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Bio-FET

► Nanostructure Field Effect Transistor Biosensors

Biofilms in Microfluidic Devices

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Synonyms

Floccules; Microbial aggregations

Definition

Biofilms are aggregations of microbes that are encased by extracellular polymeric substances (EPS) and adhere to surfaces or interfaces. Biofilms exist in a very wide diversity of environments, and microfluidic devices are being increasingly utilized to study and understand their formation and properties.

Overview

Microbes often form aggregates on interfaces, and due to a production of EPS, the aggregates become encased in a matrix [1]. Though microbes in a biofilm are physiologically distinct from bacteria growing in a free swimming state (planktonic bacteria), biofilm growth is a complex process that is typically initiated by planktonic bacteria themselves. Biofilm growth is initiated with bacterial adhesion to a surface, followed by events such as growth, EPS secretion, and morphological and physiological changes. Microbial biofilms

are excellent examples of multi-scale phenomena. Cell-to-cell communication, which plays a role in biofilm formation, is molecular in nature, but occurs over a scale of several cells. Adhesion events occur at the nanometer scale and are mediated by pili or flagella, while the cells themselves are typically micron-sized. Finally the biofilms themselves typically range between 10 and 1,000 μm in thickness. These length scales are compatible with the scale of microfluidic devices, thus making such tools useful for exploring the spatiotemporal properties of biofilms. Moreover, microfluidic devices are often optimized for online optical monitoring and/or incorporation of sensors. These factors make microfluidic devices appropriate for studying biofilms. For example, the effect of miniscule changes in molecular cues (such as nanomolar concentrations) can be characterized and studied easily with microfluidic devices. Another advantage of microfluidics is that they enable the precise control of the microenvironment, thereby allowing biofilms to be subjected to controlled external stimuli. Thus, when molecular cues or signals are externally applied, minute responses in the biofilm can be effectively studied. The use of microfluidics offers distinct advantages for fundamental studies regarding the nature, properties, and evolution of microbial biofilms. Beyond being a platform for such studies, microfluidics is being increasingly applied toward miniaturized device creation. In this entry, some of the basic methodologies involved in biofilm studies in microfluidic devices are first discussed, followed by a discussion on some of the key findings reported in this area.

Methodology

Microfluidics

Microfluidics is the precise control and manipulation of fluids contained to miniaturized channels (typical length scale <100 μm). In the microfluidics regime, fluid flow is laminar, and flow is dominated by Stokes drag and surface tension effects. The study of biofilms in microfluidic devices typically requires device design and fabrication, controlled microbial growth, and analysis. Microfluidic device fabrication by itself is a significantly evolved science. There are several different techniques for device fabrication including, but not limited to, various micromachining processes and polymer-based soft-lithography. Complex structures such as micropumps, microvalves and mixers can also be incorporated on microfluidic devices with the help of different microfabrication techniques. The techniques of microfabrication are beyond the scope of this article and interested readers can refer to one or more manuscripts on this topic [2, 3].

Biofilms

A wide range of microbial species produce biofilms. Once the appropriate device is fabricated, controlled biofilm growth in the device may be desirable. For controlled in situ biofilm growth in a microfluidic device, a dilute microbial culture may be introduced into the microfluidic device. The diluted samples are made from liquid microbial cultures once the culture achieves a specified optical density (OD). A fluid port usually provides a means for the introduction of the inoculum into the device. Depending on the microorganism and its microenvironment and the specific experimental need, proper biofilm growth can require anywhere between a few hours to several days. During this interval, it might be desirable to control environmental conditions such as temperature and humidity. In such circumstances, the device is typically housed in an incubator. Depending on the organism, aerobic or anaerobic environment may be necessary. For microfluidic devices made from PDMS or similar permeable polymers, maintaining an aerobic environment is usually not an issue. On the other hand, to maintain anaerobic conditions typically necessitates more complex device fabrication techniques. Analysis of biofilm formation may be done by various forms of microscopy. Microfluidic devices usually lend themselves to optical microscopy with considerable ease – one of the reasons why it is popular as a diagnostic setup. Use of thin-walled chambers and optically clear materials in microfluidic devices allows probing through optical means and use of high-magnification lenses. Confocal laser scanning microscopy (CLSM) has been demonstrated as a tool for integrating microfluidics in studying the evolution and structural heterogeneity of biofilms [4]. Other forms of microscopy may also be employed such as scanning electron microscopy (SEM) and atomic force microscopy (AFM). Besides microscopy, micro- and nanosensors can also be easily incorporated into a microfluidic device for in situ monitoring. For example, micro-electrodes fabricated on

a glass substrate can be incorporated in a microfluidic device for electrochemical impedance spectroscopy studies.

