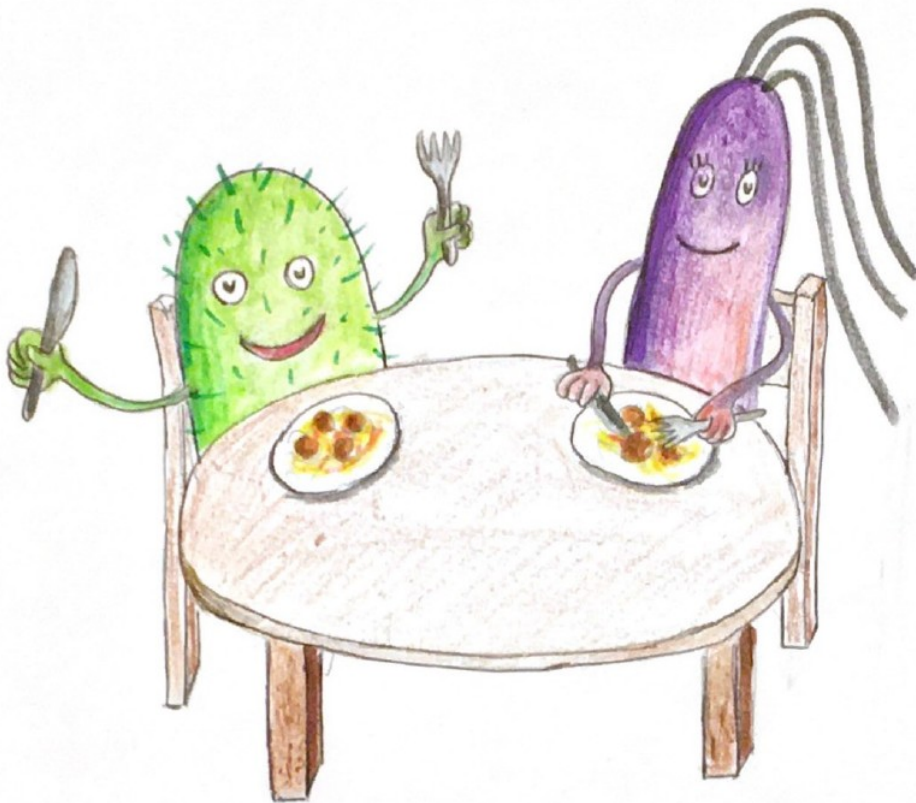


Starvation: food deprivation stress

Mum: I'm so hungry! Do microbes get hungry too?



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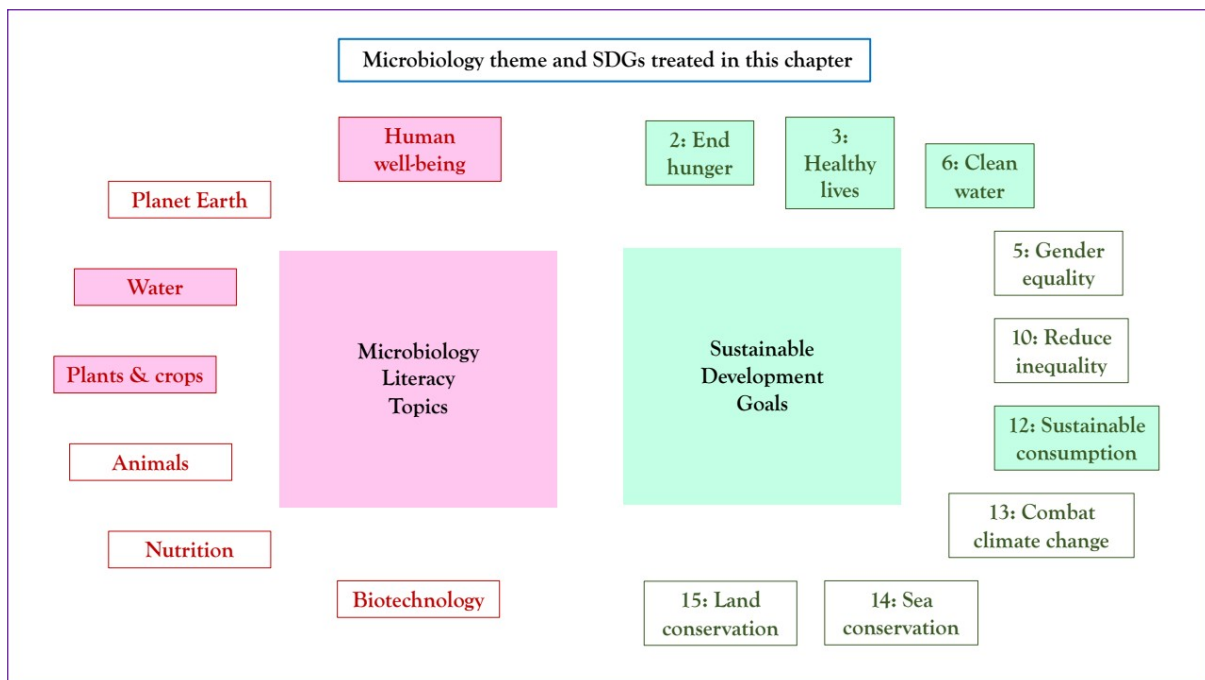
Food deprivation stress

