Mechano-Nanoarchitectonics for Bio-Functions at Interfaces

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Architecting well-designed interfacial structures is crucial for fabrication of better bio-related devices such as bio-sensors. A dynamic nature of the interfacial structures with appropriate mechanical properties is advantageous for interactions with bio-related substances. In this short review, a new term, mechano-nanoarchitectonics, has been proposed. This terminology represents nanoarchitectonics methodology for formation of functional structures and regulation of their properties with the aid of mechanical processes. An interfacial two-dimensional environment is an ideal medium to connect macroscopic mechanical actions and nanoscale functions. The review starts with rather traditional topics on how to architect biocomponents at interfaces for bio-reactors and bio-sensors, then covers current active research on mechanical control of bio-functions at dynamic interfaces and emerging topics of mechanical control of DNA origami array and cell differentiation control.

Keywords Interface, molecular recognition, nanoarchitectonics, mechanical, mechanobiology, receptor, DNA origami, cell differentiation, sensor, Langmuir-Blodgett film

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1 Introduction

Sensors have the task of sensitively transmitting information of external substances, stimuli, and environment to man-made machines. The fabrication of high performance sensors requires well-considered design of interfacial structures where various sensing units including nanomaterials, functional molecules,

and biomaterials have to be organized in a rational arrangement.¹ Especially, properties and functions of biomolecules as sensing elements are highly sensitive to their orientation, packing, mutual arrangement, positioning sequence, and their mechanical environments. Therefore, interfacial construction is crucial for fabrication of better bio-sensors. The fabricated structures have to possess a dynamic nature with appropriate mechanical properties because interactions with bio-related substances have a dynamic nature in most cases.

Recently, nanoarchitectonics as a new paradigm of nano-level fabrications has been proposed by Masakazu Aono.² This concept is now widely accepted by materials preparation,³ structure fabrications,⁴ and various applications including catalysis,⁵ energy technology,⁶ environmental applications,⁷ and biological/biomimetic science.⁸ Of course, the above-mentioned topics of sensing application⁹ and interfacial fabrications¹⁰ are also included as target fields. In nanoscale worlds, as targets of nanoarchitectonics, uncertainty and unreliability based on various fluctuations including thermal disturbance, statistical distributions, and unexpected mutual interactions are unavoidable.¹¹ Therefore, various functional structures have to be architected upon harmonized assemblies and combinations of interactions and effect-controlled actions. Based on these fundamental concepts, nanoarchitectonics effectively handles

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Fig. 1 Glucose sensor made of LB film of lipid-coated glucose oxidase (GOD) complexes.

dynamic properties and functions of nanoscale components,¹² and fit well with the construction of interfacial structures for dynamic bio-functions such as bio-sensing.

Among various external factors that can induce dynamic properties, mechanical stimuli are common in many cases and play an important role in the dynamic functions of biological processes. This has drawn attention as mechanobiology in recent research.¹³ In this short review, a new term, mechano-nanoarchitectonics, has been proposed. This terminology represents nanoarchitectonics methodology for formation of functional structures and regulation of their properties with the aid of mechanical processes. As described later in this review, an interfacial two-dimensional environment is an ideal medium to connect macroscopic mechanical actions with nanoscale functions. This review especially focuses on various bio-related functions at interfacial media and mechano-nanoarchitectonics. Thus its title becomes mechano-nanoarchitectonics for bio-functions at interfaces. The review starts with rather traditional topics on how to architect biocomponents at interfaces for bio-reactors and bio-sensors, and then addresses current active research on mechanical control of bio-functions at dynamic interfaces and the emerging topics of mechanical control of DNA origami array and cell differentiation control.

2 Architecting Biocomponents at Interfaces

In order to make facile connections between biofunctional molecules and man-made sensor devices, strategies to architect nanostructures of functional biomolecules on the device surfaces as thin films are crucial. Various methods including self-assembled monolayer (SAM) technique, Langmuir-Blodgett (LB) method, and layer-by-layer (LbL) assembly have been used for this purpose.¹⁴ For example, the LB method is an excellent method to exactly fabricate monomolecular films. However, placing biomolecules on a water surface often induces unfavorable denaturation of biomolecules due to high surface tension of the water surface. In some cases, protection of biomolecules by covering them with appropriate amphiphilic components suppresses this unfavorable nature of the LB method. In the method illustrated in Fig. 1, lipid-coated complexes of enzyme (glucose oxidase, GOD in this example) were used as monolayer components.¹⁵ The lipid-coated GOD complexes were simply prepared by mixing aqueous solutions of GOD and lipid molecules. The resulting precipitates are

Fig. 2 Multi-enzyme reactor from LbL films of two enzymes, glucoamylase (GA) and glucose oxidase (GOD).

soluble in organic solvents and therefore easily spread on a water surface as a monomolecular film without causing serious denaturation of GOD. The formed films were transferred on to a Pt-electrode to demonstrate electrochemical glucose sensing.

