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REVIEW

Current status of water environment and their microbial biosensor techniques – Part II: Recent trends in microbial biosensor development

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Abstract

In Part I of the present review series, I presented the current state of the water environment by focusing on Japanese cases and discussed the need to further develop microbial biosensor technologies for the actual water environment. I comprehensively present trends after approximately 2010 in microbial biosensor development for the water environment. In the first section, after briefly summarizing historical studies, recent studies on microbial biosensor principles are introduced. In the second section, recent application studies for the water environment are also introduced. Finally, I conclude the present review series by describing the need to further develop microbial biosensor technologies.

Keywords Comprehensive review · Microbial biosensor · Environmental biosensor · Organic pollution · Eutrophication · Toxicity

Abbreviations

BL	Bioluminescence
BOD	Biochemical oxygen demand
C. albicans	*Candida albicans*
C. butyricum	*Clostridium butyricum*
C. violaceum	*Chromobacterium violaceum*
CL	Chemiluminescence
CNT	Carbon nanotube
COD	Chemical oxygen demand
DCIP	2,6-Dichlorophenolindophenol
DM	Double mediator
DO	Dissolved oxygen
DOM	Dissolved organic matter
E. coli	*Escherichia coli*
FCN	Ferricyanide
FIA	Flow injection analysis
FL	Fluorescence
GFP	Green fluorescent protein
LASs	Linear alkylbenzene sulfonates
M. aeruginosa	*Microcystis aeruginosa*
MDC	Microbial desalination cell
MEMS	Microelectromechanical system
MFC	Microbial fuel cell
MWCNT	Multiwall carbon nanotube
N	Nitrogen
NP	Nonylphenol
P	Phosphorus
P. agardhii	*Planktothrix agardhii*
P. aeruginosa	*Pseudomonas aeruginosa*
P. fluorescens	*Pseudomonas fluorescens*
RCI	Redox color indicator
S. cerevisiae	*Saccharomyces cerevisiae*
SM	Single mediator
SOM	Sediment organic matter
TN	Total nitrogen
T. cutaneum	*Trichosporon cutaneum*
TP	Total phosphorus

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Overview

Biosensors make detecting molecules fast, sensitive, low-cost, and easy. Since the first biosensor using the enzyme glucose oxidase was studied by Updike and Hicks in 1967 [1], biosensors using various types of biorecognition elements, such as antibodies, sections of organisms or tissues, or living microbes, have been studied [2–7] for clinical [8–10], food

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[10–12], and environmental [12, 13] use. Various biosensors have already been put to practical use as a result of this research and development. In 2015, Bahadır and Sezgintürk comprehensively reviewed commercially available biosensors [14].

Historical and recent studies of microbial biosensor principles

Microbial fuel cells

The first microbial biosensor was studied by Karube et al. in 1977 [15]. Compared with enzyme biosensors, the microbial biosensor is less sensitive to inhibitory substances, more tolerant of measuring pH and temperature, longer lived, and cheaper, as it needs no isolation. These features of microbial biosensors have been studied widely [16] and presented in review articles of clinical [10], food [10, 11, 17–21], and environmental analysis [17–23]. We previously described in detail the early history of the structural developments of microbial biosensors [17]. Microbial biosensors are mainly classified by their sensor system (flow or batch), signal type (electrochemical or bioluminescence), microbe type (aerobe or anaerobe), microbial response (activation or inactivation), analyte specificity (specific or nonspecific), etc. In the case of the first microbial biosensor, a microbial fuel cell (MFC) system of the batch electrochemical type was employed, and the anaerobic *Clostridium butyricum* was immobilized on a Pt anode using a gel membrane. Utilizing the *C. butyricum*-MFC biosensor system, organic matters as substrates contained in the sample were anaerobically and nonspecifically assimilated by *C. butyricum*. As a result, the BOD value was measured as a current value obtained from the amount of metabolic activation of *C. butyricum*. In general, the MFC biosensor employed anaerobes.

The dissolved oxygen method

As shown in several review articles, measuring with the MFC biosensor generally takes time [24–26]. This feature was unsuitable for continuously monitoring wastewater. Thus, a practical BOD biosensor was developed by employing the aerobic *Trichosporon cutaneum* (eukaryotic microbe; IFO-10466), which was immobilized onto the surface of a dissolved oxygen (DO) electrode, and the microbial electrode was first embedded into a flow injection analysis (FIA) system in 1979 [27]. Compared with anaerobes, aerobes are 19 times more efficient at transferring energy from glucose to adenosine triphosphate (ATP). In addition, *T. cutaneum* was suitable for a BOD biosensor because it has various assimilation properties against organic matter and stability as a yeast. For these reasons, yeast cells have been used very frequently in microbial biosensor development [28, 29].

The electrochemical mediator method

The next-generation BOD biosensor was improved to be highly sensitive to organic matter by using the electrochemical mediator (EM) method. In 2000, Pasco et al. (New Zealand) [30] and Yoshida et al. (Japan) [31] each developed an EM type microbial biosensor employing potassium ferricyanide (FCN) as a redox mediator and bacteria (prokaryotic microbe). The EM method was realized by employing electrochemically active microbes that can transfer extracellular electrons to terminal electron acceptors (e.g., electrodes) using an EM. The current generated reflects the activity of the microbial respiratory chain. This single-mediator (SM) electrochemical system was applied to the MFC technique as a ferro-ferricyanide system [32], and the MFC biosensors employing the mediator have been widely studied [24–26]. The mediator solved the problem of oxygen solubility in the sample solution, which was a problem of the DO type BOD biosensor at the time. On the other hand, we further studied the features of the SM electrochemical biosensor for determining high concentrations of organic matters and developed a compost monitor in 2001 [33]. This feature of the SM biosensor also enabled the development in 2001 of both an electrochemical microbial chip and a mobile monitor for on-site BOD monitoring [34].

Yamashoji et al. (Japan) in 1996 [35] and Baronian et al. (New Zealand) in 2002 [36] studied double-mediator (DM) electrochemical systems using FCN, menadione, and yeast *S. cerevisiae*. Yamashoji et al. actively studied microbial screening in 2013 [37] and microbial detection in 2017 [38], and Baronian et al., from 2011 to 2015, also studied estrogen, applying the SM (FCN) or DM (menadione and FCN) electrochemical system [39–41]. Subsequently, we applied the DM electrochemical system using FCN and menadione (hydrophobic) to a BOD biosensor for practical use. The DM electrochemical biosensor enabled us to obtain an electrochemical signal from bakery yeast, *Saccharomyces cerevisiae*, which is a stable and easily available microbe. Namely, an electrochemical signal could not be obtained from *S. cerevisiae* with the SM system. As a result, a disposable microbial sensor chip was developed in 2007–2008 [42, 43], and the principle also enabled alcohol measurement in 2009 [44]. Pasco et al. and Lagarde and Jaffrezic-Renault reviewed such developments of microbial biosensors by applying an SM or DM system in 2011 [45, 46]. Moreover, applying the DM electrochemical principle, we developed a chemiluminescence BOD (CL-BOD) method in 2007 [47]. To my knowledge, this is the only study in the history of microbial biosensor developments to apply a CL reaction to the BOD method. However, the CL microbial biosensing method might hold

promise as a highly sensitive measurement as realized in our enzyme biosensor techniques [48–50].

Recent developments in the EM method

Recent developments in applying the SM electrochemical system to microbial biosensors are as follows: coupling *p*-benzoquinone and *Escherichia coli* in 2013 or *p*-benzoquinone and microbial consortium in 2016 by Li et al. for sensing toxicity (China) [51, 52]; coupling FCN and *Chromobacterium violaceum* R1 for BOD by Khor et al. (Malaysia) in 2015 [53]; and coupling 2,6-dichlorophenolindophenol (DCIP) and *Candida albicans* for a viability assay by the international group of Hassan (Egypt) and Bilitewski (Germany) in 2011 [54] and 2013 [55].

Furthermore, the mediator method was applied to electrical wiring by using conductive nanomaterials. In 2011, Demirkol and Timur (Turkey) used carbon nanotubes (CNTs) for electrical wiring between electrodes and *Pseudomonas fluorescens* using FCN [56]. Šefčovičová et al. (Slovakia) also used CNTs in an MFC biosensor for electrical wiring between electrodes and *Gluconobacter oxydans* using FCN [57].