Storyline

All living organisms need to eat, and many higher life forms spend a large part of their days foraging for food. The same is true for unicellular organisms such as bacteria. But what happens when they run out of food? By learning more about how bacteria survive **substrate** (food) deprivation, scientists are hoping to harness this ability to our advantage. For example, we want to find new antibiotics that can target dormant or starving bacteria, since these the stress responses of these bacteria seem to protect them against the types of antibiotics that we normally use. Additionally, the stress responses of starved bacteria can make them especially good at removing pollutants from water and other environments because they become eager to use those pollutants as food. Finally, many types of bacteria can perform helpful functions that increase crop growth, but if want to harness those activities we must understand how the helpful bacteria survive periods of starvation in the soil before they find a plant with which to associate.

The Microbiology and Societal Context

The microbiology: bacterial stress responses; alarmones; bacterial population dynamics; regulation of gene expression; microbial sensing of environmental signals *Sustainability issues:* human health, antibiotic resistance, resource utilisation, conservation, bioremediation.



Food Deprivation stress – the Microbiology

1. All living things need to eat! Humans can go without food for only a few days before our bodies begin to break down, and malnutrition is a huge health problem around the world. Why do we so urgently and constantly need to eat? Food is converted in our bodies into two essential things: energy and building blocks. For more detailed information about how microbes use food, please see Topic Framework “What do microbes eat and what happens to the food?”

a. **Energy** is required to power chemical reactions inside our body, including muscle movement, electrical signals in our brains, nerve signals connecting our brains to our muscles, growing bigger, and replacing cells in our body that wear out, such as skin cells that fall off over time.

Bacteria don't have muscles like we do, but many of them can still move using tiny propellers called flagella. They don't have brains like we do, but they can still sense food or danger or friends in their environments and carry out responses that depend on what they sense. Bacteria also make new copies of themselves – they multiply – any time they can find enough food to support this.

The energy from food is converted into different types of carrier molecules that can store it for later use. For example, **ATP** stores energy in the form of high-energy chemical bonds, that can later be broken to release the energy and power many types of chemical reactions in cells. Some bacteria called **autotrophs** can capture energy from sunlight (these are **photoautotrophs**, or photosynthetic bacteria), or even from high energy inorganic chemicals (like the **chemolithotrophs** of deep-sea vents). These bacteria don't have to find **organic chemicals** in their environment to convert into energy. However, many bacteria are like us, and need to consume organic material (food) as a source of energy; these are called **heterotrophs**.

