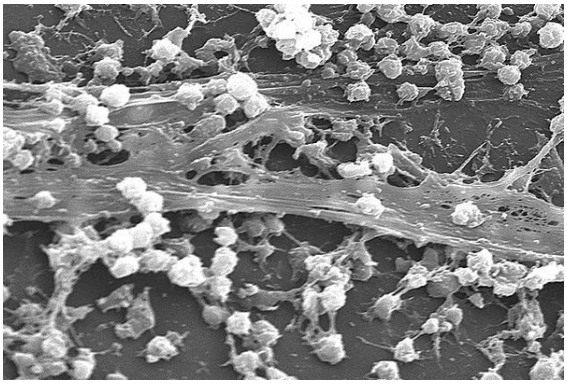
Biofilm

For biographic motion picture, see Biographical film.
IUPAC definition



Staphylococcus aureus *biofilm on an indwelling catheter*

Aggregate of microorganisms in which cells that are frequently embedded within a self-produced matrix of extracellular polymeric substance (EPS) adhere to each other and/or to a surface.

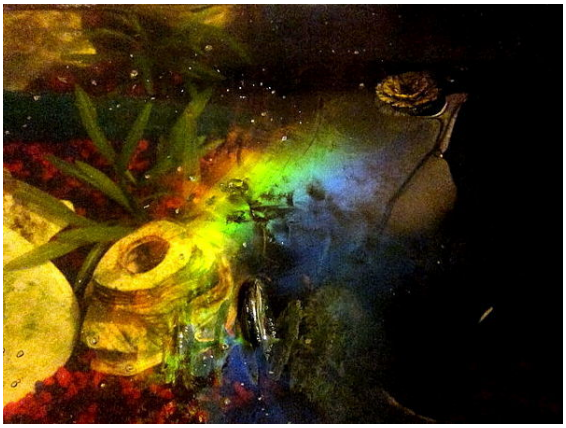
Note 1: A biofilm is a system that can be adapted internally to environmental conditions by its inhabitants.

Note 2: The self-produced matrix of extracellular polymeric substance, which is also referred to as slime, is a polymeric conglomeration generally composed of extracellular *biopolymers* in various structural forms.[1]

A **biofilm** is any group of microorganisms in which cells stick to each other and often these cells adhere to a surface. These adherent cells are frequently embedded within a self-produced matrix of extracellular polymeric substance (EPS). Biofilm extracellular polymeric substance, which is also referred to as **slime** (although not everything described as slime is a biofilm), is a polymeric conglomeration generally composed of extracellular DNA, proteins, and polysaccharides. Biofilms may form on living or non-living surfaces and can be prevalent in natural, industrial and hospital settings.[2][3] The microbial cells growing in a biofilm are physiologically distinct from planktonic cells of the same organism, which, by contrast, are single-cells that may float or swim in a liquid medium.

Microbes form a biofilm in response to many factors, which may include cellular recognition of specific or nonspecific attachment sites on a surface, nutritional cues, or in some cases, by exposure of planktonic cells to subinhibitory concentrations of antibiotics.[4][5] When a cell switches to the biofilm mode of growth, it undergoes a phenotypic shift in behavior in which large suites of genes are differentially regulated.[6]

1 Formation



An iridescent biofilm on the surface of a fish tank.

Formation of a biofilm begins with the attachment of free-floating microorganisms to a surface. These first colonists adhere to the surface initially through weak, reversible adhesion via van der Waals forces. If the colonists are not immediately separated from the surface, they can anchor themselves more permanently using cell adhesion structures such as pili. Hydrophobicity also plays an important role in determining the ability of bacteria to form biofilms, as those with increased hydrophobicity have reduced repulsion between the extracellular matrix and the bacterium.[7]