Hassan and his group members, Sedki, Wollenberger, and El-Sherbiny et al. (Egypt and Germany) have actively studied electrical wiring techniques using multiwall carbon nanotubes (MWCNTs) for a microbial viability assay [58–60]. They applied the DM electrochemical system, consisting of DCIP and FCN, to a cell viability assay of *Staphylococcus aureus* in 2016 [58]. In addition, they also studied direct electrochemical wiring systems (i.e., mediator-free systems) between MWCNTs detecting *Streptomyces* Spp. in 2014 [59] and between graphene-chitosan nanocomposite and *E. coli* or *Pseudomonas aeruginosa* in 2017 [60].

Choi et al. (Korea) have also studied direct electrochemical wiring techniques using MWCNTs since 2006 [61, 62]. They have developed one-step γ-irradiation techniques for making a quantum dot-modified multi-wall carbon nanotube (QD-MWNT) film onto an electrode surface [61]. In 2011, Kim, Kwen, and Choi developed CdS-MWCNTs and Cu_2S-MWCNTs, and each QD-MWNT covered an electrode surface [62]. *Alcaligenes* sp. cells were directly adsorbed onto the surface of the QD-MWNT-modified electrode and detected phenolic compounds. In 2012, Anu Prathap and Sawant et al. (India) applied direct electrochemical wiring to a microbial biosensor using polyaniline as a conductive polymer [63]. In the same year, Mittal, Singh, and Kumar (India) also applied direct electrochemical wiring to a chlorella biosensor using glassy carbon [64].

Direct electrochemical wiring is an excellent technique that enables "mediator free" or "reagent free" biosensing, and is applicable to the continuous measurements for organic matters or microbial assay; however, this technique requires electrochemically active microbes and the physical contact of a redox active microbial moiety, including redox proteins such as cytochromes or bacterial nanowires, with the electrode surface.

The redox color indicator method

Since 2000, we have actively studied microbial biosensor applications employing DCIP as a redox color indicator (RCI). DCIP has been applied to absorptiometric BOD measurement using a spectrophotometer [65] and a high throughput microplate reader [66]. Furthermore, RCIs have been used successfully in microbial biosensor chips and portable devices [67], marine BOD measurement [68], toxicity measurements (as inactivation of microbial metabolic response) [69], and microbial detection [70]. In 2013, Zhai and Dong et al. (China) studied a colorimetric microbial bioassay for toxicity using neutral red (NR) and *P. fluorescens* [71]. The presence of toxicants in a sample of water damaged cells and caused the adsorption of NR onto the cell surface. After the incubation of the measurement mixture, the absorbance of residual NR was increased by increasing the amounts of toxic substances. In the same year, they demonstrated microbial respiration for a toxicity assay. FCN was then reduced by the respiration of *E. coli* to ferrocyanide, which formed Prussian blue (PB). They applied the principle to a toxicity assay, i.e., PB formation was regulated by increasing the sample's toxicity [72]. Thus, the RCI method is simply measuring the analyte by absorptiometry; however, in general, in terms of measurement sensitivity, it is inferior to the fluorometric method introduced next.

The fluorometric method

In addition to the application of an RCI, in 2007, we applied fluorometric damped metabolic oscillation caused in a living yeast cell to a microbial biosensor and demonstrate a new possibility of simultaneously measuring multiple indices for both the substrate-specific biosensing of assimilatable organic matter [73] and toxic actions [74]. As shown here, applications of the microbial biosensor to the BOD measurement were very reasonable, and several articles were reviewed [75–77]. In addition to the BOD measurement, the microbial biosensor that senses nonspecific toxicity is also useful for assessing the availability of environmental water in terms of both humans and ecological safety [78]. In particular, yeast cells are suitable for acute toxicity biosensing of cyanide in a eukaryote that has mitochondria [79, 80]. The fluorometric method needs the right source and a slit for excitation light and an emission light detector; therefore, the principle is limited to laboratory use, in general.

The bioluminescence method

In developing a microbial biosensor device, the application of bioluminescence (BL) is one of the most significant techniques, along with electrochemical methods. The most important feature of the BL method is that it does not require a light source for measurement. This feature is suitable for highly sensitive and on-site monitoring of both environmental waters and wastewater by constructing portable devices. Therefore, the BL method has been eagerly adopted for microbial biosensor development. The early history of BL for microbial biosensing was well described by Chang et al. in 1981 [81] and Keane et al. in 2002 [82]. In 1981, Bulich and Isenberg (USA) developed a Microtox assay that was used practically for measuring the toxicity of environmental samples [83]. Toxicity was measured by monitoring the light production of reconstituted freeze-dried cells of wild-type BL marine bacteria. Bacterial BL depends on cellular respiration; any inhibition of cellular metabolism due to toxicity results in decreased light emission of affected cells. Applying this principle, in 1993, Hyun et al. (Korea and Japan) developed a BOD biosensor that increased bacterial BL by metabolic activation [84]. Since then, environmental stresses, such as heavy metals and organic solvents, were nonspecifically measured by using recombinant *E. coli*, which fused bacterial luciferase (*lux*) genes as a reporter. Then in 1994, Van Dyk et al. (USA) developed a stress-sensitive BL *E. coli* sensor [85]. In 1997, Belkin et al. (Israel) improved the fusion techniques for measuring DNA damage, protein damage, and the inhibition of fatty acid synthesis [86]. Thus, other reporter genes, such as the firefly luciferase gene (*luc*) [87] and green fluorescent protein (GFP) gene (*gfp*) [88], have been employed in microbial biosensors, although in the cases of GFP measurement as fluorescence (FL), excitation light is necessary.

In 1962, GFP was discovered from the jellyfish *Aequorea victoria* by Japanese scientist Osamu Shimomura, who was awarded the Nobel Prize in Chemistry in 2008. Since the 1990s, the development of genetically engineered FL microbes for the specific measurement of toxic substances has also been developed proactively. These studies using BL microbes were summarized in several review articles [86, 89–91], and microbial biosensor designs, such as mobile types that apply smartphone functions, were also reviewed [92–94]. Next, developments in these BL biosensors will be reviewed, and a recent trend of remarkable research groups will be introduced.

Recent developments in the BL method

Ahn, Jung, and Gu et al. (Korea) developed several microbial biosensor devices of both the array types and a dip-stick type, which employed stress-specific *E. coli* BL reporter strains [95–97]. In 2010, they studied a randomly deposited array that immobilized five different reporter strains and their corresponding fluorescent dyes in alginate microbeads that were randomly arrayed in 1 mm diameter wells [95]. In this study, each bead immobilized a kind of stress-specific *E. coli* and its independently colored fluorescent dye. The specific stress was detected as the BL intensity emitted from each bead and determined based upon the intensity of the correspondingly colored fluorescent dye. By measuring the spectra and intensities of both BL and FL, five different stress substances were simultaneously determined. In their subsequent study in 2014, this principle was applied to a dipstick type biosensor [96]. They also developed a Geno-Tox cell array biochip using stress-specific BL *E. coli* for DNA damage response as genotoxicity [97].

Eltzov, Axelrod, and Marks et al. (Israel and Singapore) developed several pad-type BL biosensor devices employing stress-specific *E. coli* obtained from Dr. Shimshon Belkin (Israel) [98–101]. In 2015, a BL light guide pad biosensor for room air toxicity was developed that employed a recombinant *E. coli* TV1061 [98]. The biosensor was fixed onto the ceiling of the room, and BL light was detected by the optical fiber effect, using a liquid light guide and a photomultiplier. They attempted to connect this biosensor to a commercially available remote product. Using this technique, they developed a microbial biosensor for water toxicity that employed several recombinant *E. coli* bacteria [99]. In 2016, they improved the water toxicity pad biosensor to enhance practicality by replacing the photomultiplier with a CMOS photodetector [100]. They applied the recombinant *E. coli* to the putative carcinogenic potential, which is not for water quality estimation [101].

Roda, Cevenini, and Michelini et al. (Italy and USA) have been actively developing a portable biosensor device employing recombinant BL microbes [102–105]. In 2011, they developed a BL cell-based biosensor that consists of a CCD camera and a multi-wall cartridge with immobilized cells [102]. The BL light emitted in the cartridge was detected by the camera through the fiberoptic taper. In this study, recombinant yeast and *E. coli* were used for sex hormones. In 2016, a smartphone camera was used for BL detection in toxicity assays [103]. They then fabricated 3D-printed cell minicartridges and a smartphone adaptor and developed another type of a smartphone-based BL cell biosensor [104]. They made a 3D-printed multi-wall cartridge, and BL emitted from the cartridge was detected using the smartphone camera. Such 3D-printing techniques and smartphone refurbishment will be powerful tools for the development of mobile biosensors. As another powerful tool for BL biosensor devices, particularly for chip-based whole-cell biosensors, they employed recombinant BL magnetotactic bacteria in 2013 [105]. For example, such bacteria make it possible to control both fixing and moving cells by moving the magnetic field and measuring continuously by adding a washing process.

