AIMS Bioengineering, 2(4): 437-448.
DOI: 10.3934/bioeng.2015.4.437
Received date 6 August 2015,
Accepted date 14 October 2015,
Published date 22 October 2015

http://www.aimspress.com/

Short review

Beneficial biofilms

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Abstract: Surface-adherent biofilm growth is a common trait of bacteria and other microorganisms in nature. Within biofilms, organisms are present in high density and are enmeshed in an organic matrix containing polysaccharides and other molecules. The close proximity of organisms within biofilms facilitates microbial interactions and signaling, including many metabolic processes in which consortia rather than individual organisms participate. Biofilm growth also enables microorganisms to withstand chemical and biological stresses. Here, we review some current literature and document representative beneficial aspects of biofilms using examples from wastewater treatment, microbial fuel cells, biological repair (biocementation) of stonework, and biofilm protection against *Candida albicans* infections. Finally, we address a chemical ecology strategy whereby desired microbial succession and beneficial biofilm formation can be encouraged via manipulation of culture conditions and bacterial signaling.

Keywords: quorum signaling; microbial fuel cell; biocementation; competition; syntrophic metabolism

1. Introduction

Early microbiologists including van Leeuwenhoek, Pasteur, and Zobell noticed a tendency for microorganisms to grow on surfaces (reviewed in [1]). Although several cell surface structures, notably pili, and capsules were associated with adhesion [2,3], the significance of surface-adherent microorganisms and the term biofilm was only fully realized during the 1980's by the work of Costerton, Høiby, and their contemporaries (reviewed in [4,5]). Notable issues associated with biofilms include their resistance to antimicrobial agents, and predation by protozoa and phagocytic cells associated with the immune system. The biofilm mode of growth enables organisms to withstand a number of environmental stresses including adverse chemical and physical environments [4]. While there is considerable literature related to negative aspects of biofilms including chronic infections and industrial biofouling and corrosion (reviewed in [4,6]), there are a number of positive aspects associated with biofilms. Here we describe several examples of beneficial biofilms and investigate potential strategies whereby such biofilms can be enhanced. Through this brief coverage of the topic, we hope to encourage further research in this area.

2. Microbial Interactions within Biofilms

In their natural environments, bacteria and other microorganisms typically attach to surfaces as polymicrobial biofilm communities. Certainly the biofilm mode of growth enables organisms to interact with each other as well as persist in flowing environments such as rivers [7] and urinary catheters [8]. Although the term biofilm is commonly associated with microbial communities at a liquid-solid interface, microbial mats and pellicles at liquid-air interfaces [9] also exhibit features in common with biofilm communities on liquid-solid interfaces. As well microbial flocs, aggregates of microorganisms suspended in liquids, exhibit similar properties to biofilm communities on surfaces [10]. For the purposes of this review, the term biofilm will be used to describe any surface-adherent microbial community. In the context of biogeochemical cycling, a variety of processes are naturally associated with biofilm communities. These include decomposition of insoluble materials including ligno-cellulosic plant materials [11] and even mineral and rock formation [12].

Chemical and physical environments within biofilms can change dramatically within very short distances. Indeed chemical and physical microenvironments are unique aspects of biofilm structure and contribute to the highly varied physiology, growth, gene expression, and distribution of organisms within these microbial communities [13,14]. One notable example is the prevalence of microaerophilic and anaerobic organisms within polymicrobial biofilms in the aerobic environment of the human mouth [15]. Here, aerobic community members scavenge oxygen, thus allowing anaerobes such as *Fusobacterium nucleatum* to thrive. As living communities, biofilm populations are not static but change as a consequence of nutrient availability and microbial succession. Microorganisms are also able to communicate through a variety of chemical signals [16]. Notable signaling mechanisms identified include a variety of quorum signals notably acylated homoserine lactones (AHLs) prominent in many gram negative biofilms; small peptides in gram positive biofilms, often referred to as bacterial pheromones [17]; and autoinducer 2 (AI-2) [18,19] which are present in most bacterial biofilms. Chemical signaling has also been described in Archaea [20] and eukaryotic biofilms [21] and recently signaling through direct contact mechanisms between organisms has also been described (reviewed in [22]).