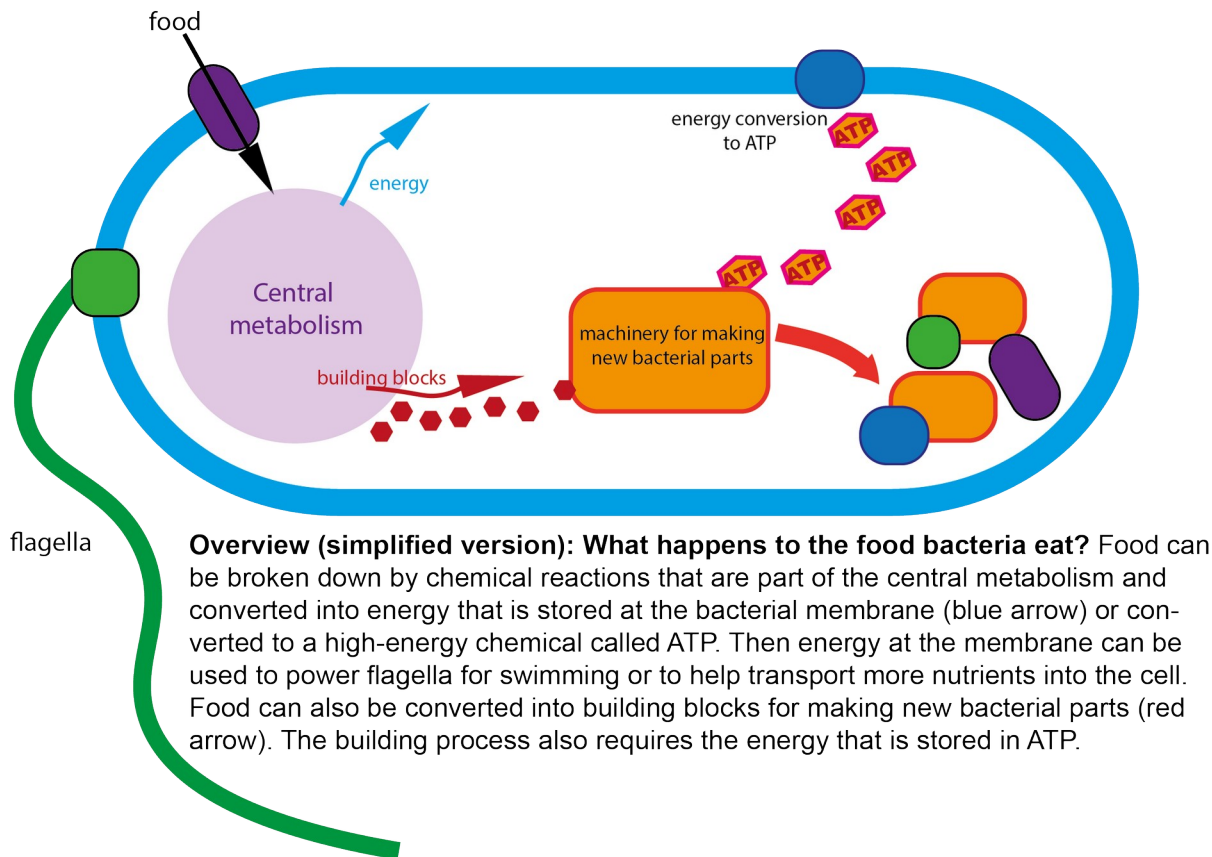
b. **Building blocks** on the other hand are required for building new parts or growing bigger. The key building blocks that bacteria need contain the elements carbon, nitrogen, phosphorous, and sulphur (plus other elements in much smaller quantities). These elements are joined together in compounds like sugars, fatty acids, **amino acids**, and **nucleotides**, which are molecules that can be used to build larger cellular structures and machines. Nucleotides are joined into DNA and RNA molecules, which carry the genetic information that defines the bacterium. Amino acids are linked together in long strings to make proteins, which then fold and fit together to form the tiny machines that carry out the cell's activities. Fatty acids are used to make the cell membrane and cell wall, which contain and protect the cell. All bacteria need to acquire these essential elements from their environment to build new cellular components.

2. What causes bacteria to run out of food? Bacteria are very resourceful and can live in almost every environment. This is one way in which bacteria have evolved to deal with shortages of food – they have just acquired the ability to use new and different kinds of molecules as food.

Some environments do not have very much food of any kind available or have other kinds of stresses present (too hot, too cold, too salty, or too acidic for example). These environments tend to have relatively low total numbers of bacteria, and the bacteria there grow very slowly all the time. They have evolved over many millions of years to get by with poor nutrient sources, and even if you give them plenty of food, they still can't grow quickly. Although they are always subsisting on a very limited amount of food and energy from their

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environment, they do not have to compete with many other bacteria, so growing very slowly is not a problem.