Recently, Thouand et al. (France) developed a practical BL biosensor device that employs recombinant BL bacteria [106–112]. In 2011, Charrier et al. developed a new multi-channel Lumisens III biosensor [106, 107], which was the improved third generation of their 2007 Lumisens II biosensor [108]. They fabricated a disposable card that they employed in the assembly of a multi-strain biosensor. Jouanneau et al. studied a specific decision tree method for identifying heavy metal in water samples [109]. In 2012, Jouanneau et al. further developed a Lumisens IV biosensor that added a nutrient supply into the multi-strain immobilized well card and improved data analysis by providing the software Metalsoft [110]. Thus, the Lumisens IV biosensor made possible reliable monitoring and the estimation of heavy metal levels in water. In addition, in 2016, Affi et al. studied numerical modeling of the dynamic response obtained from a BL bacterial biosensor [111]. In 2016, Jouanneau et al. developed a marine microbial biosensor that employed the wild BL bacterial strain *Aliivibrio fischeri* [112]. Then, *A. fischeri* was immobilized into a disposable card using an agarose matrix.

In 2017, Prévéral and Ginet et al. (France) also developed a practical BL p*Ars-lux* arsenite biosensor using lyophilized recombinant *E. coli* cells [113]. The arsenite biosensor is intended to raise the alarm when a contamination threshold is reached. They investigated the survival potential after the lyophilization of recombinant *E. coli* cells and the storage stability as the shelf life at 4 °C. As a result, the lyophilized arsenite biosensor was functional after 7 mo, with a practical detection limit of 0.2 μM. Compared with the lifetime of the microbial biosensor, which is around 1 mo or more [17], a long shelf life will be needed for the future development of microbial biosensors.

FL-based microbial biosensors have been studied by two groups in recent years. In 2014, Tseng and Yeh et al. (Taiwan) developed a gold-specific microbial biosensor [114]. They employed heavy metal-tolerant proteobacteria *Ralstonia eutropha* as a host and recombinant bacteria by introducing the sensor system of *Cupriavidus metallidurans cupR* regulon into *R. eutropha* in order to detect Au^{3+}. Then, the genetic organization was the Au-induced RFP [red fluorescent protein (*rfp*) gene] expression in *PcupC-rfp* in *R. eutropha*. Further investigation of the mechanisms underlying *CupC* function is in progress. In 2016, Jha et al. (USA) studied an engineered specificity switch in a transcription factor and applied it to a microbial biosensor for organophosphate hydrolysis [115]. They engineered a novel specificity in an Acinetobacter transcription factor, PobR, to detect organophosphate hydrolysis and measured the response via a FL protein reporter expressed from a PobR promoter. In general, a FL-based microbial biosensor is required to excite the light source and shield the light case to construct a portable device. For this purpose, a 2017 study of a smartphone-based FL detector by Lee et al. (Korea) can be helpful [116].

As shown here, the BL method has evolved into the most reliable practical microbial biosensor technique; however, the pollution of the recombinant microbes used in this technique into the environment is a cause for concern.

Miniaturization

Miniaturization—the compact integration of a biosensor system—has been studied, especially for medical use. For example, one goal of the medical field is constructing an in-body implantable device consisting of a micro-total analysis system (μTAS) using a micromachining technique [117]. The need of the environmental field for compact integration has also increased [118]. Thus, studies on microbial biosensors constructed by microfluidic devices [119], a microelectromechanical system (MEMS) [120], and microscale MFCs [121] have recently been carried out. For examples of silicon-based microdevices fabricated by silicon micromachining process, Dávila et al. studied a microfabricated MFC device in 2011 [122], and Zhao and Dong (Norway) studied a BL-cell-based microfluidic chip in 2013 [123]. Furthermore, nanoscale designs were applied to the microbial biosensor [124, 125]. In addition, studies on array-type microbial biosensors, including single cell arrays, have also been carried out for high throughput measurement [126, 127]. Studies on biochip immobilizing microbes have increased; for reference, we have also developed and patented several types of microbial and other biochips [34, 42, 67, 128–132]. Studies on screen-printed biochips for microbiology were reviewed [133], and the relationship between the analyte and the electrochemical biosensor for proper matching was reviewed [134]. Using electroactive biofilm as a microbial biosensor element has also increased, and the studies were also reviewed [135, 136].

Microbial immobilization

To construct a microbial biosensor device with continuous monitoring or repetitive measurements, microbial immobilization is a significant fabrication process. Here, recent remarkable studies are introduced (methods using mediator or conductive materials were explained earlier). Yoetz-Kopelman et al. (Israel) found a simple-step method of electrostatically immobilizing bacterial cells onto the electrochemical device; (1) linker bounding polyacrylamide beads were electrostatically immobilized onto the gold surface of a working electrode, and (2) *E. coli* cells were electrostatically immobilized onto the linker bounding surface of the polyacrylamide beads [137]. They named this method "Cells-on-Beads." This novel method enabled high-density cell loading onto the electrode surface area without any damage to cell viability. In subsequent modeling studies, they and Pandey compared sensitivity in the case of Cells-on-Beads and cell suspension, and they

showed that as the total cell population gets close to the electrode, the response time becomes faster [138]. This might indicate that a better response is obtained when the bacterial cells are uniformly immobilized onto the linker-binding electrode surface.

Adányi et al. (Hungary and Germany) have studied a label-free optical waveguide light-mode spectroscopy (OWLS) sensor [139]. The OWLS sensor detects evanescence changes caused by the changing thickness of the evanescent field. The technique has been applied to developing immunosensors or chromogenic surface Plasmon resonance (SPR) biosensors [140]. In 2013, they applied a new microbial immobilization technique to label-free OWLS for use as microbial biosensors [141, 142]. For this purpose, they employed biosilica-producing recombinant *E. coli* [143], which forms siliceous sponges on the outside of *E. coli.* Bacteria were immobilized by their production of biosilica onto the surface of SiO_2-sensing elements (evanescent field) using the OWLS microbial biosensor. The sensor signal was obtained as cell amounts on the sensing element, i.e., cell contacts with growth factor inhibitors or enhancers lead the sensor signal. Therefore, results from microbial biosensors take time to obtain due to waiting for bacterial cell growth.

In this section, the histories and current status of developments in microbial biosensor devices were described, focusing on sensor principles. In the next section, the status of current developments in microbial biosensors for water pollution is described, focusing on pollutants as analytes.

Recent studies of microbial biosensors for water pollution

Since the previous review article in 2010, microbial biosensors for water pollution have improved. Analyte, microbial biosensors for BOD (organic matters), toxicity, and other pollutants have been actively developed; and the sensor principles, both BL and MFC methods have been actively employed.

BOD biosensors

Recent developments in Japan

This section documents the achievement of Dr. Isao Karube, the Japanese researcher who developed the world's first BOD biosensor [15]. In recent years, BOD biosensors have been developed by several groups in Japan or through international collaboration (Kashem and Suzuki et al. [144], Ivandini and Einaga et al. [145], Yamashita et al. [146], and Nakano et al. [147]). Kashem and Suzuki et al. developed a fluorometric BOD biosensor chip that employed ruthenium(II) dye as a dissolved oxygen indicator and baker's yeast cells as biorecognition elements [144]. Such a fluorometric biosensor might be improved and made portable by applying an organic EL-type smartphone if the light color of the display can be controlled. Ivandini and Einaga et al. constructed an oxygen-sensitive gold-modified boron-doped diamond electrode and applied it to an amperometric BOD measurement using yeast *Rhodotorula* sp. [145]. Yamashita et al. developed a novel and practical in situ BOD biosensor by improving the MFC. They employed an open-type anode, directly inserted into an intermittently aerated tank filled with livestock wastewater, and exoelectrogenic anaerobes, *Geobacter* spp., naturally immobilized onto the surface of the anode. The BOD biosensor enabled continuous monitoring for 71 d without any maintenance [146]. Nakano et al. developed a flow-type amperometric BOD biosensor using FCN dissolved in a carrier solution, although it is necessary to pay attention to the amount of wastewater that contains FCN. The sample was obtained from the distillate of a Japanese liquor, shochu, as a high BOD wastewater sample [147].

In addition to this study, microbial biosensors for easily biodegradable organic matters have also been developed recently worldwide, e.g., for ethanol, by Šefčovičová and Tkac et al. (Slovakia, 2011 to 2015) [57, 148, 149], and for glucose, by Aslan and Anik (Turkey, 2016) [150].