3. Biofilm Physiology

The biochemical processes within biofilms are typically conducted by consortia of microorganisms in which a particular process is conducted by the biofilm community as a whole; and individual community members contribute specific responsibilities. The metabolic interactions within polymicrobial biofilms have been compared to tissues in multicellular organisms, in that individual cells become specialized as to their specific role in the overall biofilm community metabolism [23]. In some cases, organisms enter an obligatory synergistic metabolic association (syntrophic metabolism) in order to perform an otherwise energetically unfavorable metabolic process [24]. Syntrophic metabolism was originally documented as interspecies hydrogen transfer between fermenting organisms such as *Ruminococcus albus* and methanogenic Archaea, but is now widely recognized in a number of different environments [25]. Certainly the close association of syntrophic participants within a biofilm facilitates these reactions. Another notable example of physiological associations commonly encountered within beneficial biofilms in sewage treatment, is the association of *Nitrosococcus* sp and other ammonia-oxidizing bacteria with nitrite-oxidizing bacteria including *Nitrospira* sp [26]. Here, highly soluble nitrite produced by ammonia oxidation can be quickly used by nitrite oxidizing bacteria, growing in immediate proximity within a biofilm. Such metabolic interactions would not be practical in suspended (i.e. planktonic) populations.

4. Exploitation of Biofilm Physiology Benefits

Beneficial biofilms are frequently employed in wastewater treatment. Suspended solid matter within wastewater is rapidly colonized by bacterial biofilms prior to decomposition. The biofilm-mediated waste decomposition is not limited to human waste but has also been found practical in treatment of wastewater from agricultural animal facilities and food processing factories. A common example is a trickling filter (reviewed in [27]). Here wastewater is sprayed onto a gravel bed whereon a biofilm community develops and the microbial consortia within the biofilm, decomposes the organic matter within the wastewater. Depending upon the biofilm communities, such biofilm bioreactors can be used to remove organic carbon and/or nitrogen [28]. In commercial aquaculture and large-scale aquaria, elevated levels of NH_4^+ arise from nitrogenous animal waste. Dissolved ammonia can be quite toxic to many forms of aquatic life and so biofilters have been developed which incorporate biofilms of nitrifying bacteria (ammonia oxidizing and nitrite oxidizing bacteria) to convert NH_4^+ to the less toxic NO_3^-. In some newer bioreactors, the aerobic nitrification and anaerobic denitrification processes (NO_3^- reduction to N_2) are combined [29] resulting in removal of the excess nitrogen from the system. Recent developments in technology associated with wastewater filters have included refinements in materials used to support biofilms, inoculation parameters, and the control of potential bacterial predators [28].

Many biological reactions involve oxidation and reduction reactions, which necessarily result in electron flow. Consequently, there has been considerable interest in exploiting biofilm electron flow in microbial fuel cells. In one design of a microbial fuel cell (Figure 1) [30], the chamber consists of two main components that serve as an anode and cathode that are partitioned by a semi permeable, proton exchange membrane between the two. The proton exchange membrane serves to divide an aerobic and anaerobic environment while allowing the movement of hydrogen ions. The anode serves as an anaerobic chamber and as the final electron acceptor. As microbes metabolize organic carbon they generate protons, electrons, and CO_2 as by products. Electrons are then shuttled to the cathode via a conduction line and the resulting current can be harvested for use. As electrons move to the cathode the semi-permeable membrane simultaneously passes hydrogen ions which are then oxidized by an oxidizing agent, such as oxygen, to recombine the hydrogen and electrons [31,32]. Many industries are now considering the use of MFCs for a wide variety of liquid effluent such as wastewater from potato processing, agricultural animal wastewater and human waste [32]. A fairly recent study related to space flight used human feces wastewater with a two-chamber MFC which resulted in a maximum power density of 70.8 mW/m^2 and the removal efficiency of total chemical oxygen demand (TCOD), reached 71%, 88% and 44%, when operated for 190 h. The implications show that MFCs are applicable and fitting for treating human feces wastewater. The power generation was even further improved by 47% when fermented in a pretreatment process [33].