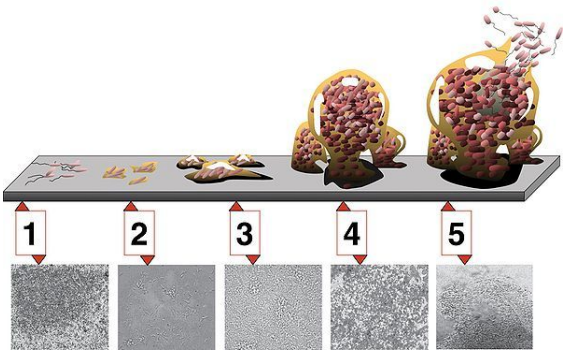
Some species are not able to attach to a surface on their own but are instead able to anchor themselves to the matrix or directly to earlier colonists. It is during this colonization that the cells are able to communicate via quorum sensing (QS) using products such as AHL. Some bacteria are unable to form biofilms as successfully due to their limited motility. Non-motile bacteria cannot recognize the surface or aggregate together as easily as motile bacteria.[7] Once colonization has begun, the biofilm grows through a combination of cell division and recruitment. Polysaccharide matrices typically enclose bacterial biofilms. In addition to the polysaccharides, these matrices may also contain material from the surrounding environment, including but not limited to minerals, soil particles, and blood components, such as ery-

throcytes and fibrin.[7] The final stage of biofilm formation is known as dispersion, and is the stage in which the biofilm is established and may only change in shape and size.

The development of a biofilm may allow for an aggregate cell colony (or colonies) to be increasingly resistant to antibiotics. Cell-cell communication or quorum sensing has been shown to be involved in the formation of biofilm in several bacterial species.[8]

A. baumannii is infamous for its ability to form biofilms both on inanimate objects as well as biotic surfaces. *A. baumannii* has been reported to commence secretion of exopolysaccharides once it has successfully adhered to a surface, be it hydrophilic or hydrophobic like glass or plastic, respectively, or surfaces of living cells. Previous findings indicate that within the protective environment of the biofilm, the pathogen remains protected from starvation, desiccation and the action of antibiotics. As such, the ability to form biofilms alone may be linked to the increased virulence in some of the strains. Direct evidence to support this hypothesis is still lacking. However, reports have shown that multi-drug resistant strains are efficient biofilm producers, indicating a direct relationship between biofilm formation and antibiotic resistance. Other reports have shown that the biofilm-associated protein (BAP) in *A. baumannii*, involved in biofilm formation, is capable of stimulating humoral response in mice, which suggests that it may have a role in virulence. The ability of *A. baumannii* to form biofilms has been shown to be related to certain outer membrane surface-associated proteins like OmpA and BAP as well as certain pili-associated adhesins. The presence of metal cations has also been reported to be required for biofilm formation as indicated by the reduced ability of *A. baumannii* to produce biofilms in presence of chelators like ethylenediaminetetraacetic acid (EDTA). The formation of CsuA/BABCDE-dependent pili appears to be essential for biofilm adherence to and formation on abiotic surfaces and the assembly of these pili seems to involve chaperone and usher-like proteins. However, this system does not seem to be involved in the adherence of *A. baumannii* to living cells, and the underlying mechanisms governing attachment to biotic surfaces still remain to be elucidated. Formation of biofilm by *A. baumannii* is under tight regulation both at the transcriptional and translational levels involving highly efficient and cross-linked two-component regulatory systems. However, the identification of these regulatory systems has not yet been achieved. Quorum sensing has also been implicated in the regulation of biofilm formation. *A. baumannii* has been shown to be capable of producing quorum-sensing molecules, namely N-acylhomoserine lactones of various chain length with -(3-hydroxydodecanoyl)-L-HSL reported as the primary signal molecule. However, only a single autoinducer synthase gene named abaI has been identified to date. Quorum sensing is the main method of communication between the bacterial cells within the biofilm and may also serve as a mechanism to coordinate and regulate the multiple virulence factors in *A. baumannii*. There are reports indicating that quorum sensing might possibly be involved in host–pathogen interactions as well. Thus, biofilm formation and quorum sensing are important components in the wide arsenal of virulence determinants produced by *A. baumannii*.