Recent developments in other countries

Several groups have been actively developing BOD biosensors. Noteworthy groups include Arlyapov, Reshetilov, and Ponamoreva et al. (Russia) [75, 76, 151–153], Raudkivi, Raud, and Kikas et al. (Estonia) [154–160] , Li and Xia et al. (China) [161, 162], and Hsieh and Chung et al. (Taiwan) [163, 164].

Arlyapov, Reshetilov, and Ponamoreva et al. tried to improve the BOD measurement quality by comparing three kinds of yeast cells: *Candida maltosa* VKM Y-2359, *Candida blankii* VKM Y-2675, and *Debaryomyces hansenii* VKM Y-2482. Each yeast was known to have broad substrate specificity to various types of organic matter. As a result, they found that *D. hansenii* had the broadest specificity in 2012 [151]. Subsequently, in 2013, they immobilized *D. hansenii* cells on a gel sheet and fixed it onto the surface of an oxygen electrode. After optimizing the measurement conditions, the BOD values of wastewater samples were determined in a practical range, and the results corresponded to results obtained by the conventional BOD_5 method — between 0.7 and 207 mg O_2 L^{-1} [152]. In 2015, they developed a capsule technique for protecting living yeast cells from harmful effects that result from exposure to heavy metal ions and UV radiation [153]. In 2011, Webber et al. (New Zealand) also evaluated bacterial strains for rapid and reliable BOD sensing using their MICREDOX assay product and identified *Arthrobacter*

globiformis as the bacterial strain capable of practical BOD measurement of effluents [165].

Raudkivi, Raud, and Kikas et al. (2008–2015) studied semi-specific biosensors for BOD measurement. Microbes with semi-specificity to organic matter were then employed. The specificity of each microbe was investigated in a study [154–158]. For instance, *Pseudomonas putida* P67 had semi-specificity to phenol [154], and *Aeromonas hydrophila* P69.1 had semi-specificity to fat [156]. As the next step, they tried to perform comprehensive BOD measurement involving qualitative and quantitative results. To this end, seven biosensors based on different semi-specific and universal microbes were constructed. The output signals of all biosensors were analyzed as "bioelectronic tongues" [159, 160]. In recent years, studies on comprehensive measurements of environmental water quality using both enzymes and microbes have been carried out worldwide [166–168]. The more complicated the BOD biosensor configuration, the more accurate the expected measured values for these technologies will be; however, it may be necessary to pay attention to ensuring that measurements can be reproduced.

Li and Xia et al. studied the fast detection of BOD measurements. For this purpose, they have been developing a single-microbial-layered structure on the gold surface of a working electrode. As a first step, in a 2016 study, bacterial cells were covalently bonded; however, the microbial electrode had low conductivity and poor biocompatibility [161]. As a second step, in 2017, the microbial layer was constructed onto the rough electrode surface, which was made by the electrodeposition of carboxyl graphene and Au nanoparticles. As a result, a practical BOD biosensor was made with a linear range of 2 to 15 mg O_2 L^{-1} at a 3 min response [162]. For fast BOD measurement, in 2015, Khor et al. (Malaysia) also developed a redox-mediated ultramicroelectrode (UME) consisting of FCN, *Chromobacterium* sp., and a fine Pt wire (10 μm diameter) that was used as a working electrode [53]. The dynamic range was 20–230 mg O_2 L^{-1}, which enabled wastewater measurements. By improving its sensitivity, the microbial biosensor can also be used for fresh water.

Hsieh and Chung et al. (2014–2016) studied mediator-less MFC biosensors for BOD measurement; they used a mixture of six bacterial strains to obtain broadest specificity to organic matter and to survive toxic conditions [163, 164]. As a result, the relationship between BOD_5 concentration and voltage output of the MFC biosensor was obtained at a substrate concentration of 5–235 mg O_2 L^{-1} as BOD_5. In general, the MFC biosensor's measurements take time, although it has long-term stability [164].

BOD biosensors that employ MFCs have been studied by many researchers in recent years. In 2011, Zhang and Angelidaki (Denmark) developed a submersible MFC biosensor for measuring both microbial activity and BOD in groundwater [169]. To obtain a stable signal, the MFC biosensor was driven into a temperature-controlled water tank. For microbial activity measurement, a bare anode was used to measure the microbial adenosine-triphosphate (ATP) concentration, and biofilm-colonized anode was prepared for BOD measurement. The MFC sensor enabled 0 to 6.52 nmol-ATP L^{-1} and up to 250 mg L^{-1} with a response time of less than 0.67 h. In 2011, Peixoto, Angelidaki, and Nogueira et al. (Portugal and Denmark) also tested for online and in situ monitoring of the biodegradable organic content of domestic wastewater using a submersible MFC biosensor [170]. In 2013, Yang et al. (China) improved the MFC biosensor for real-time BOD measurement, and a single-chamber type of MFC was developed by using carbon felt (anode) and activated sludge [171]. A stable voltage was obtained after 132 min, following the addition of synthetic wastewater (BOD concentration: 200 mg O_2 L^{-1}). Ayyaru and Dharmalingam (India, 2014–2016) also developed a single-chamber type of MFC biosensor for BOD measurement [172]. They improved a sulfonated poly(ether ether ketone) (SPEEK) membrane for microbial immobilization to an anode [173] and, compared with Nafion, a superior sensing range—up to 650 mg O_2 L^{-1}—was obtained with a response time of several hours. In 2016, Logroño et al. (Ecuador, Hungary, and Malaysia) developed a single-chamber MFC biosensor that used an Andean soil microbial consortium for rice-washed wastewater [174]. Andean soil filled the anode chamber, where soil microorganisms metabolized the wastewater, producing electrons and protons. The response time to 200 mg O_2 L^{-1} BOD was around 1 h. In 2017, Kharkwal et al. (Singapore) developed a long-lived MFC biosensor for BOD in real wastewater [175]. In place of a Pt catalyst, MnO_2 was employed as an innovative cathode catalyst for oxygen reduction in a single-chamber air-cathode MFC. This sensor maintained stability for 1.5 y. As shown here, the MFC biosensors must still reduce the response time for real-time monitoring. In 2017, Anam and Ali et al. (Pakistan) developed an H-type MFC biosensor for the non-specific detection of organic pollutants and, finally, employed natural bacterial consortia immobilized onto the surface of an anode [176]. They investigated the bacterial variation by pyrosequencing.

Compared with other microbial biosensors, MFC type BOD biosensors have inferior sensor performance, i.e., in energy efficiency due to the anaerobic condition, and are time-consuming due to the slow response and long wait before the next measurement. To solve these problems, MFC type BOD biosensors need to be miniaturized and the aerobe needs to be used as an analytical tool for direct electrochemical wiring [53, 61, 121].

BOD biosensors of the future

In general, BOD measurements utilizing microbial assimilation of biodegradable DOMs have been used for estimates of

river water or wastewater. However, as shown in Part I in the present review series, biodegradable DOMs were found to have been deeply influenced by recent organic pollution in closed water bodies such as lakes or bays, especially in densely populated regions. Therefore, both qualitative and quantitative analyses of DOMs by biomonitoring are required to understand the behavior of DOMs in the ecological aspect of the water environment. In addition, the bioavailability of DOMs in ecological and biological aspects is also required. The microbial biosensor is able to comprehensively measure various conditions in the environment; this makes it possible to measure the bioavailability of DOMs. In the next sections, I consider new microbial biosensor technologies necessary to understand the behavior of DOMs in environmental water.

Behavior of DOMs

In the case of lake water, the DOMs are mainly supplied from catchment areas, from which allochthonous DOMs are derived, and within lakes, which produce autochthonous DOMs. Allochthonous DOMs mainly consist of terrestrial humic substances and are recalcitrant to bacterial degradation, while autochthonous DOMs are produced by dominant phytoplankton, particularly in eutrophic lakes, and changed to recalcitrant DOMs by bacterial degradation [177, 178]. It is also known that microbes transform labile DOMs to humic-like matter during cell growth and decline in seawater [179, 180]. As a result, heterotrophic bacteria play critical roles in the carbon cycle of aquatic environments, and the chemical composition of recalcitrant DOMs in environmental water depends on autochthonous microbes and water sources. Concerning these studies, in 2017, Kobayashi et al. (Japan) visualized the distribution of DOMs in marine water from a satellite [181]. These techniques might enhance DOM control in environmental waters.

