Biointerface Science

Ashutosh Chilkoti and Jeffrey A. Hubbell,
Guest Editors

Abstract

Biointerface science, defined as the study and control of biomolecular interactions at surfaces, is a critical component of many aspects of biotechnology, but it has only recently begun to attract the attention it deserves as a unique interdisciplinary research area. This issue of *MRS Bulletin* explores the rich diversity of function provided by biomolecules at interfaces and the unparalleled opportunities for applications, which range from clinical diagnostics, biomaterials, and tissue engineering to genomics and proteomics. This diversity will continue to drive the evolution of biointerface science.

Keywords: *adsorption, biointerfaces, biomaterials, immobilization, patterning, tissue engineering.*

Biointerface science, defined as the study and control of biomolecular interactions with surfaces, is a critical component of many aspects of biotechnology, but it has only recently begun to attract the attention it deserves as a unique interdisciplinary research area. Although it is tempting to simply describe biointerface science as a subdiscipline of surface science, it is rather a new discipline in its own right because of the unique nature of biological macromolecules. Whereas classical surface science is typically studied by ultrahigh-vacuum techniques, biomolecules require water to function, and thus they can only be accurately studied when bathed in water along with the surfaces of interest. Compared with synthetic molecules, they are structurally larger and are often significantly more sophisticated in their structure and function, despite being created from a limited group of precursors. Furthermore, their structure—and hence, activity—are modulated by their environment in ways that frequently go far beyond what is seen with synthetic molecules. Correspondingly, biomolecules are also extremely fragile, which places fairly severe constraints on how they can be manipulated and studied: biomolecules, especially proteins, readily adsorb, unfold, and denature to adopt a new, unfolded structure at surfaces, so the utmost care must be taken in handling and studying them at surfaces. Likewise, approaches developed to manipulate synthetic molecules at interfaces may fail miserably in handling biomolecular interactions.

The paradox of biointerfaces, especially laboratory-generated ones, is that artificial surfaces can be the bane of biomolecules, yet surfaces are ubiquitous in nature. Somehow, biology has elegantly solved the problems faced by practitioners of biointerface science. In fact, nature offers many lessons that are only now beginning to serve as the inspiration for a new generation of designer biointerfaces, a sampling of which is highlighted in this issue of *MRS Bulletin*.

The prototypical example of nature's design of a biointerface is the cell membrane. Even a cursory examination of the cell membrane design offers many lessons for biointerface science. The cell membrane is composed of a lipid bilayer with receptors and channels that are embedded within or span across the membrane. Lipid bilayers are elastic and are capable of enormous deformation and compression, as seen by the ability of blood cells to squeeze through narrow capillaries. The highly functional cell membrane is, however, more than just an elastic membrane, studded as it is with myriad proteins that span both sides of the bilayer, biomolecules that shuttle chemical, mechanical, and electrical messages from the outside world to within the cell and out again. Thus, the functionality of the cellular biointerface is phenomenal.

Another problem relevant to biointerface science that nature has solved is the presentation of receptors in the correct orientation in the membrane through the use of membrane-spanning helices to optimize their activity. Thus, specialized motifs have evolved for presentation of biomolecules at interfaces—and to an extent, within them—as in the case of membrane-spanning motifs. Furthermore, the cell membrane is not a static entity, but is dynamic in a spatially distinct manner. Lateral diffusion of embedded components, such as receptors, enables formation of reversible complexes and clusters; lateral microphase separation, both of the low-molecular-weight condensed amphiphiles that form the membrane and the higher-molecular-weight components that are embedded therein, is also possible. The cell membrane is temporally dynamic as well, the embedded biomolecules having developed structures to enable the triggering of their functions (e.g., by binding additional biomolecules or by undergoing structural changes themselves). Thus, the complex cellular biointerface is capable of rapid, spatially controlled biomolecular remodeling.

Creating such spatially and temporally dynamic interfaces in which activity can be switched on and off in response to external signals with nanometer spatial resolution and on a millisecond time scale—the spatial and time scales of biology—is a formidable challenge, and one that is only now being addressed by a multidisciplinary community. Two articles in this issue, one by Mrksich and another by Lahann and Langer, provide brief summaries of ongoing work in this area, with a focus on the methods these groups developed for the synthesis of dynamic biointerfaces. The authors review methods developed to dynamically modulate biochemical and physicochemical functionality at surfaces by thermal, electrical, electrochemical, chemical, and mechanical signaling to alter cellular and biomolecular interactions at surfaces. Mrksich reviews work from his group on electrochemical control of biomolecular presentation, capable of dynamically controlling cellular interactions at surfaces with astounding fidelity. Lahann and Langer include in their review work of their own using an applied electrical potential to alter the conformation of a surface-constrained monolayer (e.g., presenting a hydrophobic face under one set of conditions and a hydrophilic face under others). Given that surface electrodes may be integrated within a host of complex lab-on-a-chip designs, the approaches presented in both articles are very powerful for application in cellular and molecular high-throughput screening and bioanalytics.