Overview (simplified version): What happens to the food bacteria eat? Food can be broken down by chemical reactions that are part of the central metabolism and converted into energy that is stored at the bacterial membrane (blue arrow) or converted to a high-energy chemical called ATP. Then energy at the membrane can be used to power flagella for swimming or to help transport more nutrients into the cell. Food can also be converted into building blocks for making new bacterial parts (red arrow). The building process also requires the energy that is stored in ATP.

In nutrient-rich environments, bacteria can grow very quickly – some species can make a new bacterium in under 10 minutes, and the common laboratory bacteria *E. coli* can divide every 20 minutes. However, they can't keep this up for long. If you started with one *E. coli* cell and gave it enough food so that it and all its progeny could keep dividing every 20 minutes, they would become more massive than the known universe in less than 3 days. Obviously, this does not happen. The fast-growing bacteria in nutrient-rich environments quickly use up the existing food, and then they must stop growing and wait for more food to become available.

Nutrient-rich environments often have large numbers of bacteria present, so they are all competing to consume newly available foods as fast as possible. This can result in a “boom and bust” dynamic where the arrival of nutrients causes a burst of very fast growth, followed by a long period of waiting where nutrients are scarce. Examples of environments where this happens can include the soil, the oceans, lakes, and even plants and the bodies of animals. A burst of nutrients in soil or the ocean could come in the form of a plant or animal that has died and can then be recycled by microbes. It can also come from pollutants that humans spill into the environment. In the case of bacteria that are stably associated with living plants or animals in a cooperative relationship, the host may be able to control when its bacterial partners have good access to food. In the case of infections, one strategy the immune system can use is to try to deprive the infecting bacteria of essential nutrients so that they cannot grow.

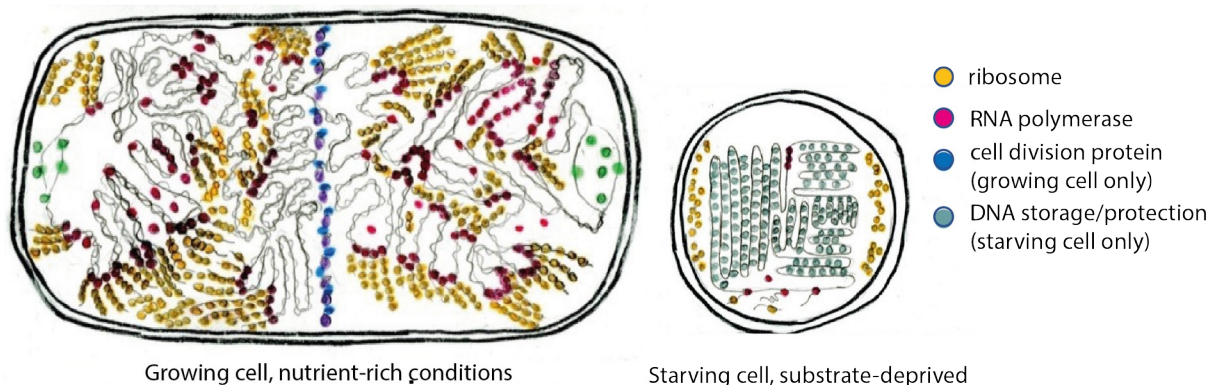
Bacteria who live in these kinds of “sometimes nutrient-rich” environments must have strategies for navigating both situations – they must be able to respond quickly and grow rapidly when nutrients are available but stop growing and conserve resources when the nutrients are used up. Very large numbers of bacteria exist in these types of situations in many

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different types of environments, and most of them must spend a lot of their time waiting for more food to become available. Therefore, they have developed multiple strategies for dealing with food deprivation. Next, we will discuss some of these strategies.

3. **What do individual bacteria do when they run out of food?** Bacteria have some strategies for dealing with starvation that work whether they are alone or part of a large group of similar bacteria. These strategies are designed to conserve resources, and they may sound familiar if you have heard advice on how we, as humans, can contribute to conservation of resources in our own environments.

a. **Reduce:** Bacteria sense when they are running low on nutrients because some of the machines (called **ribosomes**) that are normally involved in building new proteins starts to be unable to fill their “input” slots with fresh raw materials (amino acids). This triggers the production of a signalling chemical – a so-called **alarmone** – called **ppGpp**. ppGpp can bind to many different parts of the cell’s machinery, including the **RNA polymerase** (which is responsible for choosing which new proteins to make and copying out the instructions for making them), various metabolic enzymes, and some accessory factors that work with ribosomes. When it binds to all these parts, it triggers a coordinated shutdown procedure, that reduces the production of new proteins to very low levels. This decrease in new production is obvious if you look at bacteria with a microscope – they become much smaller, and many of the types of proteins that are present in growing cells are no longer made. There are at least three key points to the coordinated shut-down procedure.