Microbes for DOM biosensors

I believe that BOD biosensors can be applied to biodegradable DOM measurements of these water bodies. Then, the autochthonous and heterotrophic microbes sampled from the sediment of closed water bodies should be employed as a biorecognition element for biodegradable DOM biosensors. As other examples, eukaryote microbes, such as fungus containing yeasts, are also useful as recognition elements for biodegradable DOM measurements, which enable the assimilation of organic matter that is scarcely biodegradable. In 2014, Chen et al. studied the rapid biodegradation of numerous insoluble fine fibers in effluent. They selected marine-derived fungi *Pestalotiopsis* sp. J63 and *Penicillium janthinellum* P1 (they isolated), which might be usable as biorecognition elements for measuring biodegradable DOMs [182, 183].

For practical measurement of biodegradable DOMs, microbial biosensors should also be improved for high sensitivity (Górski, Trzebuniak, and Elżbieta; Poland, 2012) [184] and application to marine water samples (Balootaki and Hassanshahian; Iran, 2014) [185]. Further, the genetic modification of microbes to decompose diverse DOMs will also be required in the future to achieve this aim.

Currently, studies by Quek, Cord-Ruwisch, and Cheng (Australia, 2014–2015) might apply to the biodegradable DOM biosensor for marine water, although their studies are at the earlier stage of detecting assimilatable organic carbon (AOC) in ocean water. The studies have been performed for the purpose of the online monitoring of the water quality of seawater desalination plants, which are prone to the biofouling of reverse osmosis (RO) membranes [186–189]. Marine microbes originating from marine sediment and biofilm were used as an anodic compartment of MFC. Currently, acetate is measured instead of organic matter derived from microbes; however, rapid (10 min) and sensitive (5 μM acetate) measurements are performed by the MFC biosensor.

Recently, Ebrahimi, Yousefi Kebria, and Najafpour Darzi (Iran, 2017) developed microbial desalination cells (MDCs) that enabled chemical oxygen demand (COD) removal of the marine salt concentration (35 g L^{-1}) [190]. Therefore, an MDC biosensor for measuring marine DOMs might be developed by applying this technique. In addition, a 2013 study by Chee et al. (Korea) can be applied to biodegradable DOM measurements because five kinds of microbes used in the study enabled a wide range of DOMs in fresh water samples [191]. In 2014, Liu, Zhao, Dong et al. (China and Australia) developed a photoelectrocatalytic DOM microbial biosensor that combined biodegradation by a biofilm reactor and photoelectrocatalytic COD decomposition [192].

Microbes for SOM biosensors

In 2010, Namour and Jaffrezic-Renault [193] reviewed several approaches for developing microbial biosensors to measure biodegradable and total organic matter in water. In their review, they suggested requirements for increasing their operational period and, particularly, for practical monitoring by preventing biofouling and clogging. In 2010, Hong, Kim, and Chung (Korea) studied the alteration of physicochemical properties of sediment organic matters (SOMs) employing sediment microbial fuel cell systems [194]. They observed the humification and polydispersion of SOMs and showed the possibility of monitoring SOMs. In 2011, Liu et al. (China) developed a MFC biosensor for monitoring the anaerobic digestion process [195]. Such a biosensor might also be applied to the measuring of both SOMs and DOMs.

Microbes for hardy DOM biosensors

As another possibility, Liang et al. recognized in 2013 a microbial glucose electrode by displaying glucose dehydrogenase, which was displayed onto the surface of genetically engineered *E. coli* [196]. Further, in 2013, Golitsch, Bücking, and Gescher studied the surface display of protein complexes onto the outer membrane of *Shewanella oneidensis*, which probably enables membrane-spanning electron transfer [197]. Such techniques for displaying protein complexes onto the electroactive outer membrane might be promising for the development of a new microbial biosensor for DOMs, including hardy biodegradable organic matter.

Microbial biosensors for other organic matter

Detergents

In current water quality conditions, the monitoring of detergent is required; however, the development of microbial detergent biosensors has not progressed. In the 1990s, Nomura et al. developed several microbial biosensors for detergents that utilized microbial catabolic activity [198, 199]. They finally employed *Trichosporon cutaneum* as a recognition element and determined the concentration of anionic surfactants—linear alkylbenzene sulfonates (LAS)—dissolving in river water [199]. In 2016, Zhang et al. developed a MFC biosensor that employed *Shewanella* sp. WLP72 as an indicator for biotoxicity assessment and studied the toxicity of a cationic surfactant, benzalkonium chloride (BAC). BAC is known as a disinfectant and is not suitable for biodegradation. Therefore, they investigated the biodegradation ability of BAC's intermediates, which were produced by Fenton's advanced oxidation, using the MFC biosensor [200]. However, in general, measuring detergents using microbial biosensor techniques is difficult due to low specificity, although microbial display techniques might solve the problem [196, 197].

Gaseous organic matter

As organic pollution progresses, organic matter is deposited on the water bottom. Then, the atmosphere of the water bottom changes from an aerobic state to an anaerobic state with the progression of the organic matter's decomposition. As a result, methane gas is released from the water's surface. Therefore, measuring methane can be considered an indicator for measuring the degree of organic pollution. There are four reports on microbial biosensors measuring methane, including two reported by Odaka, Karube, and Suzuki (Japan) in the early 1980s [201, 202]. They constructed a gas flow system, and methane gas was detected through a gas membrane that immobilized *Methylomonas* sp. In 1997, Damgaard and Revsbech (Denmark) reported a gas flow type of microscale methane biosensor that employed methanotrophic bacteria (methane-oxidizing bacteria) [203]. Then, methane was determined through bacterial oxygen consumption. In 2015, Zarei and Farahbakhsh (Iran) developed a gas flow type of optical methane biosensor that employed methanotrophic bacteria and gold nanoparticles [204]. For both of these studies, portable sensors might be developed in the future; however, in that case, specificity to methane may become a problem for practical use.

Sex hormones

Recently, sex hormones and their derivatives have been treated as water pollutants and are also known as endocrine disruptors.

Baronian and his group members (New Zealand) have studied their original electrochemical techniques [30, 36]. Applying their experiences, a microbial biosensor for sex hormones has been developed [39–41, 205]. Yeast is known to have an estrogen-binding protein (EBP) that mediates the oxidation of NAD(P)H to provide $NAD(P)^+$ for the process of cell catabolism. In 2007, Baronian and Gurazada showed that 17β-estradiol can be quantified using *S. cerevisiae* cells as the detection element and the DM (menadione and FCN) electrochemical system to measure NAD(P)H [205]. In 2011, Chelikani et al. tried a simpler method using *Candida albicans* cell lysate. FCN for the SM electrochemical system was used to quantify 17β-estradiol as a single hydrophilic mediator [39]. In 2012, they further investigated the influence of the growth phase on EBP production in *C. albicans* and the response to estrogen using mediated electrochemical systems [40]. It was found that the EBP production and estrogen response may vary with the growth phase strain. Subsequently, in 2015, they constructed a recombinant EBP using industrial yeast, and 17β-estradiol was finally detected by the immunological method, employing SPR [41].

In 2011, Plekhanova et al. (Sweden and Ukraine) developed a microbial biosensor for monitoring the biodegradation of nonylphenol polyethoxylates (NPE) in wastewater [206]. NPE is known as a nonylphenol derivative suspected of having estrogenic effects. For this purpose, destructor bacteria were employed as aerobically biodegrading bacteria of NPE, and NPE was detected through the bacteria's oxygen consumption.

In 2011, Roda and Branchini et al. (Italy, USA) developed a practical multiplexed BL device for sex hormones [102]. Roda and his group members have been actively studying recombinant BL microbes and portable biosensor devices [89, 91, 93, 103–105]. Applying their experiences, the study employed five kinds of recombinant microbes (yeast and *E. coli*) for total androgenic and estrogenic activity measurements. As analytes, testosterone, 17β-estradiol, and the xenoestrogen bisphenol A (BPA) were measured qualitatively

and quantitatively. In addition, the microbial biosensors showed the potential for rapid screening of endocrine disruptors in environmental or food samples.

In 2017, Bazin et al. (France and Korea) studied biological effects such as the estrogenic activity and toxicity of wastewater samples using different recombinant BL microbes [207]. Gu's group has also studied array- or dipstick-based recombinant BL microbial biosensors [95–97]. They applied their experience to measuring estrogenic activity by 17β-estradiol using recombinant yeast BY4741 (toxicity was measured using five recombinant *E. coli* bacteria strains; oxidative, protein damage, cell membrane damage, or cellular toxicity).

By using recombinant techniques, sex hormones and their derivatives as target analytes have become qualitatively and quantitatively measurable. In the future, such measurable analytes will be increased, and the development of a device that can measure analytes simultaneously will also be accelerated. However, many of these substances are often contained in sewage treatment water. Therefore, it will be necessary to develop continuous biomonitoring systems.