However, LB films tend to form too-dense packed structures that are disadvantageous in diffusion of target substances within the films. Therefore, less compacted and rather rough nanoarchitectonics strategies are required. Although the LB method basically needs well packed assembly on a water surface, the LbL assembly is based on simple material adsorption and highly packed states of adsorbed materials are not necessary.¹⁶ Therefore, structural motifs of LbL films allow small molecules and ions to highly permeate through the films.¹⁷ In addition, architecting variously layered structures from multiple kinds of biomolecules is possible and enables us to architect multi-enzyme reactors.¹⁸ As depicted in Fig. 2, multilayered LbL films of two enzymes, glucoamylase (GA) and GOD, were architected on the surface of a permeable ultrafilter. GA molecules at the outer layer first hydrolyze starch as a substrate into glucose that was then converted to gluconolactone with production of hydrogen peroxide by GOD at the underneath layer. Only the resulting products of small molecules go out through filtrate. Several nanoarchitectonics factors, including layer sequences of the enzymes and separation of the enzyme layers to avoid interference between them were confirmed as crucial factors to architect bioreactors with highest efficiency.

Instead of immobilizing proteins themselves, protein-like receptor structures can be architected upon assembly of simple short dipeptides at interfacial media.¹⁹ As exemplified in Fig. 3, assemblies of two kinds of amphiphilic of dialkyl dipeptide-type receptor and guanidinium-type receptor were formed at the air-water interface to discriminate two aqueous guest dipeptides, GlyLeu and LeuGly. Because the receptor components are assembled within a confined two-dimensional plane, optimized binding motifs like actual biological receptors can be spontaneously architected through mechanical compression of the monolayer. In these cases, the guanidinium receptor site strongly induces binding motif with C-terminal insertion of the aqueous dipeptides through strong interaction between guanidinium and carboxylate. In addition to formation capabilities of several hydrogen bonding, binding efficiencies of the guest dipeptide are controlled by the location of the hydrophobic side chains of the guest and their steric hindrance. In the case of GlyLeu binding, both unfavorable contact of Leu side chain to water phase and steric hindrances between side

Fig. 3 Formation of binding sites for dipeptides (GlyLeu and LeuGly) from dialkyl dipeptide-type receptor and guanidinium-type receptor.

Fig. 4 Comparison of molecular recognition efficiencies at various interfacial media using guanidinium-phosphate model molecular recognition.

chains of guest and receptor can be avoided, resulting in a high binding constant. On the other hand, location of guest side chains and steric effect becomes rather disadvantageous in binding of LeuGly with lower binding constant. As seen in these examples, self-assembling process within a confined interfacial environment would be a useful method to nanoarchitect receptor sites for biosensing.

Not limited to binding of aqueous dipeptides, molecular

recognition systems for various biomolecules such as sugars, amino acids, nucleic acid bases, and nucleotides on the basis of complementary hydrogen bonding were architected.²⁰ However, this fact may sound odd because formation of hydrogen bonding in polar media such as water should be unfavorable. In order to figure out this anomaly in molecular recognition at an aqueous interface, systematic comparison of molecular recognition efficiencies at various interfacial media using the guanidinium-

Fig. 5 Mechanical control of molecular machine with open-close actions: (A) steroid cyclophane; (B) molecular pliers.