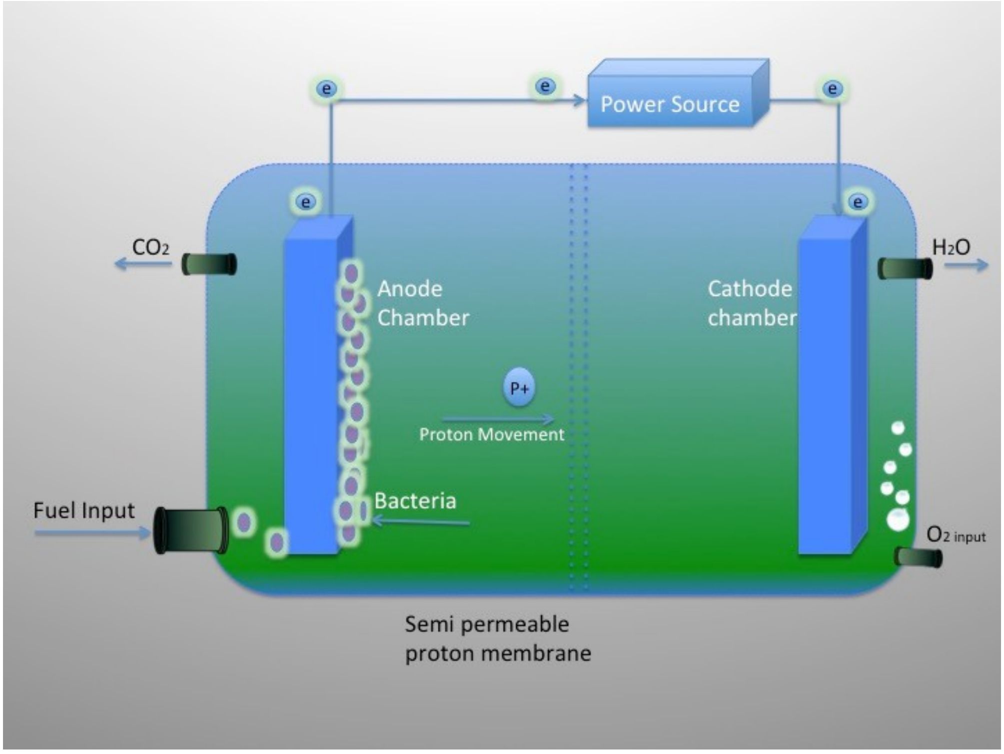

Figure 1. Schematic showing how different microbial species within a biofilm can cooperate during a metabolic activity. The oxidation and reduction processes that occur during wastewater treatment generate an electric potential, which can be harvested for use in a microbial fuel cell [31,32].

Traditional studies of bacterial catabolism identified sugars and other soluble compounds as electron donors and similarly soluble molecules (e.g. O_2, NO_3^-, and SO_4^{2-}) as terminal electron acceptors during respiration. Bacteria are able to use insoluble substrates as electron donors and recipients and have developed elaborate mechanisms whereby electrically conductive pili-like appendages (nanowires) are able to transmit electrons. In some cases, electrically conducting nanowires contain cytochrome-like molecules [34], whereas in other cases aromatic amino acids have been shown to conduct charges [35]. In the absence of nanowires, some molecules such as phenazines have been used as electron shuttles [36]. Although galvanic action within biofilms has been described in the negative context of microbial induced corrosion [37], benefits of biofilm-mediated electrical generation can be achieved by the designs of appropriate biological reactors and culturing parameters (Figure 1) [35]. Development of microbial fuel cells is an active area of research, and represents an exciting application of beneficial biofilms.

