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BioMEMS for biosensors and closed-loop drug delivery

Joel Coffel, Eric Nuxoll*

Department of Chemical and Biochemical Engineering, 4133 Seamans Center for the Engineering Arts & Sciences, University of Iowa, Iowa City, IA 52242, USA

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ABSTRACT

The efficacy of pharmaceutical treatments can be greatly enhanced by physiological feedback from the patient using biosensors, though this is often invasive or infeasible. By adapting microelectromechanical systems (MEMS) technology to miniaturize such biosensors, previously inaccessible signals can be obtained, often from inside the patient. This is enabled by the device's extremely small footprint which minimizes both power consumption and implantation trauma, as well as the transport time for chemical analytes, in turn decreasing the sensor's response time. MEMS fabrication also allows mass production which can be easily scaled without sacrificing its high reproducibility and reliability, and allows seamless integration with control circuitry and telemetry which is already produced using the same materials and fabrication steps. By integrating these systems with drug delivery devices, many of which are also MEMS-based, closed loop drug delivery can be achieved. This paper surveys the types of signal transduction devices available for biosensing—primarily electrochemical, optical, and mechanical—looking at their implementation *via* MEMS technology. The impact of MEMS technology on the challenges of biosensor development, particularly safety, power consumption, degradation, fouling, and foreign body response, are also discussed.

1. Introduction

Physiological measurements to optimize drug delivery can be inconvenient, invasive, or even painful, limiting their frequency and therefore utility. One strategy for enhancing the frequency and accuracy of these measurements is incorporation of microelectromechanical systems (MEMS) technology (Madou, 2011; Tilli et al., 2015). In general, MEMS are defined by their small (submillimeter) length scale and their top-down fabrication techniques, where features are precisely machined from larger starting materials, as opposed to, for instance, self-assembly from smaller components based on their physicochemical interactions (Siegel et al., 2009). The advantages which biologically-oriented MEMS (BioMEMS) technology (Badilescu and Muthukumaran, 2011; Bashir and Wereley, 2006; Folch, 2012) can impart on biosensing, the ways in which it is being incorporated, and the challenges it must still overcome are the topic of this mini-review.

MEMS technology has been developed most extensively for the semiconductor industry, where machining tens of billions transistors into precisely aligned, interconnected arrays with no defects on a few square centimeters of silicon has become standard (Courtland, 2017). This is achieved by selectively processing parts of the silicon surface through a polymer stencil which protects the rest of the surface. The exposed surface may be etched away, chemically modified (doped), or covered with other materials (metals, insulators, *etc.*) while the protected surface is not. The stencil's features may be cut sequentially by a laser, an electron beam, or even a mechanical stylus, but most often they are all formed simultaneously in a photosensitive polymer by shining light through a mask onto it, selectively stabilizing or degrading the polymer in regions corresponding to the stencil features (photolithography). Once the less-stable material is washed away, the polymer stencil remains. This process may be repeated dozens of times, each with a different etching, doping, or deposition process, to reliably build micron- or nanometer-scale devices in quantities limited only by the size and number of wafers processed.

This approach to biosensor construction offers several potential advantages over conventional fabrication routes: First, the extremely small size of the systems permits applications which would be infeasible at larger length scales; for instance, sensing elements can be inserted in otherwise inaccessible locations. For measurements involving diffusive transport, the lag time decreases with the square of the transport length, strongly decreasing with device size. Smaller devices typically have lower power requirements and consume sacrificial chemicals at a slower rate, increasing potential device lifetime. Second, the fabrication processes are well-established and highly scalable, allowing rapid mass production of devices with extremely high reliability. Third, biosensors manufactured using MEMS processes and materials are particularly well-suited to integration with other MEMS devices, such as computer controls, wireless telemetry, and drug delivery modules.

* Corresponding author.
E-mail address: eric-nuxoll@uiowa.edu (E. Nuxoll).

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Already, BioMEMS technologies are permeating the development of drug delivery devices (Hilt and Peppas, 2005; Nuxoll, 2013), from microneedles for painless transdermal or intradermal delivery of biologics (Bhatnagar et al., 2017; Kim et al., 2012; Larraneta et al., 2016) to implanted microreservoir arrays delivering bone growth hormones (Farra et al., 2012). By integrating these delivery systems with computer control systems and biosensors, closed-loop drug delivery therapies can be achieved. In fact, some of the same simple devices used to transduce a physiological signal for reporting (*i.e.*, for biosensors) may also be used to transduce a signal for chemical release (*i.e.*, for drug delivery). The next section will survey these transduction devices by signal type, including electrochemical, optical, and mechanical transducers. The subsequent section will review recent progress in interfacing BioMEMS sensors with the body. Corrosion, fouling, and especially the foreign body response pose larger challenges to biosensors than to drug delivery systems. Though biosensors already comprise a 15 billion USD market with anticipated 9% annual growth (MarketsandMarkets, 2017; P&S Market Research, 2016), overcoming these challenges would allow permanent integration of biosensors in the body and expand their role in medicine enormously.

2. Signal transduction

The common function of all biosensors is transduction of a physiological signal, for instance a chemical analyte concentration, to a transmittable signal, typically electrical. Most of these transduction processes can be placed in one of three categories: electrochemical transduction where the analyte concentration directly causes a change in the potential, impedence, charge accumulation, or current density of a circuit; optical transduction which relies on the analyte's absorption or emission of light, either for direct visual observation or to generate an electrical signal; and mechanical transduction in which the analyte prompts a change in the shape (deflection) or motion (oscillation) of a mechanical component such as a cantilever or piezoelectric membrane, which in turn is transduced to an electrical signal. In some cases, of course, the physiological signal itself is electrical, in which case transduction is simply the reception and conditioning of the physiological electrical impulse.