Microbial biosensors for eutrophication

Recent organic pollution in environmental waters has mainly occurred after eutrophication, which produces voluminous biomass by cyanobacterial water bloom. Therefore, to maintain water quality, nutrient salts must be measured. In general, nutrient biosensors employ enzymatic reactions that enable substrate-specific measurements [208–214]. In 2014, Goron and Raizada (Canada) comprehensively reviewed transgenic microbial biosensors for macro- and micronutrients [215].

Nitrogen compounds · Phosphorus compounds

Gillor and Belkin et al. (Israel) developed BL cyanobacterial sensing systems for monitoring the bioavailability of phosphorus [216] or nitrogen [217]. These sensing systems were developed by advanced genetic engineering techniques in the early 2000s [218, 219]. They finally were able to quantify the bioavailable concentrations of these essential macronutrients in a freshwater lake in 2010 [220]. In 2012, Faraghi and Ebrahimi (Iran) studied a nitrite-fed microbial fuel cell and found that nitrite can be oxidized to nitrate in the absence of O_2 [221]. They did not isolate the bacteria; however, they studied the removal of nitrate from drinking water in 2017, using biological methods [222]. In the future, they might develop a nitrite microbial biosensor especially for high-rate anaerobic water areas. In 2013, Raud and Kikas et al. (Estonia) isolated the nitrifying bacterium *Nitrosomonas* sp. and developed an ammonium nitrogen (NH_4^+–N) biosensor for high-rate ammonia wastewaters [223]. Zuki et al. (Malaysia, 2018) recently developed an optical whole cell biosensor that enables the visual quantitation of nitrite ions; nitrite-degrading microorganisms were then immobilized onto the surface of transparent microbeads [224]. The three microbial biosensors mentioned above might be applied to high-rate anaerobic water areas. In addition, increasing the sensitivity of the microbial biosensor will be necessary to predict eutrophication because these nutrients influence environmental waters in small amounts.

Sulfur compounds

Sulfur is known to be a nutrient salt, and sulfide is released from existing anaerobic sediment of bottom water, which is produced as organic pollution progresses. Recently, two groups developed sulfide biosensors using sulfide-oxidizing bacteria. In 2014, Qi, Zhang, and Wan et al. (China) developed an amperometric sulfide sensor employing *Thiobacillus thioparus* cells [225]. The sensor enabled both the selective detection of sulfide and the detection of sulfate-reducing bacteria. Ebrahimi, Vosoughi, and Amoabediny et al. (Iran, 2014–2015) developed a gas flow type of amperometric microbial biosensor employing *T. thioparus* cells. Hydrogen sulfide was detected by the oxygen consumption of *T. thioparus* cells [226, 227]. They also detected sulfate-reducing bacteria. However, it is difficult to improve the gas flow biosensor as a mobile type. In the future, the development of such mobile devices will be necessary.

Metal ions

Iron is known as a nutrient salt and is released from anaerobic sediment. When the iron ion concentration increases, water bloom is formed, as well as phosphate and nitrate ions in closed environmental waters. In 2008, Gupta et al. (India) developed a spectrophotometric Fe^{3+} biosensor. Fe^{3+} was absorptiometrically detected as a fluorescent siderophore, which was released from *P. fluorescens* culture [228]. In 2015, Tran et al. (Vietnam, Korea, Malaysia, and China) developed an MFC biosensor for Fe^{2+} and Mn^{2+} that employed lithotrophic iron-oxidizing bacterial consortia [229]. Although Ni^{2+} or Pb^{2+} reduced Fe^{2+}-associated electricity generation, the possibility of specifically sensing both Fe^{2+} and Mn^{2+} was indicated. As shown here, studies of microbial biosensors to estimate eutrophication were explained, and one research trend was found to be the development of a mobile biosensor for on-site monitoring.

Microbial activities

As another influence of eutrophication, increased microbial activity in environmental waters cannot be ignored. Thus, microbial biosensors have been developed in recent years. Yamashoji et al. (Japan) have studied microbial DM systems

[35, 37, 38]. Although their research interests are food and clinical analyses using double redox mediators menadione and FCN, these techniques can also be applied to environmental water analyses. In 2013, Yamashoji et al. developed a microbial screening test that employed a menadione-catalyzed CL assay [37]. In 2017, they developed a method for determining yeast cell activity that employed the synergistic reduction of toluylene blue [38].

In 2014, Liang, San Park, and Yoon (USA) developed a smartphone-based biosensor for microbial contamination [230]. By the irradiation of near infrared LED light on the sample surface, scatter signals were evaluated using both a gyro sensor and the digital camera of a smartphone.

In 20111, Demirkol and Timur (Turkey) developed a microbial activity biosensor that employed an electrochemical single-mediator system [56]. They employed bacterial wiring using MWCNTs and FCN and detected *P. fluorescens* cells. Hassan, Sedki, Wollenberger, and El-Sherbiny et al. (Egypt and Germany) have actively developed several microbial activity biosensors that employ direct electrochemical wiring systems [58–60]. In 2014, they detected *Streptomyces* Spp. using MWCNTs [59]. In 2013, using redox color indicator, DCIP, we developed an absorptiometric microbial activity biosensing method for both yeast and bacterial cells [65]. In 2016, an electrochemical DM system consisting of DCIP and FCN was developed for the cell viability of *Staphylococcus aureus* [58]. Further in 2017, a graphene oxide-hyperbranched chitosan nanocomposite was applied to real-time bacterial cell viability analysis, and cell viabilities of both *E. coli* and *P. aeruginosa* were measured [60]. As described here, several types of microbial biosensors have been developed for eutrophication. In the future, it will be necessary to develop a microbial biosensor adapted to the water environment induced by both eutrophication and organic pollution effects.

Microbial biosensors for water toxification

Current water pollution is mainly induced by several pollutants, such as nutrient salts and DOMs. Most pollutants are anthropogenically released in sewage, domestic life, industries, and farms. These influences subsequently induce ecotoxicity problems, especially in closed water areas such as lakes and bays. From such a background, many microbial biosensors have been developed, in particular, employing recombinant BL microbial cells or MFCs for measuring toxicity or toxic substances [25, 26, 89, 90, 231–234].

The growth of phytoplankton by eutrophication leads to cyanotoxin production and the alkalization of surface water. In addition, a large amount of organic matter accumulated on the water bottom due to the growth of phytoplankton changes its bottom state from aerobic to anaerobic as it decomposes. As a result, the elution of toxic substances such as heavy metals by this reductive environment will affect aquatic organisms and our health. To prevent such a situation, the monitoring of water quality is very important. The microbial biosensor is able to solve the problem as one tool for measuring water quality. In this section, recent developments are described.

Microcystin-LR

In general, the bioanalysis for cyanotoxin uses an immunological tool such as enzyme-linked immunosorbent assay (ELISA). However, in 2015, Mankiewicz-Boczek et al. (Poland) developed a microbial biosensor for cyanotoxins, including microcystin-LR, which is the most toxic cyanotoxin to both aquatic organisms and human health [235]. They employed two types of recombinant BL cell lines (NHRTOX and OXIBIOS); however, sensor responses to cyanobacterial extracts showed the possible existence of unknown toxic substances. Thus, further study is necessary.

Alkalization

For the alkalization of environmental water, Hassan, Van Ginkel, and Oh (Korea and USA) developed in 2013 a microbial biosensor employing sulfur-oxidizing bacteria [236]. The bacteria oxidize sulfur particles under aerobic conditions to produce sulfuric acid. Changes in conductivity and pH could measure alkalinity and organic matter in sample waters, respectively. On the other hand, an acidic toxicity MFC sensor was developed by Shen et al. (Singapore, 2012) [237]. After optimization, a single-chamber air cathode MFC using a proton exchange bulkhead membrane had a fast response to an acidic sample after 3.5 min of retention time. These microbial biosensors were sensitive to pH; such techniques might be used to measure the influence of alkalization caused by water-bloom formation.

Toxification

To monitor wastewater quality, it is necessary to raise an alarm promptly and reliably against the inflow of toxic substances. However, conventional MFC biosensors have various barriers to responding to such toxic substances.