2 Development



Five stages of biofilm development: (1) Initial attachment, (2) Irreversible attachment, (3) Maturation I, (4) Maturation II, and (5) Dispersion. Each stage of development in the diagram is paired with a photomicrograph of a developing P. aeruginosa *biofilm. All photomicrographs are shown to the same scale.*

There are five stages of biofilm development (see illustration at right):

1. *Initial attachment*:
2. *Irreversible attachment*:
3. *Maturation I*:
4. *Maturation II*:
5. *Dispersion*:

In conclusion, it appears that targeting QS to mitigate membrane biofouling is a promising technology for the enhancement of efficiency and performance in membrane systems. Results from recent investigations verified the existence of a correlation between QS activity and membrane biofouling. Different strategies have been demonstrated to target QS activity, in order to mitigate membrane biofouling. However, current validation methods for QS must be improved and optimized, with its particular toxicity effects on bacterial viability. Furthermore, emergence of bacterial resistance to QS inhibitors and its adverse effects must be evaluated in-depth. Future advances in membrane biofouling mitigation based on QS can be expected from further fundamental research.

3 Dispersal

Dispersal of cells from the biofilm colony is an essential stage of the biofilm life cycle. Dispersal enables biofilms to spread and colonize new surfaces. Enzymes that degrade the biofilm extracellular matrix, such as dispersin B and deoxyribonuclease, may play a role in biofilm dispersal.[9][10] Biofilm matrix degrading enzymes may be useful as anti-biofilm agents.[11][12] Recent evidence has shown that a fatty acid messenger, *cis*−2-decenoic acid, is capable of inducing dispersion and inhibiting growth of biofilm colonies. Secreted by *Pseudomonas aeruginosa*, this compound induces cyclo heteromorphic cells in several species of bacteria and the yeast *Candida albicans*.[13] Nitric oxide has also been shown to trigger the dispersal of biofilms of several bacteria species[14][15] at sub-toxic concentrations. Nitric oxide has the potential for the treatment of patients that suffer from chronic infections caused by biofilms.[16]

It is generally assumed that cells dispersed from biofilms immediately go into the planktonic growth phase. However, recent studies have shown that the physiology of dispersed cells from *Pseudomonas aeruginosa* biofilms is highly different from those of planktonic and biofilm cells.[17][18] Hence, the dispersal process is a unique stage during the transition from biofilm to planktonic lifestyle in bacteria. Dispersed cells are found to be highly virulent against macrophages and *Caenorhabditis elegans*, but highly sensitive towards iron stress, as compared with planktonic cells.[17]

4 Properties

Biofilms are usually found on solid substrates submerged in or exposed to an aqueous solution, although they can form as floating mats on liquid surfaces and also on the surface of leaves, particularly in high humidity climates. Given sufficient resources for growth, a biofilm will quickly grow to be macroscopic (visible to the naked eye). Biofilms can contain many different types of microorganism, e.g. bacteria, archaea, protozoa, fungi and algae; each group performs specialized metabolic functions. However, some organisms will form single-species films under certain conditions. The social structure (cooperation/competition) within a biofilm depends highly on the different species present.[19]

4.1 Extracellular matrix

The biofilm is held together and protected by a matrix of secreted polymeric compounds called EPS. EPS is an abbreviation for either extracellular polymeric substance or exopolysaccharide, although the latter one only refers to the polysaccharide moiety of EPS. In fact, the EPS matrix consists not only of polysaccharides but also of proteins (which may be the major component in environmental and waste water biofilms) and nucleic acids. A large proportion of the EPS is more or less strongly hydrated, however, hydrophobic EPS also occur; one example is cellulose which is produced by a range of microorganisms. This matrix encases the cells within it and facilitates communication among them through biochemical signals as well as gene exchange. The EPS matrix is an important key to the evolutionary success of biofilms. One reason is that it traps extracellular enzymes and keeps them in close proximity to the cells. Thus, the matrix represents an external digestion system and allows for stable synergistic microconsortia of different species (Wingender and Flemming, Nat. Rev. Microbiol. 8, 623-633). Some biofilms have been found to contain water channels that help distribute nutrients and signalling molecules.[20] This matrix is strong enough that under certain conditions, biofilms can become fossilized (Stromatolites).

Bacteria living in a biofilm usually have significantly different properties from free-floating bacteria of the same species, as the dense and protected environment of the film allows them to cooperate and interact in various ways. One benefit of this environment is increased resistance to detergents and antibiotics, as the dense extracellular matrix and the outer layer of cells protect the interior of the community. In some cases antibiotic resistance can be increased a thousandfold.[21] Lateral gene transfer is greatly facilitated in biofilms and leads to a more stable biofilm structure.[22] Extracellular DNA is a major structural component of many different microbial biofilms.[23] Enzymatic degradation of extracellular DNA can weaken the biofilm structure and release microbial cells from the surface.