Biocementation is another potential beneficial aspect of biofilms that can be used to slow down and in some cases reverse degradation of some stone-constructed buildings, monuments, and even statues [38]. Here, bacteria that can promote mineral deposition are incorporated into a paste containing a variety of calcium salts, urea (if urease-producing bacteria are involved), and a carbon source. In the case of urease-producing bacteria, the hydrolysis of urea produces NH_3 and CO_2 and elevates pH [39]. The resultant NH_4^+, OH^- and CO_3^{2-} ions, elevate pH and causes precipitation of Ca^{2+} as calcite ($CaCO_3$). The charged polymers within biofilm matrices can also bind metal ions and promote mineral formation [40]. As well the biofilm matrix can serve as an adhesive to connect the calcite mineral components. While this concept does have potential, care must be taken since a number of microorganisms are also involved in rock weathering and decomposition [41].

5. Biofilm as Protective Communities

Microbial competition is a natural feature within bacterial populations including biofilms. There are several situations in which higher organisms encourage biofilm formation by protective biofilms. One example of this feature is in the green macroalga, *Ulva lactuca*. This organism encourages colonization by the marine gram negative bacterium, *Pseudoalteromonas tunicate*. This endophytic bacterium produces antifouling compounds that inhibit colonization by other undesirable bacteria [42]. Another example of biofilm protection is found with wheat rhizosphere colonization by *Pseudomonas chlororaphis* (aureofaciens), which confers protection of wheat plants from fungal diseases [43].

Of relevance to human health is the microbiome, as microorganisms associated with humans are estimated to outnumber host cells by ten-fold [44]. Within the microbiome, bacteria often grow and function as biofilms on tissue surfaces or within the mucosa. One notable case of microbiome protection of humans deals with the prevention of *Clostridium difficile* infections. *C. difficile*, a minor component of normal flora, will grow when other competing normal flora are diminished as a consequence of clindamycin and other broad-spectrum antibiotic therapy. A number of theories related to the mechanisms of normal flora protection against *C. difficile* have been suggested (reviewed in [45]) but the exact mechanism(s) of protection remain elusive due to the complexity of the intestinal flora. Another example of protective biofilms is the protection offered against the fungal pathogen, *Candida albicans*, by normal flora in the oral cavity and female reproductive tract. As is the case with *C. difficile*, depletion of the normal flora can result in an overgrowth of *C. albicans* and resulting oral or vaginal candidiasis [46]. There have been instances where individual mechanisms have been identified wherein specific bacterial species can inhibit *C. albicans* virulence [46,47], but this does not explain the general phenomenon of enhanced *C. albicans* growth when the complex normal flora is diminished. There was a recent report of antagonism of one oral bacterium, *Aggregatibacter actinomycetemcomitans* against the fungal pathogen, *Candida albicans* via the quorum signal, AI-2 [48]. *C. albicans* is an opportunistic pathogen in several environments including the oral cavity and the female reproductive tract. Under normal circumstances, *C. albicans* overgrowth and associated pathology are prevented by the innate immune system and competition from the normal flora. In light of the Bachtiar et al study [48], and the prevalence of AI-2 in many oral biofilms [19], there is speculation that oral and vaginal biofilms may protect the human host against *C. albicans* infection by virtue of AI-2 production [49], although other mechanisms may be involved.

6. A Potential Strategy for Encouraging Beneficial Biofilms

Due to the economic and medical importance of biofilms, there have been considerable scientific and engineering effort to design surfaces and coatings to control bacterial adhesion and subsequent biofilm formation. Because of negative aspects of many biofilms associated with corrosion or chronic infections [4], the majority of this work has been focused on biofilm prevention or removal. Examples of research include modification of surface topography and chemistry [50], coatings [51] and the applications of various biocides [52]. In these cases, the strategy is to try to make a colonization-resistant surface or alternatively kill and remove adherent bacteria, however this strategy does not work well in nature. A number of different bacteria may colonize a surface that might be resistant to one species, or alternatively an antimicrobial surface may be colonized by dead bacteria, which can then shield living organisms [4,53]. More recently, compounds have been identified that interfere with bacterial quorum signaling [54], and so target a key signal needed in microcolony formation and biofilm maturation. Quorum signaling has also been associated with the antibiotic tolerance phenotype in biofilms and not surprisingly, treatment of experimental biofilm infections with combination antibiotics and quorum-inhibiting compounds has shown some promise in vitro and in vivo [55]. Other compounds have been identified as potential detachment signals [56,57], which would promote the dispersion of preexisting biofilms and presumably loss of biofilm-mediated antimicrobial tolerance.