Bacterial cells reduce, re-use, and recycle when starved for nutrients. The cell on the left represents a rapidly growing bacterium, crowded with active RNA polymerases and ribosomes, and preparing to divide into two new cells. The cell on the right represents a bacterium that has been deprived of nutrients. It has become much smaller as it has dramatically reduced the amount of new proteins it is producing. It is preparing to re-use ribosomes by storing them away in a safe state at the edges of the cell, and it is protecting its DNA from damage by coating it in proteins that keep it safe. The small amount of activity of a few RNA polymerases and ribosomes is driven by recycling some damaged or unneeded enzymes.

i. *First, the coordination is important.* The cell needs to shut down lots of interconnected processes in such a way that the machinery is not damaged and does not waste energy. This is like what might happen in a factory – you can’t just randomly shut off different machinery in a factory because each assembly line feeds into another one, and if they are shut down in the wrong order, back-ups and damage can happen.

ii. *Second, the shut-down must happen before the cells are completely out of nutrients.* They must keep some of the key building blocks in reserve so that they can respond to additional emergencies that might occur while they are in “shut-down” mode and also so that

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they can ramp things back up again when fresh nutrients become available. If a bacterium spends absolutely all of its resources before it manages to complete the safe shut-down procedure, it is less likely to be able to survive and recover quickly.

iii. *Third, the “shut-down” mode is not completely inactive*, but instead cells are able to make very small amounts of new things at a much lower rate (about 100-1000 times lower) than their rate of production when they had plenty of nutrients. This is important for survival because it allows for repair of damage and responses to changes in the environment.

b. **Re-use:** How do bacteria keep doing a small number of essential things when they are out of fresh nutrients? One strategy is to preserve existing molecules in a functional state for longer. There is evidence that some molecular machinery that is temporarily not needed can be “boxed up” for protection and stored in an inactive state. Many types of protein and mRNA molecules may be used for longer periods of time and discarded much more slowly.

c. **Recycle:** Bacteria also recycle old parts when they don’t have any fresh nutrients. They completely break down some enzymes (proteins) that they don’t need and then use the constituent molecular building blocks (amino acids) to build new and different enzymes that better fit their needs at the time. They also can recycle enzymes that have been damaged. Sometimes, a whole bacterial cell may die, and its neighbours will then recycle the materials from the dead cell.