phosphate model molecular recognition pair was carried out (Fig. 4).²¹ In aqueous dispersion, the binding constant of the guanidinium-phosphate pair is only 1.4 M^{-1} (0.9 kJ mol^{-1}) but placing the same recognition pair to mesoscopic interfaces such as micelle and lipid bilayer surfaces induces a significant increase of the binding constant to $10^2 - 10^4 \text{ M}^{-1}$ ($11 - 25 \text{ kJ mol}^{-1}$). Surprisingly, the binding constant of the guanidinium-phosphate pair becomes $10^6 - 10^7 \text{ M}^{-1}$ ($34 - 42 \text{ kJ mol}^{-1}$) at a macroscopic interface such as air-water interface. The significant enhancement of binding efficiency at interfacial media can be explained by strong influence from low-dielectric media at the interface according to model quantum chemical calculations.²² These facts mean that the most important factors would be environmental factors and not molecular structures themselves. Although we have been making considerable efforts in designing and synthesizing various receptor molecules for better recognition capabilities, architecting the interfacial environment can much more efficiently enhance molecular sensing capabilities. Nanoarchitecting receptor structures at interfacial media is a crucial factor for fabricating high-performance bio-sensing systems.

3 Mechanical Control of Bio-Functions at Dynamic Interfaces

Interfaces (surfaces) are different from bulk. This is a central concept of surface science. As seen in examples mentioned above, molecular interactions for molecular sensing are actually significantly altered at interfacial media. Unlike such common sense in surface science, another important task of interface is explained in the following section. Another important role of interfaces is the connection between macroscopic mechanical actions and nano-level molecular functions.

Within the lateral directions of dynamic interfaces such as water surface, macroscopic motions including compression, expansion, and bending are freely applied. If thickness of the interfacial media is kept within nanometer-size, macroscopic mechanical actions in the lateral direction can be linked with molecular functions along the thickness direction. At the dynamic interface, regulation of molecular functions by macroscopic mechanical motions becomes possible. Based on this concept, we have proposed a new conceptual paradigm,

hand-operating nanotechnology, which enables us to operate molecular machines by hand-motion-like macroscopic action at interfacial media such as the air-water interface.²³ In the example shown in Fig. 5A, closure and opening of steroid cyclophane as a molecular machine are synchronized with macroscopic motions of monolayer compression and expansion.²⁴ Because these molecular motions correspond to cavity formation and opening, the capture and release of an aqueous guest molecule were simultaneously demonstrated, *i.e.*, molecular-level phenomena of guest capture and release can be regulated by visible-size mechanical motions. Motions of another molecular machine, molecular pliers (Fig. 5B), were similarly monitored and analyzed by molecular dynamic simulation and thermodynamic calculation.²⁵ These calculations revealed that energy efficiency for conversion from macroscopic mechanical motions to molecular energy is surprisingly high (nearly 100%).

This methodology can be applied for more delicate structural tuning of molecular receptors architected at a dynamic interface. For example, a molecular receptor, an armed cyclen (a 1,4,7,10-tetraazacyclododecane core with four cholesteric side arms as *N*-substituents), was structurally tuned by mechanical compression of its monomolecular layer at the air-water interface (Fig. 6).²⁶ This receptor unit has a chiral nature with either of Δ - or Λ -type enantiomer due to the helicity of the sidearm arrangement. Its chiral sense and extent can be sensitively tuned depending on molecular packing within the two-dimensional layer upon macroscopic compression of its monolayer. This situation induces tuning of the surface chiral environment facing the water phase. Accordingly binding behaviors of aqueous amino acids such as valine and leucine to a chirally architected surface were investigated. Although binding affinity to D-leucine was greater than those of L-leucine at all the pressure conditions, inversion of chiral selectivity from D-isomer to L-isomer was observed for binding of aqueous valine guest as the surface pressure increased. The latter fact indicates that the chiral selectivity of the molecular receptor can be tuned by macroscopic mechanical motions of its monolayer structure. Mechanical pressures applied in the lateral direction are continuously shifting the most stable conformation of the molecular receptor at the air-water interface, resulting in dramatic changes of chiral selectivity of guest binding.

In another example, a cholesterol-substituted triazacyclononane

Fig. 6 Mechanical control of chiral recognition by the monolayer of armed cyclen (a 1,4,7,10-tetraazacyclododecane core with four cholesteric side arms as *N*-substituents).