The third article in this issue, by Yang et al., is also on the design of a dynamic biointerface, highlighting the pioneering work of this group in translating a purely two-dimensional approach into the third dimension using a triggered interface. They review their approach to creating multicellular tissue constructs by "cell-sheet engineering," in which cells that are cultured on a temperature-responsive polymer

https://doi.org/10.1557/mrs2005.48 Published online by Cambridge University Press

surface can be released simply by thermally triggering the phase transition of the immobilized polymer. In this way, entire sheets of cells can be lifted off with their associated extracellular matrix intact. Layering of these sheets then provides an elegant route to recapitulating three-dimensional tissues. This approach has seen significant success in a number of tissue engineering areas, most notably in transplanting cells to the cornea to repair damage to the eye caused by disease or injury.

Spatial confinement of molecules is another area of active interest in biointerface science. Chen et al. review a recently developed methodology to pattern adhesive patches on the length scale of the cell and the subcellular process, which in turn pattern the attachment of cells as individuals and as communities. They show that one can use patterned surfaces to position cells in well-defined shapes and proximity for cell biological studies and use structured surfaces as a biomechanical readout for the forces involved in cell attachment and migration.

Extending to a yet finer scale, many cellular machines involved in cell sensing, adhesion, and migration exist as protein clusters at the 100 nm length scale, yet our ability to present biomolecules in heterogeneous structures at this length scale is limited. The article by Vörös et al. describes a new methodology to accomplish this, presenting biological recognition patterns (binding sites for biological molecules or cells) on a substrate that is nearly perfectly lacking in biological recognition at the ~100 nm length scale.

In nature, biointerfaces exist with water on both sides, whereas most biointerfaces studied in a laboratory are presented on a hard organic or inorganic support. The article by Terrettaz and Vogel addresses this, reviewing their work in creating supported biomembranes, with water on both sides, containing embedded ion channels to permit selected chemical and electrical connectivity between the two sides. These highly functional materials are useful in studying the basic biophysics of the ion channels and as readout mechanisms in drug screening and biodiagnostics. This work in many ways exemplifies the integration of biology into bio-inspired interfaces and highlights how such designer interfaces are likely to be of increasing utility in fundamental studies in cell biology and biophysics, as well as biotechnological applications.

Myriad challenges in biointerface science remain that make it a fascinating area of research and fertile ground for new applications.

One challenge for the future is to bring together recent advances in materials science and molecular biology: sophisticated surface and interface analysis methods will enable new experimental tools which, combined with advanced theoretical models to describe biointerfacial phenomena, will elucidate the physical concepts and rules that allow predictive, model-driven research, similar to the interfacial understanding that has been successfully developed for semiconductor and catalytic processes. A second, equally important, objective is to accelerate the rate at which new developments in biomolecular design and engineering are brought into the domain of physical scientists and, conversely, to educate biologists about the precision techniques that are now available to position, manipulate, and interrogate biomolecules at length scales from the single molecule upward in two and three dimensions. Together, this intellectual interplay will lead to a new bio-inspired paradigm for the way in which molecules are designed, studied, and exploited for the vast number of biotechnological applications in which biomolecules meet surfaces. This objective will only be achieved by the collaborative efforts of (bio)chemists who synthesize novel classes of biomolecules (peptide nucleic acid, peptidomimetics, aptamers, ribozymes, and engineered proteins), with the diverse ensemble of scientists who have developed the tools to position biomolecules with molecular precision (proximal probe methods, nanocontact and microcontact methods, e-beam and x-ray lithography, and bottom-up self-assembly methods). Included in this collaboration will be scientists who have developed new spectroscopic techniques to interrogate these molecules at the solid–liquid interface and individuals who integrate these diverse aspects into functional devices (applied physicists, analytical chemists, and bioengineers).