Key Findings

Microfluidic devices, in conjunction with microscopy and other analytical techniques, enable flexible and novel approaches for probing the multiple determinants of biofilm formation. Two factors shaping the dynamics of biofilm formation are fluid dynamics and cell phenotype. Fluid dynamics determine shear forces that govern cell attachment and detachment rates, which can alter whether or not a biofilm will form, biofilm depth, biofilm density, and surface coverage. On the other hand, cell phenotype dictates important processes such as EPS production, growth rate, and flocculation, all of which can also have profound effects on biofilm structure and function. Cell phenotype, in turn, is a function of both environmental cues and cell-cell communication. Accordingly, recent studies have harnessed microfluidic technology to probe the effects of fluidic dynamics, cell phenotype, and cell-cell communication. Mathematical modeling efforts have integrated these findings and guided further investigations.

Influence of Fluid Dynamics on Biofilms

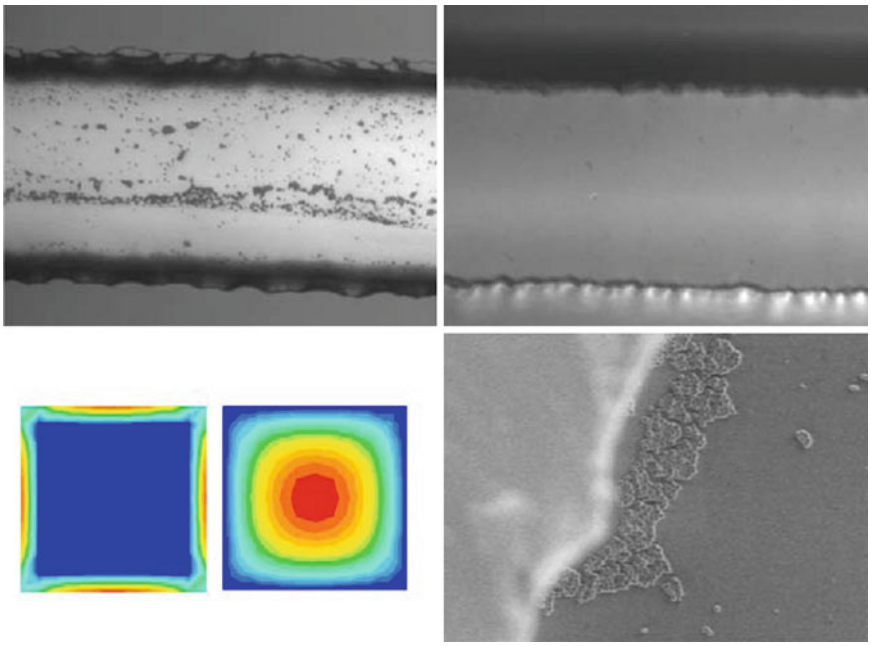
Several studies have examined the effects of hydrodynamics on biofilm development. For example, microfluidic devices were used by Lee at al. [5] to study the influences of hydrodynamics of local microenvironments of *Staphylococcus epidermis* biofilm formation (Fig. 1). They observed that at high flow velocity, the cells formed an elongated biofilm morphology, and at low fluid velocity clump-like multilayered biofilms were produced. The results of this study indicate that microfluidic devices with embedded microvalves can perhaps be used for screening the effects of therapeutic reagents, and as novel tools for developing predictable in vitro models of biofilm-related infections. Also, Rusconi et al. [6] studied suspended filamentous biofilms in a microfluidic device. Experiments with several bacterial strains under high flow inside the miniaturized channels demonstrated the link between the extracellular matrix and the development of biofilm structures. Secondary vertical motion from the numerical simulations of the flow in the curved channels of the microfluidic device proved that the hydrodynamic forces were key in influencing the formation of suspended biofilm filamentous structures. Another study by Richter et al. [7] examined the influence of shear stress on the growth and structure of fungal biofilms using microfluidic systems. Electrode structures were incorporated into a microfluidic device for performing cellular dielectric spectroscopy, enabling real-time, noninvasive quantification of cell morphology changes. Increase in shear stress caused a significant change in the biofilm formation patterns, and the addition of amphotericin B resulted in distinct dynamic behavior of the biofilm.