Fig. 7 Mechanically tuned discrimination of uridine and thymidine derivatives by the monolayer of cholesterol-substituted triazacyclononane.

was used as a molecular receptor at the air-water interface (Fig. 7).²⁷ This receptor unit possesses several interactive sites including three carbonyl groups and three ternary amino groups. Mechanical compression of the monolayer assembly of this receptor induces tuning of the two-dimensional arrangement of these hydrogen-bond-capable groups. In this case, bindings of aqueous thymine and uracil derivatives to the receptor monolayer were investigated at various surface pressures (various mechanical compression states). Basically, discrimination of thymine over uracil is quite difficult because their structural difference is the presence of one methyl group. Natural DNA and RNA cannot actually distinguish them. However, our mechanical tuning system can be optimized to maximize differences of binding constants between these two guests upon lateral pressure application. At optimized conditions ($[\text{LiCl}] = 10 \text{ mM}$ in subphase at surface pressure of 35 mN m^{-1}), binding constant for uracil becomes more than 60 times larger than that for thymine. It could be stated that mechanical tuning of molecular receptors at interfaces can allow for molecular recognition capability that is better than those of standard biological systems.

Mechanical tuning of molecular receptors can be categorized as a new mode of molecular recognition. Figure 8 roughly summarizes energy diagrams for various types of molecular recognition.²⁸ In the case of traditional molecular recognition (Fig. 8A), which is achieved by crown ethers and cyclodextrins, recognition selectivity and efficiency are determined solely by

the most stable energy state. Based on this basic knowledge, many scientists in chemistry fields of molecular recognition always try to make crystals of host and guest molecules to obtain the most probable and most stable structure although organic molecules have high potential possibilities in flexible intermediate conformers. As pioneer work to use structure switching for modulation of molecular recognition, Shinkai and coworkers synthesized a bis(crown ether) receptor with photo-switchable azobenzene moiety.²⁹ Irradiation of visible or UV light can switch binding capabilities to particular guest molecules (Fig. 8B). This switching concept enabled us to control molecular recognition and sensing by external stimuli. This switch mechanism utilizes capabilities of flexible structure changes of organic molecules to switching molecular function. Most molecular machines in current science operated by external stimuli rely on this switching mechanism. However, the switching mechanism only uses limited numbers of molecular conformers in stepwise modes.

Unlike these two modes, we proposed here a new methodology on molecular recognition, *i.e.*, molecular tuning mechanisms (Fig. 8C). This molecular tuning mechanism uses numerous possibilities in molecular conformation with continuous structural changes upon soft mechanical forces. Newly proposed tuning mechanism with continuous conformational changes can optimize molecular conformers to best suite a particular purpose such as finest discrimination of similar guest molecules from numerous conformer candidates. This mechano-

Fig. 8 Conceptual energy diagrams for three types of molecular recognition with (A) one stable state, (B) switching, and (C) tuning mechanisms.

Fig. 9 Indicator displacement assay with control of fluorescence resonance energy transfer (FRET) that can be mechanically controlled at the air-water interface.

nanoarchitectonics approach for receptor optimization would have a major impact on molecular recognition research and provide significant contributions to the design and fabrication of bio-sensors.

The mechano-nanoarchitectonics approach is not limited to structural tuning of binding sites. Coupling of molecular recognition events with photo-electron process such as fluorescence resonance energy transfer (FRET) was also investigated.³⁰ Bio-sensing system depicted in Fig. 9 can detect an aqueous guest molecule (glucose in this case) through changes of fluorescence intensity and sensing capability can be tuned by lateral mechanical actions. For this sensing mode, an amphiphilic dilysine peptide receptor including a phenylboronic acid, a cholesterol moiety, and a carboxyfluorescein indicator were embedded at the air-water interface. The carboxyfluorescein chromophore works as a

FRET acceptor for coumarin-based indicator, 4-methylesculetin, that is originally bound to the phenylboronic acid receptor site. With the application of lateral mechanical force, the distance between the carboxyfluorescein and 4-methylesculetin becomes narrower, switching on the FRET process. Addition of a small amount of D-glucose to the water subphase beneath the switched on receptor monolayer effectively switched off the FRET process. As a result, the concentration of D-glucose guest in the aqueous phase can be sensitively quantitated from the intensity ratio of these fluorescence peaks. The proposed method was named as a mechanically-controlled indicator displacement assay (MC-IDA) and could be further applied to various biological and environmental analyses in mechanically dynamic states.

Fig. 10 Langmuir monolayer of DNA origami tiles that can be converted into supramolecular polymers by repeated dynamic motion.

4 Mechano-Nanoarchitectonics for Emerging Topics: DNA Origami Array and Cell Differentiation Control

Usages of mechano-nanoarchitectonics at dynamic interfaces are not limited to control of molecular-level receptor structures and their sensing capabilities. It is also highly useful for regulation and alignment control of more higher-level supramolecular assemblies such as DNA origami structures and nanocarbon assemblies. In this section, several recent examples on regulation of such higher level supramolecular structures and their functional control are briefly introduced.