To solve the problem, Li et al. (USA) studied "shock" biosensors to detect accidental toxicity, employing a new type of MFCs [238–240]. In their developmental studies, leading-edge techniques were applied to the new style of MFC biosensor. In 2014, Lie et al. developed a self-powered single-chamber MFC biosensor for quick response to wastewater toxicity [238]. An anode open circuit potential (OCP) was employed, and external resistance was connected to both the anode and the cathode. The output voltage from the anode OPC was measured using a multimeter. The MFC consists of a cubic-shaped small chamber (4 × 3 × 3 cm), a Pt cathode,

and a conductive carbon cloth anodic biofilm as a working electrode. The anodic electrogenic bacteria were fully acclimated after operation. By removing an anode/cathode separator, a quick response was realized. Then, a steep voltage drop was observed with the addition of an acute toxic substance (8 mg L^{-1} Cr(VI)) into the MFC chamber. In 2015, Xu et al. dramatically improved the "shock" biosensor by constructing a flat membrane-based MFC [239]. The flat membrane-based MFC biosensor was made by compacting two microporous hydrophilic filter membranes coated with conductive carbon ink and a paper reservoir. For real-time in situ wastewater monitoring, the MFC biosensor enhanced the practicability of electron transfer, rapid biofilm formation, quick and sensitive response, and long-term operation. In 2015, Xu and Liu et al. (USA and China) further developed a self-sustained shock MFC biosensor for real-time in situ wastewater monitoring [240]. This MFC biosensor is a disposable paper-based multi-anode type that integrates with a self-power management system (PMS), which harvests the energy from wastewater and supports data transmission to achieve self-sustained real-time water quality monitoring.

Stein, Keesman, and Hamelers et al. (Netherlands) also studied toxicity biosensing by employing MFCs [241–245]. In 2007, Kim and Gadd et al. (Korea and UK) carried out fundamental research related to the MFC biosensor, which triggered the study of Stein et al. [246]. In this study, a biomonitoring system using MFCs to detect the inflow of toxic substances into water systems was developed for the purpose of on-site or on-line monitoring. They found that actual wastewater shows a significant current reduction and a high inhibition ratio for toxic substances compared with laboratory tests. Based on this result, Stein et al. further investigated in 2010 the stabilization of the baseline current using an MFC biosensor [241]. The MFC biosensor consisted of two flat graphite electrodes, and the anode and cathode chambers were separated by a proton-exchange membrane. To stabilize the baseline current, strictly controlling pH and anode potential in a small range is required. From 2001 to 2002, they studied kinetic models [242], the influence of the membrane type [243], the effect of different control mechanisms [244], and the influence of the magnitude of the resistance [245]. The optimal setting for obtaining the highest sensitivity for a given sensor is currently underway.

Subsequently, the most recent developments in the toxicity sensing of MFC biosensors in 2017 are as follows: Labro et al. (New Zealand) developed a photosynthetic MFC biosensor for the generation of electrical power or the accumulation of useful compounds [247]. By employing photosynthetic bacteria, such as algae or cyanobacteria, a self-powered MFC biosensor similar to a solar cell enabling electrical energy production will be fabricated in the near future. Jiang and Liang et al. (China) developed two types of MFC biosensors for a water alert system [248, 249]. One was fabricated so that the four anode chambers are shared with one cathode for continuous monitoring [248]; another was fabricated so that both the anode and cathode are coated with biofilms [249]. In the latter MFC biosensor, the anode and cathode were connected with a potentiostat at 0 V. This leads to the highly sensitive detection of formaldehyde in both the biocathode and bioanode. In 2017, Yu and Dong et al. (China) developed a SM-based self-powered MFC biosensor using FCN for toxicity detection [250]. In general, the amount of inflow water in the MFC biosensor is often small relative to the volume of the chamber, and it often takes time for toxic substances to flow into and out of the chamber. As a result, it takes time to respond to the toxic substances, and the speed in returning to a steady state is also limited. To solve the problem, Zhang and Qin et al. (China) developed a potentiometric flow biosensor in 2013 based on the ammonia-oxidizing bacteria *Nitrosomonas europaea* for the detection of toxicity in water [251]. In this sensor, a carrier solution containing ammonia, which is a substrate of bacteria, flows through the sensor at a constant concentration. When the sample solution flows into it, it first comes into contact with the bacteria-immobilized membrane and then passes through the ammonia electrode. As a result, its response to thioacetamide (toxic compound) was immediately and sensitively obtained at the detection limits (3σ) of 0.02 μM. Up to this point, recent microbial biosensor research trends regarding toxicity detection focusing mainly on the MFC biosensor have been discussed. Next, recent research trends regarding microbial biosensors for toxicity detection using BL microorganisms are introduced.

Thouand et al. (France) have been actively developing toxicity biosensors that employ recombinant BL bacteria. Therefore, their group has also reviewed the development of recombinant BL bacteria for microbial biosensor application [231–243]. In 2011, Charrier et al. focused attention on the fact that on-line measuring within an integrated system had not yet been achieved, and they developed a multi-channel BL bacterial biosensor for the on-line detection of metals and toxicity in water [106, 107]. Their goal is to construct a multiple metal detection system (simultaneous specific- and cross-metal detection) using the Lumisens III biosensor. In the first step, they employed three strains to detect a broad range of heavy metals, and they were characterized. In this study, they found (1) the importance of the carbon source (acetate was chosen), (2) the favorable growth phase for the induction ratio (it depended on the kind of recombinant *E. coli*), and (3) a suitable matrix for bacteria (agarose was better than PVA) [106]. In the second step, a disposable card was employed in the assembly of a multi-strain biosensor for a complex mixture of metals and its classification [107]. Then, it was found that specific analysis software was necessary for data interpretation. Jouanneau et al. improved the identification of four heavy metals by using an algorithm and five recombinant BL bacteria [109]. A specific decision tree method was used

to identify heavy metals in water samples. In 2012, Jouanneau et al. further developed a Lumisens IV biosensor and improved the Metalsoft software [110]. The Lumisens IV biosensor enabled reliable monitoring and estimation of heavy metal levels in water. In 2016, Jouanneau et al. developed a marine toxicity biosensor that employed *A. fischeri*, and the influences of naphthalene on the BL were determined using the disposable card-immobilized *A. fischeri* [112]. In addition, Bittel et al. studied in 2015 multi-parametric bioassays as a new approach using Raman spectroscopy, and bacterial metabolic responses against toxic substances were observed by the elaboration of an aberrant spectra detection strategy [252]. By using recombinant techniques, toxic substances have become qualitatively and quantitatively measurable. However, it is also important to measure the influence of microorganisms that are also original features of conventional microbial biosensors. In that sense, a study using Raman spectroscopy is proposing a new method of evaluating toxicity [252], and I am looking forward to advancement in future studies.

Heavy metal ions

As described above, heavy metal ions elute from the bottom water as organic pollution progresses. On the other hand, heavy metal toxicity is known as non-biodegradable and bioaccumulative. Heavy metal enters the human body through food, water, air, or by skin absorption. It becomes toxic when not metabolized by the body and accumulates in soft tissues. Heavy metal generally inhibits microbial cells by blocking essential functional groups, displacing essential metal ions, or modifying the active conformations of biological molecules. Exposure to heavy metal ions can also lead to cellular dysfunction, such as DNA damage, enzyme alteration, and cell membrane disruption. Studies on microbial biosensors for heavy metal ions were recently reviewed by Biswas, Karn, and Kale et al. (India, 2017) [253] and, for arsenic, by several groups: Merulla and Meer et al. (Switzerland, 2013) [254], Chen and Rosen (USA, 2014) [255], and Kaur and Mittal et al. (India, 2015) [256]. Kaur and Mittal et al. (India) also reviewed arsenic biosensor developments comprehensively in 2015 [256].

In recent developments, microbial biosensors employing MFC, electrochemical, FL, or atomic force microscopy (AFM) methods were reported. In 2013, Shen and Ng et al. (Singapore) developed a MFC biosensor for copper ion (II). It was found that the shear rate influenced effective biofilm formation to the anode for sensitive detection of copper ion (II) [257].