Effect of Cell Phenotype on Attachment

In addition to hydrodynamics, cell phenotype plays an important role in biofilm formation. For example, after initial attachment, pili, flagella, and adhesins can help cells adhere to surfaces. Characterizing these determinants of cell attachment is critical for understanding the early stages of biofilm development. Using a microfluidic device, De La Fuente et al. recently examined the roles of different *Xylella fastidiosa* pili in determining cell adhesion at different flow rates [8]. To do so, they compared different genetic variants: wild-type cells, cells with only type I pili, cells with only type IV pili, and cells with no pili. They subjected these variants to different drag forces by exposing the cells to different fluid flow rates. The results enabled quantification of the role of the different pili in attachment, and the adhesion force values were within the range of adhesion forces determined by AFM and by laser tweezers for other microbes.

Cellular-Communication Inside Microfluidic Systems

Several cell processes relevant to biofilm formation, including dispersion, EPS secretion, and lipid secretion, are often regulated by cell-cell communication. Thus, several studies have focused on studying intercellular communication in biofilm contexts. Specifically, many microbes communicate through the process of quorum sensing. Quorum sensing (QS) enables a group of cells to measure their local population density through the synthesis of and response to small signal molecules that can pass from cell to cell. While quorum sensing regulates several microbial behaviors that influence biofilm formation, biofilm



Biofilms in Microfluidic Devices, Fig. 1 Microfluidic devices can be engineered to produce well-defined flow structures and shear rates. Such devices can be used to investigate hydrodynamic influences on biofilms (From Lee et al. [5]. Reproduced with kind permission from Springer Science and Business Media)

characteristics in turn strongly impact the efficiency of quorum sensing and signal transport, thus setting up an interplay between quorum sensing and biofilm formation. Consequently, microfluidic studies have been used to examine quorum sensing in a biofilm context.

Timp et al. [9] studied genetically engineered cells in microfluidic devices to explore the fundamental principles of quorum sensing in biofilms. Engineered cells were flowed through a microfluidic channel into a region where optical traps were used to position cells into defined patterns. The patterned cells were then enclosed in a hydrogel to mimic a biofilm. "Transmitter" cells synthesized an N-Acyl Homoserine Lactone (AHL) communication signal which was detected by "receiver" cells that fluoresced in response. Activation of the receiver cells by the transmitters was found to be heavily dependent on the hydrodynamics around the biofilm mimic. In particular, low flow rates corresponding to diffusion-dominated transport yielded efficient communication between transmitters and receivers, but this communication began to break down at high flow rates corresponding to convection-dominated transport. These results indicate that the density of bacteria necessary to constitute a "quorum" depends on the hydrodynamic properties of the environment. A similar conclusion was reached by Connell et al. [10] who studied QS in fabricated picoliter-scale microcavities. Specifically, the authors found that they could achieve a sixfold increase in QS-dependent gene expression by bacteria trapped within their microcavities when they reduced the external flow rate from 250 to 5 μL min^{-1}.

Another interesting aspect of QS highlighted by the Connell study was the importance of cell density, rather than total cell count as a factor governing QS behavior. In particular, because the authors were able to capture small numbers of cells in small volumes, they were able to control cell density independent of cell population size. As a result, they were able to show that as few as 150 cells are capable of exhibiting QS behavior, provided that the cells are constrained such that cell density remains relatively high. This is important, since it demonstrates the potential for small bacterial communities to exhibit some of the properties (e.g., antibiotic resistance), which are typical of biofilms. In a related study, Boedicker et al. used microfluidics to examine the QS behavior of small numbers of bacteria trapped in poly(dimethylsiloxane) (PDMS) wells [11]. In this study, the authors were able to trap as few as one to two cells in each well, and while the majority of cells needed several rounds of cell division to initiate QS, on occasion the authors found single cells expressing QS controlled genes. Again, this result showed that it is bacterial density, rather than bacterial cell numbers, that is of fundamental importance to the onset of QS behavior.