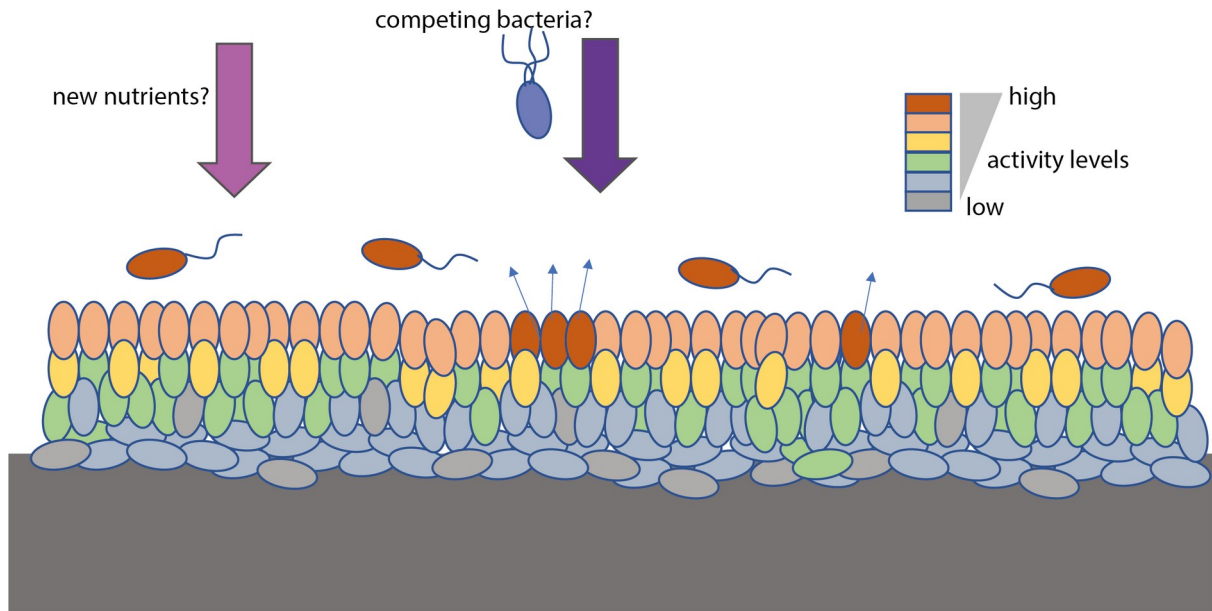
4. What do bacterial communities do when they run out of food? Some of the strategies that bacteria use to adapt to starvation only work in the context of larger communities of bacteria. In natural environments, bacteria often exist in large structures, or **biofilms** – microbial cities – with thousands, millions, or even billions of other bacteria. Many of the nearby bacteria will be members of the same family, but often bacteria of different species come in close contact with each other as well. It makes sense that different species of bacteria might have different responses to a stress like starvation. However, there is also evidence that even bacterial “siblings” can adopt different strategies during starvation, and that this might help the biofilm survive. This is referred to as **“bet-hedging”**: the bacteria don’t know how things will play out, and if their biofilm has millions of individual members, they can “bet” on many different strategies and hope that at least one of them turns out to be appropriate. As described above, they can then recycle the individual cells that carried out the non-winning strategies. This sets up some very complicated interactions that scientists are still trying to figure out. Below are some examples of strategies that require different bacteria in an environment to adopt different responses.

a. **Co-operate:** The above-mentioned scenario where bacteria can efficiently recycle cells from their own group that have died is one form of co-operation that helps the whole group to survive. There is some evidence that some species of bacteria might take things even further. The cells that struggle the most to execute the efficient shut-down procedure might instead actively produce molecules that result in their own deaths. It can be best for the group if cells that sustain the worst damage are sacrificed to provide nutrients for the other cells that are in better shape.

A very different type of cooperation can happen when two different types of bacteria are living near each other and encounter a challenging nutrient situation. Sometimes the nutrient that happens to be available cannot be used efficiently by either type of bacteria on its own, but they can work together to efficiently use the nutrient. Normally in this type of scenario, one of the types of bacteria can start to break down the nutrient and is able to get some energy from it but isn’t able to dispose of the waste products fast enough. If the other

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type of bacteria can use the waste products as a nutrient, then both partners can benefit, because now the first type of bacteria has help to deal with its waste accumulation problem, and the second type of bacteria has something it can eat. It is really true that one bacteria's trash can be another bacteria's treasure!



Bet-hedging in bacterial biofilms under nutrient-limited conditions. Different individual cells in a group of bacteria might adopt different strategies. For example, the cells at the outside edge might be the first to find any new nutrients, the most likely to try to swim away to find a better place to live, or the most likely to defend against competing bacteria. They might need to have higher levels of metabolic activity (dark orange) to do these things. On the other hand, the cells inside the biofilm might be more likely to adopt a dormant, “sleeping” state. If the rest of the biofilm dies, the dormant interior cells might still have a chance to survive. Other cells in the biofilm might have medium or low levels of activity, and can recycle nutrients from any neighbouring cells that die.

b. **Fight:** Bacteria make a huge number of different types of weapons for killing other microbes that might be competing for the same sources of nutrients. These weapons include antibiotic molecules (which we have discovered and used as medicines for ourselves when we want to kill bacteria that are causing infections) and tiny spears that can poke into nearby competitor bacteria and kill or disable them. Producing these weapons requires spending some energy and building materials, so in many cases they are made in response to sensing competitor bacteria, but before anyone has completely run out of nutrients. Often, only a small fraction of the bacteria in a colony will make these weapons at any one time, which allows other members of the colony to save their energy.