Notable studies by four groups using electrochemical methods are introduced here. In 2011, Chiou and Tseng et al. (Taiwan) developed a microfluidic electrochemical arsenite-sensing chip consisting of an arsenite concentrator [258]. Arsenite-sensitive recombinant *E. coli* cells were trapped on the working electrode by the dielectrophoretic force. Then, the *E. coli* cells were transformed with arsenite-regulated reporter plasmids and incubated with arsenite. Depending on the arsenite concentration, the recombinant *E. coli* produced *p*-aminophenol, which was electrochemically detected at 0.1 ppm of arsenite within 30 min by the microfluidic MEMS chip. In 2013, Cortés-Salazar and Girault et al. (Switzerland) also developed an arsenite-sensitive biosensor that employed recombinant *E. coli*, which produces *p*-aminophenol by the existence of arsenite [259]. The biosensor enabled the highly sensitive detection of 0.8 ppb arsenite ion (III) in tap water. In 2013, Wang et al. (China) developed a SM electrochemical biosensor—a *p*-benzoquinone-mediated amperometric biosensor employing *Psychrobacter* sp.—for detecting heavy metal ions [260]. The sensor made it possible to measure the EC_{50} value of heavy metal ions to *Psychrobacter* sp. with an incubation time of 30 min [example: 2.6 mg L^{-1} Cu (II)]. In 2017, Prabhakaran and Subramanian et al. (India and France) developed a carbon paste electrode modified with *Citrobacter freundii* bacterial cells for the detection of chromium (III) and (VI) ions [261]. Employing bacterial reduction of chromium ions on the electrode surface and the differential pulse cathodic stripping voltammetric technique, Cr(III) and Cr(VI) ions were sensitively detected at 1×10^{-7} M and 1×10^{-9} M, respectively.

Notable studies by four groups regarding the FL heavy metal ion sensor are introduced here. In 2015, Li and Chen et al. (China) developed a highly active arsenite-induced *arsR* operon by successive FL-activated cell sorting. As a result, a sensitive arsenite FL *E. coli* biosensor was constructed [262]. In 2016, Asif and Sen et al. (India) developed an effective method of immobilization for a microbial FL sensor for detecting heavy metals [263]. In conventional microbial FL sensors, when measured in the state of cell suspension, the FL intensity decreases due to scattered light, which is unsuitable for high-sensitivity detection. To overcome the problem, FL *E. coli* DH5α cells were immobilized, using a polyethylenimine matrix, onto the surface of a glass slide, and direct FL light from the recombinant cells was detected. Kim and Lee et al. (Korea) recently developed several FL biosensors for highly specific and sensitive detection of lead or cadmium ions [264, 265]. In 2015, a chemostat-like microbial biosensor consisting of a high-throughput microfluidic chip device was constructed [264]. In 2016, a synthetic CadC-T7 genetic circuitry was introduced into each *E. coli* strain for specific detection [265]. The FL *E. coli* strain also enabled highly sensitive detection by intracellular signal amplification. In 2017, Kumar, Verma, and Singh (India) constructed a plasmid pNV12 as sensing element for cadmium and developed a cadmium-specific FL biosensor [266]. In 2017, Bereza-Malcolm and Franks et al. (Australia) studied multiple uses of cadmium-responsive FL biosensors that employed five recombinant Gram-negative bacterial cells

[267]. The importance of the simultaneous use of several bacterial species in the biosensors was suggested for obtaining reliable results.

Using AFM, Gammoudi and Dejous et al. (France and Tunisia) developed in 2014 a bacteria-based microfluidic Love-wave biosensor [268]. A Love wave is a guided shear horizontal surface acoustic wave (guided SH-SAW). Compared with their previous study in 2010, the biosensor's sensitivity and response time to cadmium (II) or mercury (II) was improved [269]. For example, with respect to cadmium (II), the appearance of the structural dissolution of *E. coli* cells was confirmed by multiple indices, the detection limit was 10^{-9} M, and the response time was within 60 s. As described above, heavy metal ions have become qualitatively and quantitatively measurable by employing recombinant microbes. However, further development of microbial biosensors for measuring the toxicity of heavy metal ions is also important.

Harmful organic matter

Other microbial biosensors for harmful organic matter are finally introduced. In 2011, Biran and Belkin et al. (Israel and Germany) constructed a bacterial genotoxicity reporter strain [270]. Then, the tightly controlled strong promoter of the *E. coli* SOS response gene was fused to the *phoA* reporter gene. The bioreporter responses to hydrogen peroxide, nalidixic acid, and mitomycin C as DNA-damaging agents were colorimetrically obtained. A similar response to nalidixic acid was also observed using a portable electrochemical device. In 2011, Hnaien and Lagarde et al. developed a CNT-modified microelectrode for impedance detection of trichloroethylene (TCE) [271]. *Pseudomonas putida* F1 cells were immobilized to the gold microelectrode, and CNT was electrically wired to the anti-TCE antibodies that were exhibited on the *P. putida* cell surface. The immunoreaction with TCE was detected as impedance changes. In general, a pesticide biosensor was employed for the immunoreaction [272, 273]. However, in 2014, Tang and Liu et al. (China) developed a microbial pesticide biosensor that employed a cell surface-display method [274]. Organic solvents have also been widely developed, and Karim and Fakhruddin (Bangladesh) reviewed the biosensor development for phenol in 2012 [275]. In 2011, Kumar and D'Souza et al. (India) developed an electrochemical microbial biosensor for the detection of methyl parathion [276]. Recombinant *E. coli* cells having organophosphorus hydrolase were immobilized on the screen-printed carbon electrode, and the sensor response was detected by the electroactive substance of *p*-nitrophenol, which is produced by organophosphorus hydrolase. In 2016, Chen and Li et al. (China) employed an anode of an MFC as an aerobic anode biosensor for *p*-nitrophenol [277]. They finally developed a portable biosensor system for in situ real-time monitoring of *p*-nitrophenol in wastewater. In 2011, Di Gennaro and Campanella et al. (Italy) developed a microbial biosensor for benzene [278]. In this study, recombinant *E. coli* produced the b benzene dioxygenase and benzene dihydrodiol dehydrogenase by the existence of benzene. Depending on the benzene concentration, catechol was produced and oxygen was consumed by pyrocatechase. Catechol and oxygen were measured by colorimetrical and electrochemical methods, respectively.

Additional

Agricultural soil

Here, I introduce the agricultural soil biosensor that we developed in 2008 [279]. This microbial biosensor measures soil microbial relationships for crop production. If this kind of research triggered and the coziness for living organisms became measurable by microbial biosensors, we would be able to grasp the state of the ecosystem from a different point of view. To that end, it is necessary to use an allelopathy microbial biosensor (not a qualitative/quantitative analysis) that can measure competing states between living organisms as the magnitude of influence on living organisms, a microbial biosensor capable of measuring various stresses of living organisms from the habitat environment, or a microbial biosensor that can measure antioxidant capacity that is being developed as enzyme sensors for food analysis [131, 280]. Thus, improving the water environment may proceed faster if the senses of living organisms in the water environment can be read by microbial biosensors.

Mammalian cell-based biosensors

Finally, I introduce one study that does not use microbial cells as biorecognition elements; however, the properties of cells should be useful for future research on microbial biosensors. Kubisch et al. (Germany) have studied mammalian cell-based biosensors. In 2012, they developed a multiparametric cell-based toxicity sensor system for the real-time monitoring of water [281]. They chose six mammalian cell types that have no cell wall and are, therefore, more sensitive to toxic substances than microbial cells and are better able to adhere to substrates, thereby being suitable for impedance measurement. Each cell line was seeded on a metabolic chip (Bionas), which incorporates an impedance electrode (morphology), oxygen electrode (respiration), and pH electrode (metabolism). The sensor responded to the acidification, morphology, and respiration of the mammalian cells through contact with the water samples. This kind of mammalian cell biosensor might enable us to measure the comprehensive toxicity in water in the future just as well as microbial biosensors.

Conclusion

Following the previous review in 2010 [22], in Part I of the present review series [282], the current status of the water environment and recent studies on water quality investigations in Japan were described. Subsequently, I summarized the research trends of recent microbial biosensors in as much detail as possible and introduced future perspectives of microbial biosensor developments by focusing on the current status of the water environment. In concluding the present review series, I suggest developing a microbial DOM biosensor for monitoring water quality in closed water bodies such as lakes and bays. In general, the amount of organic matter contained in a closed water body is estimated by COD or TOC measurement. However, as described in Part I, the amount of organic matter is influenced by the behavior of DOMs. Therefore, from an ecological aspect, the amount of organic matter must be estimated by biomonitoring using biological tools.

In addition, recent advances in the development of microbial biosensors, in particular the recombinant technologies, have made it possible to qualitatively and quantitatively determine an analyte as with enzyme sensors. However, not much progress has been made on a device for measuring the comprehensive response (nonspecific response) obtained from a microorganism, which is a conventional technique. In the future, it is considered necessary to develop microbial biosensors capable of measuring various stimuli received by microorganisms. Finding a way to use Raman spectroscopy may be the key to achieving this task [252], and a device combining these two types of microbial biosensors is important for the comprehensive measurement of environmental waters.

To solve these problems, the further development of microbial biosensor technologies will be required in the future. Finally, it would be a pleasure if the present review series could contribute even a little to the development of new microbial biosensors.

Compliance with ethical standards

Conflict of interest The author declares that he has no competing interests.

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