
vortex required to adjust indivi[...]
vortex
  - Particular important in fomr[...]

http://tamar.tau.ac.il/~eshel/html/intelligence_of_Bacteria.html

Transition to Sporulation

- Mechanism to recognize low nutrient level
- In low nutrient conditions, reversal of movement terminates and individual cells join into streams going into mounds
  - Dependent on C-signaling through cell contact that also regulates expression of numerous genes required for spore formation



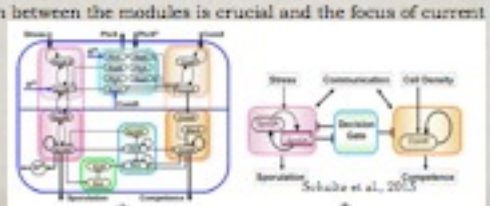
Bassler and Losick, 2006

Multi-colony Communities

- Sub-gingival plaque contains hundreds of species from 20 genera of bacteria, each with appox. 10 million bacteria

Sporulation (model: B. Subtilis 168)

- Last resort: released material can be taken up by competent cells (used as food sources, for DNA repair, and as new genetic resources for combating stress)
- Starved bacteria emit chemical message of stress, used by others to gauge own response
  - Decisions to send message for or against sporulation
  - If majority, then sporulation
- Network of inputs culminating in phosphorylation of Spo0A, sporulation master regulator
  - Inputs record population density, stress levels of nearby bacteria
- Two modules--sporulation timer (adaptable clock adjusted by stress levels of other cells) and competence switch (controlled by quorum sensing unit)
  - Coordination between the modules is crucial and the focus of current research


Schultz et al., 2013

Chemotactic Signaling

- Bacteria emit both attractive (food-like molecules) and repulsive signals
- Different colony structures form with different food levels
  - As food levels increase, increased expansion and bushiness
  - At low levels, increased repellant signal

High Intermediate Low