c. **Sleep:** Some bacteria can enter an extremely low-activity dormant state in which they use almost no energy and are very protected from many types of environmental threats like drying out, high temperatures, UV radiation, and dangerous chemicals. Bacteria in these states are called “spores”. Spores are analogous to seeds produced by plants. They are protected by a tough outer coat, and it has been estimated that they can last for hundreds of years under some conditions. Not all bacteria can make spores, and even when they can, a colony of bacteria will

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usually only commit a small fraction of its cells to forming spores when nutrients become limiting. Spores may be the “safest” state in which these bacteria can spend long periods of starvation, but it takes a long time to emerge from the spore state through a process called germination. Therefore, if nutrients are missing for only a short period of time, bacteria that didn’t form spores may have an advantage, because they can resume growth faster.

d. **Seek out new territory:** There is evidence that some members of a bacterial population will prepare to travel when food becomes scarce. Exactly how they do this depends on the bacterial species. For example, some bacteria can make propeller-like appendages called flagella, and they can use this to swim quickly through liquid. Other bacteria can make a slippery substance that helps them skate along a solid surface. Still other kinds of bacteria cannot actively move at all, but they seem to let go of each other when nutrients become limiting. This breaks up the colony and allows them to more easily be transported to a new location by flowing liquid. These activities all have energy costs, but they may result in some members of the bacterial population finding a new home with a better nutrient supply. While some of the bacteria in a population may try to survive by spending as little energy as possible, others spend a lot of energy to try to find a new, better place to live, or to build weapons to attack nearby bacteria that are different species. Even if many of the strategies that are attempted fail, the bacterial population can quickly be replenished if just a few of the individuals are successful in surviving until more nutrients are available.

Relevance for Sustainable Development Goals

- **Goal 2: End hunger, achieve food security and improved nutrition and promote sustainable agriculture.** Bacteria can help crop plants to grow faster and produce more. They live in association with plants because plants can help them obtain carbon, and they can in turn help the plants obtain nitrogen and phosphorus. Better understanding of this cooperation could help us improve agricultural efficiency and decrease reliance on chemical fertilisers. However, the soil that is a bit further away from the plant root often does not have enough carbon to allow bacteria to grow. If we want to help bacteria to help plants, we must understand how they survive food deprivation in the soil and find a plant to partner up with.

- **Goal 3: Ensure well-being and promote healthy lives at all ages.** We have trillions of bacteria living on our skin, in our mouths, and in our guts, and we are just starting to understand the importance of keeping our bacterial friends happy and healthy if we ourselves wish to be healthy. Sometimes, the health-promoting “good” bacteria can lose out to dangerous bacteria that can grow too much and damage our tissues – we call this situation a bacterial infection. Normally, we take antibiotics to kill off the dangerous bacteria, and if the antibiotics can kill most of the bacteria in an infection, the balance between our immune systems and the good bacteria can usually be restored. However, we now know that bacteria can sometimes survive antibiotics by being dormant (a response to starvation) and that antibiotics can sometimes kill too many of the good bacteria, leaving an open source of food for dangerous bacteria to pursue. A better understanding of how bacteria compete for food in our bodies can help us design better antibiotics.

- **Goal 6: Ensure availability and sustainable management of water and sanitation for all.** Clean water is actually not a very good environment for most bacteria to live in – there is not enough food! Therefore, ensuring that people have clean water to drink is a very good way to decrease the chances of infection by dangerous bacteria. Interestingly, there are some kinds of bacteria that have been put to work in water treatment facilities to help with the water cleaning process. It turns out that these bacteria have evolved to be very good at extracting even

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tiny amounts of nutrients from water, because they have become very accustomed to being deprived of food. When wastewater comes into the treatment plant, it is full of nutrients from fertilisers that people use in their gardens, from the dirty dishes they washed in their sinks, and from the wastes they flushed down the toilet. The bacteria in the wastewater treatment plant are not given any other nutrients so they are ready to eat up as many nutrients from the wastewater as possible. Once they have filled up on nutrients, they sink to the bottom of the pool they are in, and the water can be moved along to the next step in the process, leaving the bacteria and all the nutrients they consumed behind. Because these bacteria are so good at extracting nutrients from water, once they have finished it is much less likely that dangerous bacteria will find enough left-over nutrients to grow. Scientists are still learning more about how to get bacteria to do their most efficient work to help us clean our water.