2.1. Electrochemical transduction

Typical electrochemical systems are arranged in a three-electrode configuration in which the working electrode measures the potential established by the metal/electrolyte interface versus a reference electrode (*e.g.* a Ag/AgCl electrode) and a counter electrode completes the circuit. The electrochemical signal results from the diffusion of the targeted analyte from the bulk environment to the working electrode or to an analyte-sensitive material placed between the working and counter electrodes. A shift in potential at the working electrode (potentiometric), a change in conductance of the electrolyte between the working and counter electrode, an accumulation of charge (coulometric), or a rise or decrease in current (amperometric) indicates a change in concentration of the sensed molecule (Gencoglu and Minerick, 2014; Li et al., 2007). Electrical impedance spectroscopy is an additional, alternating current technique to sense changes in charge transfer resistance or capacitance on an electrode. As most of the integral components of electrochemical sensors are electrical circuit components, they are particularly well-suited to optimization using MEMS technology. Metal electrodes, insulating materials and catalysts can all be arranged in thin layers and patterned at the micron scale to create precisely ordered arrays of electrodes which are easily integrated with other circuit components.

2.1.1. Glucose sensors

The global market for continuous glucose monitoring systems was nearly $0.6 billion in 2015 and is expected to exceed $6.0 billion by 2022 (Allied Market Research, 2016). This growth is driven not only by increasing prevalence of diabetes (WHO, 2017) and improved access to health resources (French et al., 2016), but also by tremendous progress in glucose sensing technology. Transcutaneous glucose sensors the size of a needle now provide real-time blood glucose levels, allowing patients to monitor minute-to-minute fluctuations in their blood glucose throughout the day(US-FDA, 2016a,b). Their accuracy and reliability has permitted their use for automatic feedback in an insulin pump system; in late 2016 Medtronic's MiniMed 670G system became the first-ever truly closed-loop drug delivery system approved by the U.S. Food and Drug Administration (US-FDA, 2016a). The signal transduction for the 670G system, along with most other continuous glucose sensors is electrochemical. First, glucose is enzymatically oxidized at the electrode surface producing hydrogen peroxide as a product. Besides converting the glucose to a more chemically active chemical, enzymes provide the selectivity that helps ensure that only the target analyte influences the output signal. Immobilized glucose oxidase is the standard oxidizing enzyme on most glucose-sensing electrodes, though glucose-1-dehydrogenase and hexokinase have also been used (Yoo and Lee, 2010). Stoichiometric amounts of hydrogen peroxide are produced based on the local glucose concentration. Hydrogen peroxide is then oxidized, producing an electrical signal detected by one of the methods described earlier (*e.g.* amperometric, potentiometric, *etc.*). The immobilized enzyme and electrode are typically covered with a membrane to slow the transport of glucose to the electrode. This creates a constant, dominant transport resistance, dwarfing any variable physiological transport resistance to ensure that the rate of glucose reaching the electrode for oxidation is precisely proportional to the concentration of glucose in the blood. For oxygen-dependent enzyme systems, the membrane must allow a larger flux of oxygen, to ensure that it is always in excess so that glucose is always the limiting analyte being measured. And, it should prevent other oxidizable physiological species (*e.g.*, ascorbic acid) from reaching the electrode and influencing the reading. All of these functions are enhanced by increased membrane resistance, but that results in decreased hydrogen peroxide concentrations requiring increased sensitivity to hydrogen peroxide and lower peroxide detection limits. Alternatively, the electrode may catalytically reduce the remaining oxygen, comparing the depleted oxygen concentration around the immobilized glucose enzyme against the non-depleted oxygen concentration measured by a separate reference sensor (Gough et al., 2010; Lucisano et al., 2017). Fully implantable sensors using this approach have functioned in pigs for over a year (Gough et al., 2010) and were just demonstrated in humans for six months (Lucisano et al., 2017). This follows the footsteps of six-month trials of fully implantable peroxide-based glucose sensors dating back well over a decade (Gilligan et al., 2004).

These implantable systems in particular underscore the importance of MEMS technology to electrochemical biosensing, where the electrodes are integrated with the circuitry needed to drive the system and wirelessly transmit the output signal (McKean and Gough, 1988), reducing the footprint and power consumption of the system significantly. Moreover, MEMS technology has helped push the detection limit of hydrogen peroxide using electrochemical sensors down to submicromolar concentrations. The simplest example of an electrode for hydrogen peroxide oxidation is a strip of bare platinum (Kim et al., 1999; Zhu et al., 1994). Dividing this strip into an array of Pt working electrodes has been shown to increase hydrogen peroxide detection through increased total charge accumulation (Sassa et al., 2010). Spacing, size, and number of Pt strips have been optimized to increase the total charge in this coulometric detection technique with 40, 10 μm-wide electrodes spaced 10 μm apart. The limit of H_2O_2 detection using this array reached 410 nM H_2O_2. Other metal catalysts that have been micropatterned to decompose hydrogen peroxide include iridium, palladium, gold, silver, and manganese dioxide (Chen and Chatterjee, 2013). One glucose sensor currently in clinical trials uses an array of eight electrodes made from carbon paste, glucose oxidase, and