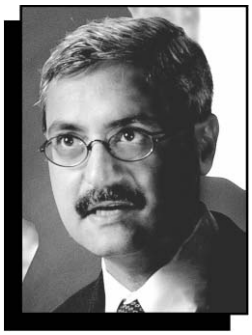
Although biomolecules can be difficult beasts to tame, the potential rewards of doing so are enormous—the rich diversity of function provided by biomolecules offers unparalleled opportunities for applications, which range from clinical diagnostics, biomaterials, and tissue engineering to genomics and proteomics. This diversity will continue to drive the evolution of biointerface science. □

Ashutosh Chilkoti, Guest Editor for this issue of *MRS Bulletin*, has been the associate director of the Center for Biologically Inspired Materials and Materials Systems at Duke University since 2002. He holds a BTech degree in chemical engineering from the Indian Institute of Technology in Delhi and a PhD degree in chemical engineering from the University of Washington. He was a postdoctoral fellow in the Department of Bioengineering at the University of Washington from 1992 to 1995. Chilkoti was appointed as an assistant professor of biomedical engineering at Duke University in 1996 and promoted to associate professor in 2002.

Chilkoti won a CAREER Award from the National Science Foundation in 1998, the 3M non-tenured faculty award in 2002, and a distinguished research award from the Pratt School of Engineering at Duke in 2003. He serves on the editorial board of *Biomolecular Engineering* and has co-authored more than 85 publications. He has 10 patents either awarded or in submission.

Chilkoti can be reached by e-mail at ashutosh.chilkoti@duke.edu.

Jeffrey A. Hubbell, Guest Editor for this issue of *MRS Bulletin*, is a professor in the Integrative Biosciences Institute and the Institute for Chemical Sciences and Engineering at École Polytechnique Fédérale de Lausanne (EPFL) in Switzerland. He received a BS degree from Kansas State University and his PhD degree from Rice University. Trained as a chemical engineer, he investigates topics in regenerative medicine and pharmacobiology, including biomaterials and drug delivery systems for tissue engineering, novel materials for targeted drug delivery, and non-viral approaches to delivery of gene-based pharmaceuticals.



Ashutosh Chilkoti

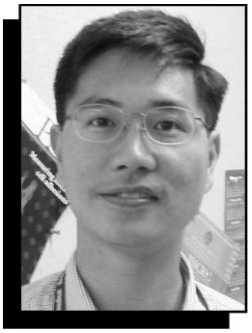
Jeffrey A. Hubbell

Hubbell can be reached by e-mail at jeffrey.hubbell@epfl.ch.

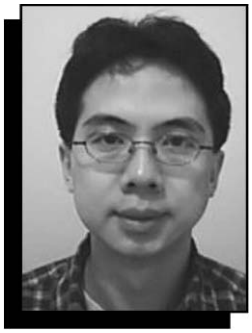
Thomas Blättler is a materials scientist working on his PhD degree in the Laboratory for Surface Science and

https://doi.org/10.1557/mrs2005.48 Published online by Cambridge University Press

Thomas Blättler



Christopher S. Chen



Xingyu Jiang

Joerg Lahann

Robert Langer

Milan Mrksich

Teruo Okano

Samuel Terrettaz

Marcus Textor

Horst Vogel

Technology at the Swiss Federal Institute of Technology (ETH) Zurich. His research is focused on nanochemical patterning, combining selective molecular-assembly systems, colloidal lithography for nanoarray technology, and single-protein investigations.

Blättler can be reached by e-mail at thomas.blaettler@mat.ethz.ch.

Christopher S. Chen is the Skirkanich Associate Professor of Innovation at the University of Pennsylvania. He holds an AB degree in biochemistry from Harvard University, an MS degree in mechanical engineering from MIT, and a PhD degree in medical engineering and medical physics from the Harvard–MIT Health Sciences and Technology Program. He earned his MD from Harvard Medical School, and he was an assistant professor in biomedical engineering and oncology at the Johns Hopkins University prior to his current appointment at Penn. The goal of Chen's research is to identify the underlying mechanisms by which cells coordinate with each other to build tissues, and to apply this knowledge in fundamental studies of stem cell, endothelial cell, and cancer cell biology. His current interests include biomaterial interfaces, the application of micro- and nanotechnologies to cells, cell adhesion, and cell mechanics.

Chen has received numerous honors for his research, including the Presidential Early Career Award for Scientists and Engineers and the Office of Naval Research Young Investigator Award. He serves on the Board of Trustees for the Society for BioMEMS and Biomedical Nanotechnology, and he is a fellow for the DARPA Defense Sciences Research Council.

Chen can be reached by e-mail at chrischen@seas.upenn.edu.

Xingyu Jiang is a postdoctoral research associate at Harvard University. He received his BS degree from the University of Chicago in 1999 and his PhD degree from Harvard (with G.M. Whitesides) in 2004. His present research interests are surface chemistry, analytical chemistry, microfluidics, and cell biology.

Jiang can be reached by e-mail at xjiang@gmwgroup.harvard.edu.