Another aspect of QS and microbial aggregation was investigated by Park et al. [12], who devised a microfluidic device resembling a maze. They investigated the growth of *Escherichia coli* cells in the device. They found that the device geometry affected aggregation of the cells. Their results led them to conclude that self-attraction in microbes could allow them to easily exceed critical QS densities.

Collectively, these studies exemplify the flexibility offered by microfluidic systems to precisely define the cell's microenvironment, including cell position, confinement geometry, and fluid flow rate. These studies have begun to shed light on fundamental questions such as when quorum sensing is truly used to sense local population as opposed to merely sensing environmental conditions such as the local diffusion rate or degree of confinement. Thus, microfluidics is enabling the study of biological principles that would otherwise not be possible using conventional approaches in biology. We next focus on how data from these unique experimental studies can be used to validate mathematical models of biofilm formation and lead to new insights.

Mathematical Biofilm Modeling and Microfluidics

Thus far several determinants of the process of biofilm formation including fluid dynamics, cell phenotype, and cell-cell communication have been discussed. The complex nature of biofilm formation makes mathematical modeling challenging, yet critical for developing a fundamental quantitative understanding of the underpinnings of the process. Proper mathematical models take into account the multistaged process with its broad range of time and length scales. Mathematical development of biofilms has been long pursued with substantial developments having taken place in the past two decades. Klapper and Dockery present a comprehensive review of mathematical model development for biofilms [13]. Today, rapid developments in the biofilm community are pushing the need for better and comprehensive models; microfluidics presents itself as an invaluable aid to the modeling community. Microfluidics not only affords researchers to explore in real time biofilm growth and dynamics, but it also allows for a controlled microenvironment that can be adjusted to suit the need of the user. A controlled microfluidic environment amenable to probing by various sensors can allow researchers to pursue valuable validation experiments for proposed models. In one such study, Janakiraman et al. [14] used a microfuidic device to study biofilm development of *Pseudomonas aeruginosa* PA14, where mass and species transport effected biofilm development and vice versa. Their use of a microfluidic device allowed assessment of biofilm growth variation with shear rates, finally leading to model validation. The validated model, which took into account mass transport and its effect on quorum sensing, allowed valuable conclusions such as that flow rate could be used to turn on and turn off quorum sensing within the biofilm. Experimentally validated models like the one presented by Janakiraman et al. [14] allow a greater understanding of biofilm kinetics. In another study, Volfson et al. [15] used microfluidic devices to investigate spatial ordering and self-organization of microbes in a microfluidic device. The authors were investigating the role of contact biomechanics in the formation of dense colonies and toward this end they used a controlled microfluidic device to monitor the two-dimensional growth of motile microbes. The experimental investigations were combined with discrete element simulations (DES), and the authors showed that biomechanical interactions could lead to highly ordered structures in a microbial colony. Such investigations can help in the complete understanding of the role of various environmental and self-generated factors that play a role in biofilm formation. Deeper quantitative understanding of biofilm formation, resulting from the interplay between modeling and experimental validation with microfluidics, will drive progress in various applications.

Other Uses of Lab-On-A-Chip Technologies

Lab-on-a-chip (LoC) technologies refer to a suite of technologies that have evolved primarily over the last decade, where complex operations such as cell culture and sensing are integrated in a miniaturized platform. Apart from sensors, LoC technologies allow microfluidic systems to be interfaced with other systems such as micro-electro-mechanical (MEMs) and opto-electric systems. MEMs devices in LoC systems have been harnessed for various studies on microbial biofilms. Several different MEMs devices have been used to pursue biofilm-related studies, thus providing key insights into fundamental phenomena such as cellular self-organization in biofilms and the role of motility [16]. Purely electrical systems have also been incorporated into LoC systems and have been

employed to investigate physiological heterogeneity within microbial biofilms [17]. Emerging lab-on-a-chip technologies can also benefit biofilm research. For example, novel opto-electric techniques [18] might find a use in biofilm engineering. Rapid electro kinetic patterning (REP) is an opto-electric technique, which can be used to manipulate micro- and nanosized objects noninvasively in a microfluidic device. REP has already been used to capture an aggregation of *Shewanella oneidensis* MR-1 in a microfluidic device and place it at user-defined intervals using an infrared laser and electric fields [18]. Such an approach could be used to trigger and organize the formation of beneficial biofilms.