However, biofilms are not always less susceptible to antibiotics. For instance, the biofilm form of *Pseudomonas aeruginosa* has no greater resistance to antimicrobials than do stationary-phase planktonic cells, although when the biofilm is compared to logarithmic-phase planktonic cells, the biofilm does have greater resistance to antimicrobials. This resistance to antibiotics in both stationary-phase cells and biofilms may be due to the presence of persister cells.[24]

5 Habitat

Biofilms are ubiquitous. Nearly every species of microorganism, not only bacteria and archaea, have mechanisms by which they can adhere to surfaces and to each other. Biofilms will form on virtually every non-shedding surface in a non-sterile aqueous (or very humid) environment.

- Biofilms can be found on rocks and pebbles at the bottom of most streams or rivers and often form on the surface of stagnant pools of water. In fact, biofilms are important components of food chains

Mats of bacterial biofilm color the hot springs in Yellowstone National Park. The longest raised mat area is about half a meter long.

Thermophilic bacteria in the outflow of Mickey Hot Springs, Oregon, approximately 20 mm thick.

in rivers and streams and are grazed by the aquatic invertebrates upon which many fish feed.

- Biofilms can grow in the most extreme environments: from, for example, the extremely hot, briny waters of hot springs ranging from very acidic to very alkaline, to frozen glaciers.
- In the human environment, biofilms can grow in showers very easily since they provide a moist and warm environment for the biofilm to thrive. Biofilms can form inside water and sewage pipes and cause clogging and corrosion. Biofilms on floors and counters can make sanitation difficult in food preparation areas.
- Biofilms in cooling- or heating-water systems are known to reduce heat transfer.[25]
- Biofilms in marine engineering systems, such as pipelines of the offshore oil and gas industry,[26] can lead to substantial corrosion problems. Corrosion is mainly due to abiotic factors; however, at least 20% of corrosion is caused by microorganisms that are attached to the metal subsurface (i.e., microbially influenced corrosion).
- Bacterial adhesion to boat hulls serves as the foundation for biofouling of seagoing vessels. Once a film of bacteria forms, it is easier for other marine organisms such as barnacles to attach. Such fouling can reduce maximum vessel speed by up to 20%, prolonging voyages and consuming fuel. Time in dry dock for refitting and repainting reduces the productivity of shipping assets, and the useful life of ships is also reduced due to corrosion and mechanical removal (scraping) of marine organisms from ships' hulls.
- Biofilms can also be harnessed for constructive purposes. For example, many sewage treatment plants include a treatment stage in which waste water passes over biofilms grown on filters, which extract and digest organic compounds. In such biofilms, bacteria are mainly responsible for removal of organic matter (BOD), while protozoa and rotifers are mainly responsible for removal of suspended solids (SS), including pathogens and other microorganisms. Slow sand filters rely on biofilm development in the same way to filter surface water from lake, spring or river sources for drinking purposes. What we regard as clean water is effectively a waste material to these microcellular organisms.
- Biofilms can help eliminate petroleum oil from contaminated oceans or marine systems. The oil is eliminated by the hydrocarbon-degrading activities of microbial communities, in particular by a remarkable recently discovered group of specialists, the so-called hydrocarbonoclastic bacteria (HCB).[27]
- Stromatolites are layered accretionary structures formed in shallow water by the trapping, binding and cementation of sedimentary grains by microbial biofilms, especially of cyanobacteria. Stromatolites include some of the most ancient records of life on Earth, and are still forming today.
- Biofilms are present on the teeth of most animals as dental plaque, where they may cause tooth decay and gum disease.
- Biofilms are found on the surface of and inside plants. They can either contribute to crop disease or, as in the case of nitrogen-fixing Rhizobium on roots, exist symbiotically with the plant.[28] Examples of crop diseases related to biofilms include Citrus Canker, Pierce's Disease of grapes, and Bacterial Spot of plants such as peppers and tomatoes.[29]
- Biofilms are used in microbial fuel cells (MFCs) to generate electricity from a variety of starting materials, including complex organic waste and renewable biomass.[3][30][31]
- Recent studies in 2003 discovered that the immune system supports bio-film development in the large intestine. This was supported mainly with the fact that the two most abundantly produced molecules

by the immune system also support bio-film production and are associated with the bio-films developed in the gut. This is especially important because the appendix holds a mass amount of these bacterial biofilms.[32] This discovery helps to distinguish the possible function of the appendix and the idea that the appendix can help reinoculate the gut with good gut flora.