As described earlier, biofilms can be beneficial and so it is highly appropriate to consider strategies that encourage desired populations. While populations can be constructed in a microbiology laboratory, there is a question of stability once laboratory-grown biofilms are introduced into a natural setting and are subject to competition from other organisms as well as changing environmental conditions [58]. In this context, we can revisit the use of enrichment culture technology [59] to encourage desired microbial populations within biofilms. Microbial succession during the colonization of surfaces has been described in oral microbiology [19,60,61] and presumably analogous succession patterns occur in other environments. On teeth, proteins from saliva absorb onto the tooth surface forming a conditioning film, which becomes colonized by a primary population of colonizers including *Streptococcus gordonii* and *Streptococcus oralis* [60]. Secondary populations of bacteria including *Fusobacterium nucleatum* then colonize the primary colonizers, *S. gordonii* and *S. oralis*. Originally dental microbial succession was attributed to coaggregation, namely specific lectin-based interactions of adhesins from secondary colonizers including *F. nucleatum* to cell-surface polymers of *S. gordonii* and *S. oralis* [60]. More recent studies have shown that metabolite production from primary colonizers and cell signaling by AI-2 are also involved in *F. nucleatum* colonization of established dental biofilms and microbial succession processes [19,61]. Conditioning films have been found in other surfaces including urinary catheters and metal surfaces prone to corrosion [62,63]. In contrast to dental biofilms, less is known about the microbial interactions and succession processes during biofilm community formation in other environments.

Chemotaxis is an important feature during colonization as bacteria are typically attracted towards nutrients, which may arise from the conditioning film, or alternatively metabolites from a biotic surface. This has been extensively documented in the rhizosphere of plants [64] (Figure 2). In this environment, various organic compounds are produced by plant roots and these exudates have been associated with the recruitment and development of rhizosphere microbial communities that can protect the host plant from pathogens, and in many cases provide the plant, nitrogen, phosphorous and other nutrients [65]. There is now growing evidence that plants can manipulate the microbiome community composition, physiology, and microbial gene expression via root exudates [64,65]. Plants are also able to manipulate biofilms and microbial communities on leaves and other surfaces. One of the best known examples of biofilm manipulation has been described in several species of macroalgae (reviewed in [66]). Macroalgae such as *Delisea pulchra* live in marine environments with potentially high biofouling pressure, yet this plant is colonized by very few bacteria. Investigators from Denmark, Australia, and elsewhere showed that a major reason for this lack of bacterial colonization was the production of a number of quorum-inhibiting furanone compounds by *D. pulchra* [67]. *D. pulchra* is not unique in this context since a number of quorum- and biofilm-inhibiting compounds have been described in other marine algae and also invertebrates (reviewed in [66]). However one area that is largely unexplored is the role of bacterial metabolism and signaling during microbial succession in biofilm development.