Other than such appeal, LoC technologies are also being employed to fabricate miniaturized devices for applications such as current production and miniaturization of assays for clinical testing.

Future Perspectives

Microfluidic systems integrated with mechanical and/or electrical transducers and sensor components open up new ways to understand biofilm formation and bacterial surface interactions. Biofilms subjected to external stimuli through molecular cues during the growth and establishment stage can be characterized for their mechanical properties more accurately using microfluidic systems. Qualitative assessment of temporal and spatial patterns of biofilm formation against antimicrobial actions (chemical method) or electric field interference [19] or a physical disruption can be effectively studied using microfluidic systems.

Acknowledgments A. Kumar performed the work as a Eugene P. Wigner Fellow at the Oak Ridge National Laboratory (ORNL). The authors acknowledge research support from the US Department of Energy (US DOE) Office of Biological and Environmental Sciences. ORNL is managed by UT-Battelle, LLC, for the US DOE under Contract no. DEAC05-00OR22725.

Cross-References

- ▶ Micro- and Nanofluidic Devices for Medical Diagnostics
- ▶ Micro/Nano Transport in Microbial Energy Harvesting

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Biognosis

► Biomimetics

Bio-inspired CMOS Cochlea

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Synonyms

Bionic ear; Cochlea implant; Gammatone filters; Log-domain; Low-power

Definition

This chapter deals with the design and performance evaluation of a new analogue CMOS cochlea channel of increased biorealism. The design implements a recently proposed transfer function [12], namely the One-Zero Gammatone Filter (or OZGF), which provides a robust foundation for modeling a variety of auditory data such as realistic passband asymmetry, linear low-frequency tail, and level-dependent gain. Moreover, the OZGF is attractive because it can be implemented efficiently in any technological medium – analogue or digital – using standard building blocks. The channel was synthesized using novel, low-power, Class-AB, log-domain, biquadratic filters employing MOS transistors operating in their weak inversion regime. Furthermore, the chapter details the design of a new low-power automatic gain-control circuit that adapts the gain of the channel according to the input signal strength, thereby extending significantly its input dynamic range. The performance of a fourth-order OZGF channel (equivalent to an eighth-order cascaded filter structure) was evaluated through both detailed simulations and measurements from a fabricated chip using the commercially available 0.35 μm AMS CMOS process. The whole system is tuned at 3 kHz, dissipates a mere 4.46 μW of static power, accommodates 124 dB (at <5% THD) of input dynamic range at the center frequency, and is set to provide up to 70 dB of amplification for small signals.

Introduction

The first generations of high-performance cochlea designs were synthesized using g_m-C filters and relied on power-hungry linearization techniques and/or the compressive action of the AGC for extending the input DR. However, recent advances in the field of analogue filter design have led to the development of inherently compressive systems that operate internally in the nonlinear domain while preserving overall input–output linearity. The application of *companding* in filter design resulted in the successful realization of topologies that were able to attain a wider input DR with a lower power-supply requirement compared to traditional g_m-C filters employing linearized transconductors. These companding filters or processors belong to the more general class of ELIN (Externally-Linear–Internally-Nonlinear) systems [21], and their systematic synthesis is articulated in the pioneering works of Frey [7] and Tsividis [20]. It is worth noting that the need for inherently compressive filters emerged very early in the development process of micropower, high DR cochlea designs and, in fact, a bit earlier than the first 1993 Log-domain paper by Frey [6].

Since Frey's [6] paper, Log-domain circuits progressed significantly with several contributions aiming at increasing the input DR and lowering the quiescent power dissipation. The two most thoroughly studied techniques are: (a) The use of two Class-A filters in a pseudo-differential Class-AB arrangement [8] that increases the DR without spending too much power and (b) the use of an AGC scheme that dynamically changes certain biasing levels of the filter (according to a particular measure of input signal