6 Taxonomic diversity

Many different bacteria form biofilms, including gram-positive (e.g. *Bacillus* spp, *Listeria monocytogenes*, *Staphylococcus* spp, and lactic acid bacteria, including *Lactobacillus plantarum* and *Lactococcus lactis*) and gram-negative species (e.g. *Escherichia coli*, or *Pseudomonas aeruginosa*).[33]

Biofilms are formed by bacteria that colonize plants, e.g. *Pseudomonas putida*, *Pseudomonas fluorescens*, and related pseudomonads which are common plant-associated bacteria found on leaves, roots, and in the soil, and the majority of their natural isolates form biofilms.[34] Several nitrogen-fixing symbionts of legumes such as *Rhizobium leguminosarum* and *Sinorhizobium meliloti* form biofilms on legume roots and other inert surfaces.[34]

For other species in disease-associated biofilms see below.

7 Biofilms and infectious diseases

Biofilms have been found to be involved in a wide variety of microbial infections in the body, by one estimate 80% of all infections.[35] Infectious processes in which biofilms have been implicated include common problems such as bacterial vaginosis, urinary tract infections, catheter infections, middle-ear infections, formation of dental plaque,[36] gingivitis, coating contact lenses,[37] and less common but more lethal processes such as endocarditis, infections in cystic fibrosis, and infections of permanent indwelling devices such as joint prostheses and heart valves.[38][39] More recently it has been noted that bacterial biofilms may impair cutaneous wound healing and reduce topical antibacterial efficiency in healing or treating infected skin wounds.[40] Early detection of biofilms in wounds is crucial to successful chronic wound management. Although many techniques have developed to identify planktonic bacteria in viable wounds, few have been able to quickly and accurately identify bacterial biofilms. Future studies are needed to find means of identifying and monitoring biofilm colonization at the bedside to permit timely initiation of treatment.[41]

It has recently been shown that biofilms are present on the removed tissue of 80% of patients undergoing surgery for chronic sinusitis. The patients with biofilms were shown to have been denuded of cilia and goblet cells, unlike the controls without biofilms who had normal cilia and goblet cell morphology.[42] Biofilms were also found on samples from two of 10 healthy controls mentioned. The species of bacteria from interoperative cultures did not correspond to the bacteria species in the biofilm on the respective patient's tissue. In other words, the cultures were negative though the bacteria were present.[43]

Biofilms can also be formed on the inert surfaces of implanted devices such as catheters, prosthetic cardiac valves and intrauterine devices. [44]

New staining techniques are being developed to differentiate bacterial cells growing in living animals, e.g. from tissues with allergy-inflammations.[45]

Research has shown that sub-therapeutic levels of β-lactam antibiotics induce biofilm formation in *Staphylococcus aureus*. This sub-therapeutic level of antibiotic may result from the use of antibiotics as growth promoters in agriculture, or during the normal course of antibiotic therapy. The biofilm formation induced by low-level methicillin was inhibited by DNase, suggesting that the sub-therapeutic levels of antibiotic also induce extracellular DNA release.[46] Moreover, from an evolutionary point of view, the creation of the tragedy of the commons in pathogenic microbes may provide advanced therapeutic ways for chronic infections caused by biofilms via genetically engineered invasive cheaters who can invade wild-types 'cooperators' of pathogenic bacteria until cooperator populations go to extinction or overall population 'cooperators and cheaters ' go to extinction.[47]

7.1 Dental plaque

Dental plaque is an oral biofilm that adheres to the teeth and consists of many species of both fungal and bacterial cells (such as *Streptococcus mutans* and *Candida albicans*), salivary polymers and microbial extracellular products. The accumulation of microorganisms subjects the teeth and gingival tissues to high concentrations of bacterial metabolites which results in dental disease.[48]