Joerg Lahann is an assistant professor in chemical engineering, materials science and engineering, and macromolecular science and engineering at the University of Michigan. He received his PhD degree in 1998 in macromolecular chemistry from Aachen University in Germany, where he worked with Hartwig Hoecker. Subsequently, he did postdoctoral work with Robert Langer at MIT. Lahann's research is broadly related to surface engineering, with strong ties to biomedical engineering and nanotechnology. Specific aspects include designer surfaces, smart materials, and nanoscale self-assembly. Lahann has written 24 scientific articles and book contributions and has more than a dozen issued or pending patents worldwide.

Lahann can be reached by e-mail at lahann@umich.edu.

Robert Langer is the Kenneth J. Germeshausen Professor of Chemical and Biomedical Engineering at MIT. He received his BS degree from Cornell University in 1970 and his ScD degree from MIT in 1974, both in chemical engineering. He has received honorary doctorates from the Swiss Federal Institute of Technology (ETH) Zurich, the Technion in Israel, the Hebrew University of Jerusalem, Université Catholique de Louvain in Belgium, and the University of Liverpool in England. He served as a member of the U.S. Food and Drug Administration's Science Board from 1995 to 1999 and then as its chair until 2002. He has also served on 15 boards of directors and 30 scientific advisory boards of such companies as Wyeth, Alkermes, Mitsubishi Pharmaceuticals, Warner-Lambert, and Momenta Pharmaceuticals.

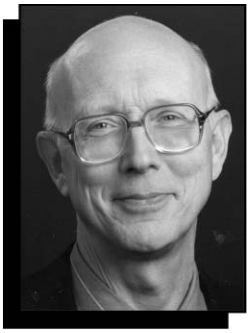
Langer has received numerous awards for his work, including the Lemelson–MIT Prize and the Charles Stark Draper Prize, and he is the only engineer to receive the Gairdner Foundation International Award. In 1989, Langer was elected to the Institute of Medicine of the U.S. National Academies, and in 1992, he was elected to both

https://doi.org/10.1557/mrs2005.48 Published online by Cambridge University Press

the National Academy of Engineering and the National Academy of Sciences. He is one of the few people elected to all three National Academies and the youngest in history (at age 43) to achieve this distinction. *Forbes* (1999) and *Bio World* (1990) named Langer as one of the 25 most important individuals in biotechnology in the world. In 2001, *Time Magazine* and CNN named Langer as one of the 100 most important people in America as well as one of the top 18 people in science or medicine in America. In 2002, *Discover* named him as one of the 20 most important people in biotechnology, and *Forbes* selected Langer as one of the 15 innovators worldwide who will reinvent our future. Langer has written more than 800 articles and has over 500 issued or pending patents worldwide.

Langer can be reached by e-mail at rlanger@mit.edu.

Janos Vörös



George M. Whitesides

Masayuki Yamato

Joseph Yang

Milan Mrksich is a professor of chemistry at the University of Chicago. He earned his BS degree in chemistry at the University of Illinois, Urbana-Champaign, and his PhD degree in organic chemistry at the California Institute of Technology before spending two years as a postdoctoral fellow at Harvard University. In 1996, he joined the faculty at the University of Chicago as an assistant professor of chemistry. He currently leads a research group working on the interface between materials and biological environments. His group designs and synthesizes surfaces having well-defined structures and properties for fundamental studies of cell adhesion, applications in biochip microarrays and exploration of protein-assembled nanostructures.

Mrksich serves on the board of governors of Argonne National Laboratory, as vice chair of the DARPA Defense Sciences Research Council, and as a member of the editorial boards of *Langmuir*, *IEEE Transactions on NanoBioscience*, *Chemistry & Biology*, and *Chemical Society Reviews*. He also serves on the scientific advisory boards of ChemoCentryx, Surface Logix, and Helicos. Among his many honors are the Camille Dreyfus Teacher–Scholar Award (2000), the TR100 Young Innovator Award (2002), and the ACS Arthur C. Cope Young Scholar Award (2003).

Mrksich can be reached by e-mail at mmrksich@uchicago.edu.

Teruo Okano is a professor and the director of the Institute of Advanced Biomedical Engineering and Science at Tokyo Women's Medical University in Japan. He currently oversees a multidisciplinary research group that uses temperature-responsive polymers for various applications such as tissue engineering, drug and gene delivery, chromatography, microfluidics, and cell-based on-chip assays.

Okano is the president of the Japanese Society for Tissue Engineering and was formerly the president of the Japanese Society for Biomaterials. He is the author or co-author of 360 peer-reviewed journal articles, as well as 109 books or book chapters. He received the 1997 Clemson Award for Basic Research from the Society for Biomaterials.