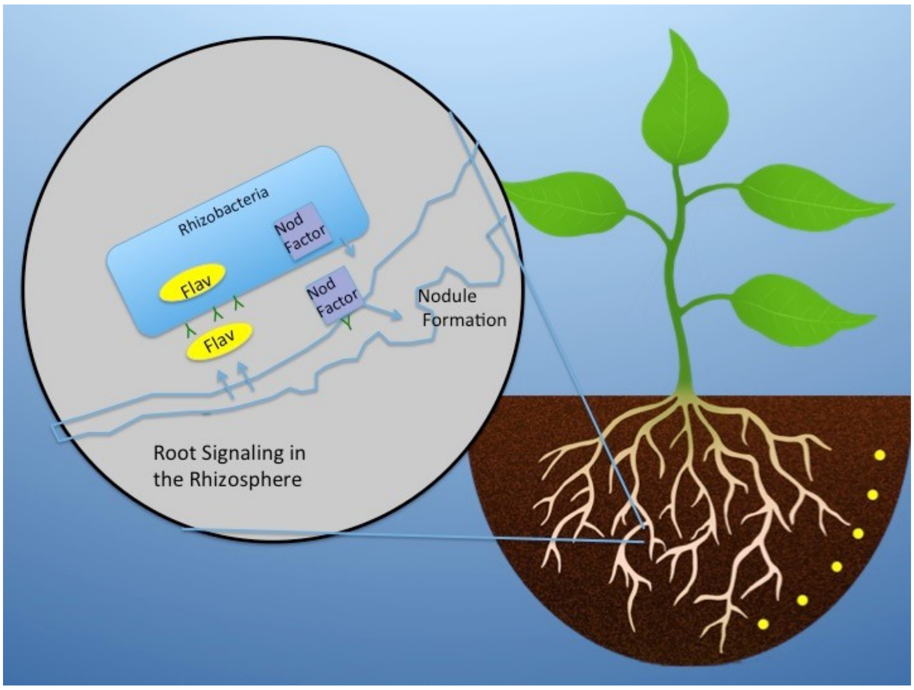

Figure 2. The rhizosphere is the region immediately adjacent to plant roots and represents an environment wherein plants can recruit and manipulate the physiology and gene expression of beneficial biofilm communities. Although the basic concepts are shown here, recent transcriptome studies by Zhang et al [64] show that rhizosphere interactions between maize and the plant-growth promoting bacterium, *Bacillus amyloliquefaciens* SQR9 are quite extensive; and can represent a model for promoting the growth and function of beneficial biofilms.

Several years ago, we employed denaturing gradient gel electrophoresis to study the diversity of bacteria in a spring fed lake that colonized dialysis tubing containing spent culture from N-acyl-homoserine lactone (AHL)-producing and AHL-non-producing cultures [68]. In this study, we observed that microbial diversity in the presence of spent culture media was significantly reduced than in the presence of abiotic controls (Figure 3), and that subtle changes occurred in the presence and absence of AHL signals. While more work needs to be done in this area, the prospect of using nutrients and signals from primary colonizers to control microbial succession, represents an intriguing strategy that can be employed to form desired, beneficial biofilms.

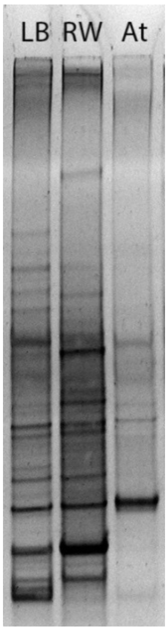

Figure 3. Potential microbial control of biofilm colonization by bacteria in a spring-fed lake. Dialysis tubing containing either spent culture media or sterile broth was placed into a spring fed lake for 5h, where it could be colonized by aquatic bacteria [68]. Tubing containing spent media from *Agrobacterium tumefaciens* (At) had low diversity, whereas control tubing containing sterile media (LB) or river water (RW) had much higher diversity, reflected in the number of bands as seen by denaturing gradient gel electrophoresis [68]. This finding suggests that bacteria may be able to control microbial succession on a surface by metabolite or signal production.

7. Conclusion

Microbial communities have been associated with surfaces since the early observations of van Leeuwenhoek [1] and at least one type of biofilm community (stromatolite-associated microbial mat) is thought to represent a very ancient form of life [12]. The biofilm mode of growth has been associated with enhanced antimicrobial resistance since the mid 1980's [69] and negative aspects of biofilms have been described in a number of medical and industrial contexts (reviewed in [4]). However there are many positive aspects of biofilms. Certainly the intimate interactions between microbial consortia are of particular use during carbon and nitrogen removal during wastewater degradation [1]. Other beneficial applications of biofilms include their use in microbial fuel cells [35] and protection of higher organisms against undesirable microorganisms [49]. One of the challenges in future research will be to refine this technology and develop protocols for encouraging the growth and persistence of desirable biofilms.

Acknowledgements

This work was made possible by the Homer E Prince Microbiology endowment and support from the Biology Department, Texas State University. RJCM would like to thank a number of current and former students and collaborators who made this work possible including MK Lyles, MB

Barnes, C Fuqua, C Longoria, A Stolzman, S Thornhill, KC Garcia, K White, and M Whiteley.

Conflict of Interest

All authors declare no conflict of interest.

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