The biofilm on the surface of teeth is frequently subject to oxidative stress[49] and acid stress.[50] Dietary carbohydrates can cause a dramatic decrease in pH in oral biofilms to values of 4 and below (acid stress).[50] A pH of 4 at body temperature of 37 °C causes depurination of DNA, leaving apurinic (AP) sites in DNA,[51] especially loss of guanine.[52]

A peptide pheromone quorum sensing signaling system in *S. mutans* includes the Competence Stimulating Peptide (CSP) that controls genetic competence.[53][54] Genetic competence is the ability of a cell to take up DNA released by another cell. Competence can lead to genetic transformation, a form of sexual interaction, favored under conditions of high cell density and/or stress where

there is maximal opportunity for interaction between the competent cell and the DNA released from nearby donor cells. This system is optimally expressed when *S. mutans* cells reside in an actively growing biofilm. Biofilm grown *S. mutans* cells are genetically transformed at a rate 10- to 600-fold higher than *S. mutans* growing as free-floating planktonic cells suspended in liquid.[53]

When the biofilm, containing *S. mutans* and related oral streptococci, is subjected to acid stress, the competence regulon is induced, leading to resistance to being killed by acid.[50] As pointed out by Michod et al., transformation in bacterial pathogens likely provides for effective and efficient recombinational repair of DNA damages.[55] It appears that *S. mutans* can survive the frequent acid stress in oral biofilms, in part, through the recombinational repair provided by competence and transformation.

7.2 *Streptococcus pneumoniae*

S. pneumoniae is the main cause of community-acquired pneumonia and meningitis in children and the elderly, and of septicemia in HIV-infected persons. When *S. pneumonia* grows in biofilms, genes are specifically expressed that respond to oxidative stress and induce competence.[56] Formation of a biofilm depends on competence stimulating peptide (CSP). CSP also functions as a quorum-sensing peptide. It not only induces biofilm formation, but also increases virulence in pneumonia and meningitis.

It has been proposed that competence development and biofilm formation is an adaptation of *S. pneumoniae* to survive the defenses of the host.[55] In particular, the host's polymorphonuclear leukocytes produce an oxidative burst to defend against the invading bacteria, and this response can kill bacteria by damaging their DNA. Competent *S. pneumoniae* in a biofilm have the survival advantage that they can more easily take up transforming DNA from nearby cells in the biofilm to use for recombinational repair of oxidative damages in their DNA. Competent *S. pneumoniae* can also secrete an enzyme (murein hydrolase) that destroys non-competent cells (fratricide) causing DNA to be released into the surrounding medium for potential use by the competent cells.[57]

7.3 Legionellosis

Legionella bacteria are known to grow under certain conditions in biofilms, in which they are protected against disinfectants. Workers in cooling towers, persons working in air conditioned rooms and people taking a shower are exposed to *Legionella* by inhalation when the systems are not well designed, constructed, or maintained.[58]

8 Biofilms in medicine

The rapidly expanding worldwide industry for biomedical devices and tissue engineering related products is already at $180 billion per year, yet this industry continues to suffer from microbial colonization. No matter the sophistication, microbial infections can develop on all medical devices and tissue engineering constructs.[59]

60-70% of nosocomial or hospital acquired infections are associated with the implantation of a biomedical device.[59] This leads to 2 million cases annually in the U.S., costing the healthcare system over $5 billion in additional healthcare expenses.[59]

If an infection develops a biofilm, it becomes even harder to treat. As the bacteria changes, it becomes more resistant to antibiotics and the body's own host defenses.[59]

9 See also

- Bacterial nanowires
- Center for Biofilm Engineering
- Chemistry of biofilm prevention
- Kombucha
- Microbial mat
- Phage therapy
- Phototrophic biofilms
- Stromatolite
- List of bacterial vaginosis microbiota

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11 Further reading

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12 External links

- Thickness analysis, organic and mineral proportion of biofilms in order to decide a treatment strategy
- Biofilms 5 International Conference, 10-12 december, Paris
- Biofilm Archive of Biofilm Research & News
- Documentary on Biofilms: The Silent Role of Biofilms in Chronic Disease
- HD Video Interviews on biofilms, antibiotics, etc. with experts

13 Text and image sources, contributors, and licenses

13.1 Text

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13.2 Images

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