Yonamine *et al.* recently demonstrated two-dimensional dynamic motion of DNA wheels, so called lipid-fueled travels of a DNA, between a patterned surface with a hydrophilic part with SiOH groups and a hydrophobic part modified with octadecyl chains.³¹ Original hydrophilic DNA wheels preferably stay on the hydrophilic surface, but the addition of lipid fuel (dioctadecyldimethylammonium bromide) promotes the shift of the DNA wheels to the hydrophobic surface upon complex formation of anionic DNA wheels and cationic fuel lipids. Because travel distances do not have strong dependence on incubation time, motions of the DNA wheels would be flying rather than two-dimensional driving. Flying of the DNA wheels is probably based on flip-flop (overturning) motions.

The first example of Langmuir monolayer and Langmuir-Blodgett (LB) films of DNA origami has been very recently reported by Yonamine *et al.* (Fig. 10).³² DNA origami pieces can be placed at the air-water interface without causing any their shape changes. Interestingly, floating DNA origami structures at the air-water interface are supramolecularly polymerized into highly anisotropic one-dimensional assemblies by application of macroscopic mechanical motions to their Langmuir monolayer. The DNA origami pieces were self-aligned in highly selected directions upon repeated compression-expansion cycles of the monolayer between 3 and 30 mN m⁻¹. The resulting structures are regarded as long belts with length up to 4900 nm, while width and height of the belts are identical to the monomeric DNA origami units. This fact means that the DNA origami structures assembled highly selectively in one particular direction. This unique supramolecular polymerization can be induced only by repeated dynamic mechanical motions, which cannot be obtained by continuous application of constant pressures.

Fig. 11 Vortex-flow LB transfer (vortex-LB) to produce both straight array and curved array of nanomaterials (fullerene whiskers).

Interfacial media sometimes play an important role on regulation of alignments of nanomaterials within a two-dimensional confined space. Shrestha and coworkers successfully produced variously-shaped nanostructures through fullerene assemblies at interfacial media.³³ Recently, this methodology was combined with a novel LB technique, so-called vortex-flow LB transfer (vortex-LB).³⁴ In this method, the vortex flow activated by the mechanical stirring induced angle-controlled alignments of fullerene whiskers (Fig. 11). The resulting mechanical assemblies of fullerene whiskers on a solid support were subjected to cell culture experiments with human osteoblast MG63. Highly oriented growth of the cells along the direction of aligned whiskers was confirmed. The similarly mechano-nanoarchitected fullerene whisker arrays were utilized as a scaffold for controls of the cell alignment and differentiation using mouse skeletal myoblast C2C12 cells.³⁵ In addition to highly aligned cell growth, myogenic differentiation in both early and late stages accompanied with cell fusion along directions of cell growth can be promoted. As seen in these examples, mechano-nanoarchitected nanocarbon arrays held promise for use as scaffold for regeneration of various tissues such as skeletal muscle tissues.

5 Perspective: Mechano-Nanoarchitectonics for Bio-Related Fields

In this short review, we introduce some concepts for mechano-control of interfacial bio-related functions using a new terminology, mechano-nanoarchitectonics. This terminology represents nanoarchitectonics methodology for formation of functional structures and regulation of their properties with the aid of mechanical processes. An interfacial two-dimensional

environment is an ideal medium to connect macroscopic mechanical actions and nanoscale functions. Examples described in this review demonstrate several interesting issues including highly enhanced molecular recognition capability, mechanical tuning of molecular receptors, DNA origami alignments, and promotion of cell differentiation. Not limited to these examples, application of the mechano-nanoarchitectonics concept could be applied to various kinds of bio-systems and bio-functions, because bio-systems are made from continuous assembly of interfacial structures and have fundamentally soft and compressive natures. The best target of this concept is probably the emerging research area of mechanobiology. Effective research on mechanobiology has to be done through rational application of mechanical stimuli to biological substances with well-defined arrangement, orientation, and organization. The latter requirements can be achieved by mechano-nanoarchitectonics at appropriate interracial environments as shown in this review. Mechanobiology would make significant progress if the mechano-architectonics concept is aggressively introduced.

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7 References

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