- **Goal 12: Ensure sustainable consumption and production patterns.** Humans are reaching a point where our environments are becoming crowded with other humans, and we sometimes must compete for resources. In some parts of the world, it is difficult for everyone to get enough food to eat. We are just starting to realise that there are not enough resources in our environment for our population to continue to grow exponentially forever, but we have not yet had to face global shortages in essential resources, and we do not have good strategies for navigating this. Bacteria have experienced running out of resources in their micro-environments probably trillions of times over their billions of years of evolution, and they have evolved strategies for dealing with this. Different bacteria have different strategies, and some seem to work better than others in any specific situation. Themes of reducing consumption, preserving and reusing cellular components, recycling damaged parts, ceasing production of toxic waste, and cooperating with neighbours can be observed for many species, and understanding how these strategies work for bacteria could inspire strategies for us to pursue on a global scale as well.

Pupil participation

1. Class discussion of the survival strategies of bacteria

- a. Which strategy would you adopt if you were a bacterium in a biofilm that was running out of food?
- b. Why is it important that bacteria coordinate slowing down their activities when they are running out of food and energy?
- c. Bacteria can coordinate to share resources sometimes, where different bacteria eat different things in the environment, or some bacteria can eat the waste products of other bacteria. Can you think of any examples of this type of cooperation in plants or animals?

2. Pupil stakeholder awareness

- a. Bacteria have evolved ways to reduce, re-use, and recycle resources, and to cooperate to use resources more efficiently when they are limiting. Do you think humans should be thinking of ways to do these things too, to conserve resources that are important for us? What are some examples of how we are already doing these things? How might we be able to do better to conserve our resources?

The Evidence Base, Further Reading and Teaching Aids

[How Do Bacteria Feed? \(sciencing.com\)](http://sciencing.com)

[Nutritional Types of Bacteria \(sciencing.com\)](http://sciencing.com)

[Scientists awaken bacteria after 100 million years \(The Scientist\)](#)

[The physiology of growth arrest \(Nature Reviews Microbiology\)](#)

[Biointeractive Winogradsky.jpg \(7200×5400\)](#)

Glossary

alarmone: a chemical signal that bacteria produce when they encounter stress to help coordinate the responses of many molecular machines

amino acid: a chemical building block that is a constituent of proteins

ATP: adenosine triphosphate, a molecule that can store energy in the form of a high-energy chemical bond

autotroph: an organism that does not need to consume organic chemicals as a source of energy

biofilms: large piles of bacteria that are held together in a sticky matrix that they make themselves

bet hedging: an overall survival strategy in which different members of a population adopt different responses to a stress to increase the chances that one of the responses adopted will be the right one for surviving the stress

central metabolism: the collection of chemical reactions that process food and partition nutrients toward energy or building blocks

chemolithotroph: an organism that does not require organic chemicals for energy but can instead use chemical reactions of inorganic chemicals as a source of energy. A type of autotroph.

DNA: The molecule that stores all the genetic information of an organism, in the form of deoxyribonucleotide sequences that are instructions for making proteins.

enzyme: A protein-based machine that can help carry out a chemical reaction.

heterotroph: An organism that requires organic chemicals as a source of energy.

inorganic chemical: Any chemical that lacks either carbon or hydrogen atoms.

mRNA: The temporary “working copy” of instructions to make a protein. The instructions are copied from the DNA sequence of deoxyribonucleotides into the mRNA sequence of ribonucleotides.

nucleotide: The basic building block of DNA and mRNA molecules; includes ATP as well.

organic chemical: Any chemical containing carbon and hydrogen atoms.

photoautotroph: An organism that can obtain energy from light.

ppGpp: A nucleotide-based signaling molecule in bacteria that is associated with nutrient deprivation and that helps to coordinate the shut-down of new protein production

RNA polymerase: An enzyme made up of several individual proteins that copies instructions from DNA into mRNA molecules.

ribosome: An enzyme made up of many individual proteins that reads the instructions from an mRNA molecule to build a protein.

substrate: The starting material on which a chemical reaction takes place.