Okano can be reached by e-mail at tokano@abmes.twmu.ac.jp.

Samuel Terrettaz has been studying ligand–receptor interactions in lipid layers with surface-sensitive techniques in Horst Vogel's group at École Polytechnique Fédérale de Lausanne (EPFL) since 1998. He began his studies in biochemistry at the Swiss Federal Institute of Technology (ETH) Zurich. In the group of M. Grätzel at the Institute of Physical Chemistry at EPFL, his work on sensitive lipid electrodes earned him a PhD degree in 1993. He then spent his postdoctoral years investigating electron transfer kinetics in the context of organic thin films at the University of Maryland at College Park and photo-induced dye aggregation at the National Institute of Materials and Chemical Research at Tsukuba in Japan.

Terrettaz can be reached by e-mail at samuel.terrettaz@epfl.ch.

Marcus Textor is a professor of biologically oriented surface science at the Swiss Federal Institute of Technology (ETH) Zurich. He graduated with a PhD degree in chemistry from the University of Zurich, followed by two years at the University of Sussex, England, in catalysis on single-crystal surfaces. From 1978 to 1994, he worked for the company Alusuisse in the development of new materials and fabrication technologies for automotive and packaging applications.

His current research and teaching interests cover the modification and characterization of surfaces and interfaces, quantitative techniques to sense *in situ* interfacial reactions, and the application of functional surfaces in the fields of biomaterials, biosensors, and drug delivery.

Textor can be reached by e-mail at marcus.textor@mat.ethz.ch.

Horst Vogel is a professor of physical chemistry at École Polytechnique Fédérale de Lausanne (EPFL) in Switzerland. He studied chemistry at the University of Würzburg in Germany. After his diploma thesis in physical chemistry, he went to the Max Planck Institute for Biophysical Chemistry in Göttingen, where he performed his PhD work on the structure of lipid membranes under M. Eigen and A. Weller. He then worked at the Max Planck Institute for Biology in Tübingen, at the Biocenter of the University of Basel, and at the Karolinska Institute in Stockholm, studying the structure and dynamics of membrane proteins.

Vogel can be reached by e-mail at horst.vogel@epfl.ch.

Janos Vörös is the senior scientist leading the Dynamic Biointerfaces Group at the Laboratory for Surface Science and Technology within the Swiss Federal Institute of Technology (ETH) Zurich. He holds an MS degree in physics and a PhD in biophysics from the Eötvös University in Budapest, Hungary. He joined ETH Zurich in 1998. Vörös's interests include understanding and controlling cellular and biomolecular surface processes at the nanoscale by physical and chemical means. His research covers aspects such as the creation of nanopatterned nonfouling surfaces with functional

https://doi.org/10.1557/mrs2005.48 Published online by Cambridge University Press

arrays of macromolecules, the development of novel experimental techniques for the study of molecular and cellular interactions, the dynamic control of macromolecule–surface interaction by electronic means for applications in neurobiology, and the use of micro/nano/biotechnology in proteomics and tissue engineering.

Vörös can be reached by e-mail at janos.voeroes@mat.ethz.ch.

George M. Whitesides is the Flowers University Professor at Harvard University. His present research interests are in physical organic chemistry, materials science, biophysics, complexity, surface science, microfluidics, self-assembly, micro- and nanoscience, cell biology, and optics. He holds an AB degree from Harvard University and a PhD from the California Institute of Technology. He worked at MIT from 1963 to 1982, at which time he returned to Harvard.

Whitesides can be reached by e-mail at gwhitesides@gmwgroup.harvard.edu.

Masayuki Yamato is an associate professor in the Institute of Advanced Biomedical Engineering and Science at Tokyo Women's Medical University in Japan. His research interests include tissue engineering, nanobiotechnology, and the study of interactions between cells and biomaterials. His work on cell-sheet engineering has led to his collaboration with over 30 medical doctors in various fields throughout Japan in studies on the regeneration of various tissues and organs. He received the 2002 Award for Young Researcher from the Japanese Society for Biomaterials and the 2003 Young Investigator Award presented by the Society for Biomaterials.

Yamato can be reached by e-mail at myamato@abmes.twmu.ac.jp.

Joseph Yang is an assistant lecturer in the Institute of Advanced Biomedical Engineering and Science at Tokyo Women's Medical University in Japan. He received his ScB degree in biochemistry and molecular biology from Brown University. His current research interests include the applications of cell-sheet engineering, particularly related to the cornea, as well as the cell biology and biochemistry of epithelial progenitor and stem cells.

Yang can be reached by e-mail at jyang@abmes.twmu.ac.jp. □

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